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Primary endoscopic bile duct stone removal for severe acute cholangitis: a retrospective study

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Abstract

Introduction: While the Tokyo Guidelines 2018 suggest primary stone removal for mild to moderate cholangitis, a guideline for severe acute cholangitis is not mentioned. We, therefore, investigated the clinical outcomes of patients with severe acute cholangitis to confirm the usefulness and safety of primary stone removal.

Method: This study included 104 severe acute cholangitis patients without gallstone pancreatitis diagnosed at our institution between January 2014 and December 2020. Patients with percutaneous transhepatic biliary drainage as the primary drainage, bile duct stenosis, and endoscopically unidentified bile duct stones were excluded from this study. The clinical results of 14 patients with primary stone removal (primary group) and 23 patients with elective stone removal (elective group) were then retrospectively examined (excluding abnormal values due to underlying diseases).

Results: Upon comparing the patient characteristics between groups, the elective group had significantly higher cardiovascular dysfunction (57% vs 7%; $p = 0.004$), septic shock (39% vs 0%; $p = 0.006$), disseminated intravascular coagulation treatment (57% vs 14%; $p = 0.016$), and positive blood cultures (91% vs 43%; $p = 0.006$) than those in the primary group. Endoscopic sphincterotomy for naïve papilla (90% vs 21%; $p = 0.01$) and endoscopic nasobiliary drainage (50% vs 9%; $p = 0.014$) were higher in the primary group, while endoscopic biliary stenting (7% vs 87%; $p < 0.001$) was lower than that in the elective group.

Discussion: There were no significant differences in adverse events or complete stone removal rates between the two groups. In the primary group, the period from the first endoscopic retrograde cholangiopancreatography to stone removal (0 days vs 12 days; $p < 0.001$) and hospitalization period (12 days vs 26 days; $p = 0.012$) were significantly shorter and the hospitalization cost ($7731 vs $18758; $p < 0.001$) was significantly lower than those in the elective group.

Conclusion: If patients are appropriately selected, bile duct stones may be safely removed for the treatment of severe acute cholangitis.

Keywords: acute cholangitis, bile duct stone, endoscopic bile stone removal, endoscopic retrograde cholangiopancreatography, severe acute cholangitis

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Introduction

Acute cholangitis refers to bile duct obstruction associated with infection: a high proportion of bile duct stones is therefore a factor in this disease, and sepsis can easily occur. The Tokyo Guidelines 2018 (TG18) recommend early or emergency drainage—in addition to antibiotic therapy—for the treatment of moderate to severe acute cholangitis (SAC); however, it is necessary to remove the causative bile duct stones after improvement is observed.[1] In

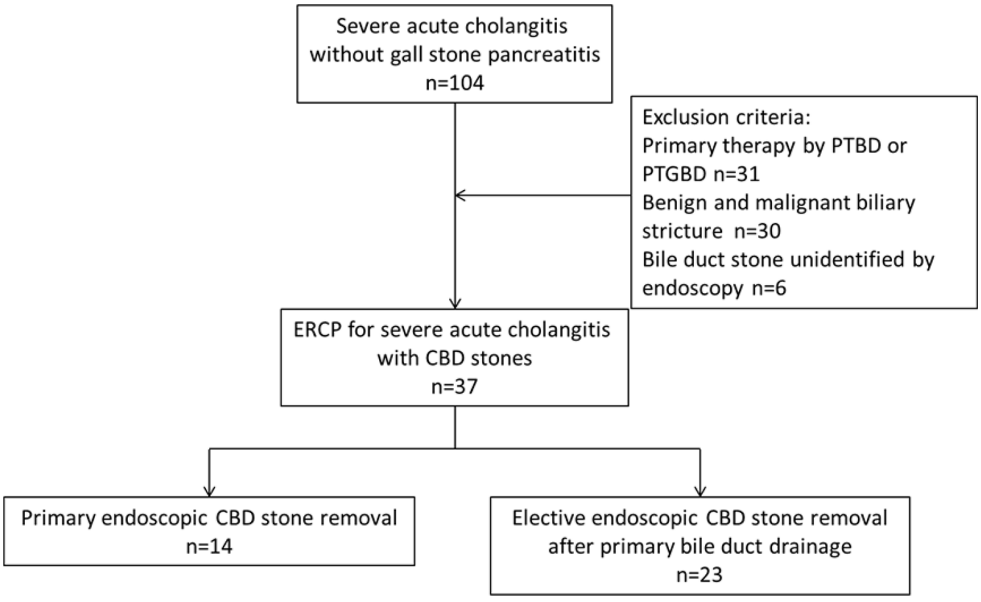

Figure 1. Flowchart of the patient selection process.
Abbreviations: CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage; PTGBD, percutaneous transhepatic gallbladder drainage.

addition, it has been reported that two sessions of treatment for mild to moderate cholangitis may increase the burden on patients and prolong hospital stay, while single-session treatments reduce the burden. It has also been reported that treatment results and complications are the same for primary and elective stone removal.[2,3] While the TG18 suggest primary stone removal in mild to moderate cholangitis, there is no information regarding the management of SAC. Similarly, cholecystectomy is recommended for mild to moderate cholecystitis in the TG18. Laparoscopic cholecystectomy in index hospitalization has been reported to result in shorter hospital stays and improved quality of life.[4] In addition, there are reports stating that surgery is possible even for severe acute cholecystitis, and the TG18 changed the TG13 recommendations to incorporate these reports.[5] Similarly, acute cholangitis guidelines can be changed.

We therefore retrospectively investigated the clinical outcomes of patients with SAC in our institution to confirm the usefulness and safety of primary stone removal in this group.

Methods

This retrospective study was approved by the Medical Ethics Committee of Showa University Hospital, and the requirement of informed consent for participation in the study was officially announced on the web page. Prior to inclusion, all patients provided written informed consent and were informed of the risks and benefits.

Patients

We included 104 patients with SAC—without gallstone pancreatitis—who were diagnosed at our institution between January 2014 and December 2020; 31 cases with percutaneous transhepatic biliary drainage (PTBD) as the primary drainage, 30 cases of benign or malignant bile duct stenosis on imaging findings, and 6 cases wherein bile duct stones were not endoscopically confirmed were excluded. We retrospectively examined the clinical results of 14 patients with primary stone removal as the first endoscopic retrograde cholangiopancreatography (ERCP) (primary group), and 23 patients who underwent endoscopic elective bile stone removal after undergoing endoscopic biliary drainage (EBD) without bile stone removal in the first ERCP (elective group) (Figure 1). The TG18 was used for the diagnosis and severity classification;[6] abnormal data and abnormal value items due to underlying diseases were excluded from the severity classification for SAC.

Devices

ERCP was performed using a duodenoscope (JF260 V; Olympus Medical Systems Corp.,

Tokyo, Japan). A sphincterotome (Autotome RX44; Boston Scientific, Natick Massachusetts, USA) and/or an ERCP catheter (MTW ERCP catheter; MTW Endoskopie, Dusseldorf, Germany) were used for bile duct cannulation. A guide wire (0.035-inch Jagwire, Boston Scientific, Natick, Massachusetts, USA and/or 0.025-inch VisiGlide 2, Olympus Medical Systems Corp., Tokyo, Japan) was used for biliary cannulation. A balloon catheter (Multi-3 V Plus; Olympus Medical Systems Corp., Tokyo, Japan) was used to remove the bile duct stones. A biliary dilation balloon catheter (Hurricane™ RX; Boston Scientific, Natick, Massachusetts, USA) and/or a CRE™ wire-guided biliary dilation balloon catheter (Boston Scientific, Natick, Massachusetts, USA) was used for endoscopic papillary balloon dilatation (EPBD) or endoscopic papillary large balloon dilatation (EPLBD). A single-use mechanical lithotriptor (LithoCrushV; Olympus Medical Systems Corp., Tokyo, Japan) was used for lithotripsy of bile duct stones. A 5-Fr pigtail nasobiliary catheter (Create Medic Co. LTD., Tokyo, Japan) or a 7-Fr 10-cm double-pigtail stent delivery system through a pass (Gadelius Medical K.K., Tokyo, Japan; Advanix™ J, Boston Scientific Natick, Massachusetts, USA) was used for biliary drainage. A 5-Fr 3-cm pancreatic spontaneous dislodgement stent (Geenen; COOK, Winston-Salem, North Carolina, USA) was used for pancreatitis prevention. A high-frequency device (Erbotom ICC 200; Erbe Elektromedizin Corp., Tuebingen, Germany) in the endocut mode was used to perform the endoscopic sphincterotomy (EST).

ERCP

ERCP was performed by an endoscopist in patients tolerant to sedatives; they were sedated with benzodiazepines, while pethidine hydrochloride and/or pentazocine were administered for analgesia, as required. Scopolamine butylbromide and/or glucagon were used as antispasmodics. All bile duct cannulations at our institution were wire-guided cannulations; if bile duct cannulation was difficult, a pancreatic guidewire technique was used, and a pancreatic duct stent was placed after the procedure. EBD was often performed on the gallbladder in patients with cholecystitis.

After inserting the cannula into the bile duct in the primary group, the infected bile was aspirated as much as possible, and a sample was submitted for culture. Bile duct stones were confirmed by endoscopic retrograde cholangiography (ERC); however, to prevent infection, ERC was performed up to the hepatic duct. For naïve papilla, EST, EPBD, and/or EPLBD were performed at the discretion of the operator; if EPLBD was needed, it was performed after EST. After EST, bile duct stones were removed using a balloon catheter and/or basket, without additional EST. After the procedure, EBD was performed and was selected for endoscopic biliary stenting (EBS) or endoscopic nasobiliary drainage (ENBD) at the operator's discretion. In case of ENBD, ENBD cholangiography was performed later; if there were no bile duct stones, the drain was removed.

In the elective group, the infected bile juice was aspirated as much as possible after bile duct cannulation during the first ERCP, and a sample was submitted for culture. EST was performed at the discretion of the operator, and EBD was performed after light ERC with or without EST. Endoscopic bile duct stone removal was performed after improvement of infection and/or withdrawal of antithrombotic drugs. In summary, EBD was performed in the elective group at the first ERCP, and endoscopic bile duct stone removal was performed at the second ERCP if there was no re-intervention. All the patients underwent elective ERCP during continued hospitalization.

Septic shock

In this study, the definitions of sepsis, severe sepsis, septic shock, and organ dysfunction were based on the revised sepsis-3 criteria.[7] Quick sequential organ failure assessment (qSOFA) was used to diagnose sepsis, defined as having two or more of the following: a respiratory rate $\geqslant$22/min, altered Glasgow Coma Scale score, and systolic blood pressure $\leqslant$100 mmHg. Patients with septic shock, defined as sepsis with persistent hypotension, required a vasopressor to maintain a mean arterial pressure $\geqslant$65 mmHg, and serum lactate levels $\geqslant$2 mmol/L.

Extracellular fluid replenishers were administered intravenously for low blood pressure, and vasopressors were used for those that did not respond to drip transfusion. Blood culture was performed simultaneously with antibacterial drug administration; blood purification therapy was performed for renal dysfunction, and oxygen administration and mechanical ventilation were performed for respiratory dysfunction.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) due to acute cholangitis was based on the diagnostic criteria of the Japanese Association for Acute Medicine; DIC was defined as a score ⩾4 points. Systemic inflammatory response syndrome (SIRS) score ⩾3, mild thrombocytopenia (platelet count: ⩾8 × 10^4/μL and <12 × 10^4/μL and >30% decrease 24 h after admission), prolonged (⩾1.2) prothrombin time-international normalized ratio (PT-INR), and a small increase in fibrin/fibrinogen degradation product (FDP) levels (⩾10 pressure, <25 μg/mL) was defined by each point. In addition, three points were assigned to severe thrombocytopenia (platelet count: <8 × 10^4/μL, >50% decrease 24 h after admission) and a decrease in FDP levels (⩾25μg/mL). Thrombomodulin, gabexate mesylate, and heparin were used for DIC. Antithrombin (AT-III) preparations were often used with AT-III <70%.

Hospitalization cost

The hospitalization cost refers to the cost from hospitalization to discharge, including endoscopic treatment, intensive medical care, and room charges. Considering the foreign exchange market at each time, the yen was converted to US dollars.

Statistical analysis

Continuous variables were expressed as medians (interquartile ranges). Data were analyzed using the Mann–Whitney *U*, χ^2 test, and Fisher's exact test was used for statistical analysis, as needed. Statistical significance was set at $p < 0.05$. All analyses were performed using the JMP software (version 15; SAS Institute Inc., North Carolina, USA).

Results

Patient characteristics

The patient characteristics are shown in Table 1. There were no significant differences in age, sex, bile duct diameter, bile duct stone diameter, multiple bile duct stones, number of gallstones, naïve papilla, history of cholecystectomy, history of emergency drainage, white blood cell count, median, platelet count, albumin levels, PT-INR, blood urea nitrogen levels, creatinine levels, C-reactive protein levels, antithrombotic drug usage, bile culture positive rate, systolic blood pressure, mean blood pressure, body temperature, respiratory rate, pulse rate, DIC score, duration of intensive care unit (ICU) stay, mechanical ventilation, continuous hemodiafiltration, γ-globulin, or polymyxin B-immobilized fiber column direct hemoperfusion usage rate between the two groups. The elective group exhibited significantly higher cardiovascular dysfunction (57% vs 7%; $p = 0.004$), usage of noradrenaline (0.05 (0–0.1) γ vs 0 (0–0) γ; $p = 0.004$), occurrence of septic shock (39% vs 0%; $p = 0.006$), DIC treatment (57% vs 14%; $p = 0.016$), positive blood culture (91% vs 43%; $p = 0.006$), total bilirubin levels (4.4 (2.1–6.4) mg/dL vs 2.3 (1.4–4.7) mg/dL; $p = 0.048$), SIRS score (3 (2–4) vs 2 (1–3); $p = 0.04$), qSOFA score (2 (1–3) vs 1 (0–2); $p = 0.037$); whereas partial pressure of oxygen/fraction of inspired oxygen ratio (304 (218–373) vs 394 (299–394); $p = 0.047$) was significantly lower than that in the primary group.

Clinical outcomes: first ERCP

The clinical outcomes are shown in Table 2. There were no significant differences in EPBD, endoscopic nasogallbladder drainage (ENGBD), endoscopic gallbladder stenting (EGBS), pancreatic spontaneous dislodgement stent, pentazocine usage, pethidine hydrochloride usage, antispasmodic drug usage, duration of antibiotic treatment, or duration of ICU stay between the two groups. For endoscopic treatment in the primary group, EST (90% vs 21%; $p = 0.01$) and EPLBD for naïve papilla (40% vs 0%; $p = 0.009$), as well as ENBD (50% vs 9%; $p = 0.014$), were significantly more; treatment time (30 (21–43) min vs 14 (10–21) min; $p = 0.021$) was also longer compared to the elective group. In the primary group, flunitrazepam usage (0.6 (0.3–1) mg vs 0.4 (0–0.5) mg; $p = 0.009$) was high, EBS (7% vs 87%; $p < 0.001$) was significant lower, and one case of residual stones was observed.

Patients with post-EST did not undergo additional EST, and four patients with post-EST in the primary group had stones removed with a balloon in the first ERCP.

Clinical outcomes: first endoscopic stone removal

The clinical outcomes are shown in Table 3. There were no significant differences in EST, EPBD,

Table1. Patient characteristics.

	Primary group ($n = 14$)	Elective group ($n = 23$)	*p* value
Age, median (IQR), years	84 (80–87)	84 (80–87)	0.406
Sex, men/women, *n* (%)	7 (50)/7 (50)	14 (61)/9 (39)	0.733
CBD diameter, median (IQR), mm	12 (9–16)	12 (10–14)	0.752
Diameter of the CBD stone, median (IQR), mm	7 (6–15)	11 (8–12)	0.591
Number of CBD stones, single/multiple, *n* (%)	7 (50)/7 (50)	13 (57)/10 (43)	0.79
Post-cholecystectomy, *n* (%)	2 (14)	7 (30)	0.269
Naïve papilla, *n* (%)	10 (71)	19 (83)	0.423
Antithrombotic drug, *n* (%)	3 (21)	13 (57)	0.065
Period from diagnosis to drainage < 24 h/$<$48 h, *n* (%)	12 (86)/2 (14)	23 (100)/0	0.062
Positive severity assessment			
Cardiovascular dysfunction, *n* (%)	1 (7)	13 (57)	0.002
Neurological dysfunction, *n* (%)	5 (36)	15 (65)	0.807
Respiratory dysfunction, *n* (%)	3 (21)	11 (48)	0.108
Renal dysfunction, *n* (%)	3 (21)	5 (22)	0.982
Hepatic dysfunction, *n* (%)	1 (7)	7 (43)	0.095
Hematological dysfunction, *n* (%)	10 (71)	9 (39)	0.057
GCS, median (IQR)	15 (14–15)	14 (13–15)	0.069
Body temperature, median (IQR), °C	37.7 (37.4–38)	38.2 (36.6–38.9)	0.28
Respiratory rate, median (IQR), /min	19 (18–24)	22 (18–27)	0.262
Pulse rate, median (IQR), /min	103 (85–109)	99 (88–114)	0.742
SBP, median (IQR), mmHg	140 (107–154)	117 (104–130)	0.11
MAP, median (IQR), mmHg	97 (76–108)	80 (75–92)	0.133
DIC score, median (IQR)	3 (1–4)	3 (3–5)	0.017
SIRS score, median (IQR)	2 (1–3)	3 (2–4)	0.04
SOFA score, median (IQR)	6 (4–7)	7 (5–10)	0.024
qSOFA score, median (IQR)	1 (0–2)	2 (1–3)	0.037
PaO2/FiO2 ratio, median (IQR)	390 (299–394)	304 (218–373)	0.047
Noradrenaline median (IQR), γ	0 (0–0)	0.05 (0–0.1)	0.004
Septic shock, *n* (%)	0 (0)	9 (39)	0.006
White blood cell count, median (IQR), /μL	11,700 (7500–15,100)	13,600 (8100–19,950)	0.222

(Continued)

Table 1. (Continued)

	Primary group ($n = 14$)	Elective group ($n = 23$)	*p* value
Platelet count, median (IQR), 10^4 /μL	9.1 (8.5–13.4)	12.6 (7.3–18.4)	0.301
PT-INR, median (IQR)	1.2 (1.1–1.2)	1.2 (1.1–1.5)	0.178
Albumin level, median (IQR), g/dL	3.4 (2.8–3.7)	2.9 (2.6–3.4)	0.113
Total bilirubin level, median (IQR), mg/dL	2.3 (1.4–4.7)	4.4 (2.1–6.4)	0.048
BUN level, median (IQR), mg/dL	32 (17–37)	27 (19–35)	0.754
Creatinine level, median (IQR), mg/dL	1.1 (0.8–1.6)	1.1 (0.7–1.7)	0.742
C-reactive protein level, median (IQR), mg/dL	9 (2–19)	15 (11–16)	0.228
Lactate level, median (IQR), mmol/L	1.8 (1.5–2.1)	2.1 (1.6–6.0)	0.395
Positive blood culture, *n* (%)	6 (43)	20 (91)	0.006
Positive bile culture, *n* (%)	11 (85)	17 (81)	0.785
Mechanical ventilation, *n* (%)	0	1 (4)	0.429
CHDF, *n* (%)	0	5 (22)	0.061
Anti-DIC drugs, *n* (%)	2 (14)	13 (57)	0.016
Intravenous immunoglobulin, *n* (%)	0	6 (26)	0.065
PMX-DHP, *n* (%)	1 (7)	4 (17)	0.091

BUN: blood urea nitrogen; CBD: common bile duct; CHDF: continuous hemodiafiltration; DIC: disseminated intravascular coagulation; EBD: endoscopic biliary drainage; FIO2, fraction of inspired oxygen; GCS: Glasgow Coma Scale; IQR, interquartile range; MAP: mean arterial pressure; PaO2, partial pressure of oxygen; PMX-DHP: polimyxin B immobilized fiber column direct hemoperfusion; PT-INR: prothrombin time-international normalized ratio; qSOFA: quick sequential organ failure assessment; SBP: systolic blood pressure; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment.

EPLBD, EBS, ENGBD, EGBS, flunitrazepam usage, pentazocine usage, pethidine hydrochloride usage, antispasmodic drug usage, treatment time, and the first complete stone removal rate of the bile duct between the two groups. For endoscopic treatment in the primary group, ENBD (50% vs 9%; $p = 0.014$) was significantly more than that in the elective group. Since cholangitis improved, there were hardly ENBD and EBS when the first stone was removed in the elective group. In the elective group, in addition to the three people with naïve papilla who underwent EPLBD, two of the four patients who underwent EST during the first ERCP underwent EPLBD. In the elective group, there was one case in which multiple large bile duct stones piled up and could not be simultaneously removed. None of the patients in the elective group underwent a second ERCP after discharge.

Adverse events

Cases of bleeding after EST and EPLBD—performed in patients with a platelet count of 6.9×10^4/μL—were observed in the primary group. Bleeding was suspected due to the progression of anemia 2 days later, and argon plasma coagulation (APC) was performed.

Re-intervention and cystic duct injuries were observed in the elective group. Re-intervention was performed again in one case 2 days after stent placement for poor drainage, and percutaneous transhepatic gallbladder drainage (PTGBD) was performed the following day in patients with cystic duct injuries. Endoscopic bile duct stone removal had no complications in the elective group. There was no significant difference between the two groups.

Table 2. Clinical outcome. First ERCP.

	Primary group ($n = 14$)	Elective group ($n = 23$)	*p* value
Primary endoscopic therapy			
EST for naïve papilla, *n* (%)	9 (90)	4 (21)	0.01
EPBD for naïve papilla, *n* (%)	1 (10)	0	0.161
EPLBD for naïve papilla, *n* (%)	4 (40)	0	0.009
ENBD, *n* (%)	7 (50)	2 (9)	0.014
EBS, *n* (%)	1 (7)	20 (87)	<0.001
ENGBD, *n* (%)	1 (7)	1 (4)	0.715
EGBS, *n* (%)	1 (7)	0	0.194
EPS, *n* (%)	0	4 (17)	0.099
Balloon catheter, *n* (%)	14 (100)	0	<0.001
Mechanical lithotripsy, *n* (%)	2 (14)	0	0.062
Sedation			
Flunitrazepam, median (IQR), mg	0.6 (0.3–1)	0.4 (0–0.5)	0.009
pentazocine, median (IQR), mg	0 (0–15)	0 (0–0)	0.079
pethidine hydrochloride, median (IQR), mg	0 (0–0)	0 (0–0)	0.453
Procedure time of ERCP, median (IQR), min	30 (21–43)	14 (10–21)	0.021
Complete stone removal when first bile duct stone removal, *n* (%)	13 (93)	0	<0.001
Adverse event			
Pancreatitis, *n* (%)	0	0	–
Bleeding, *n* (%)	1 (7)	0	0.194
Perforation, *n* (%)	0	0	–
Re-intervention, *n* (%)	0	1 (4)	0.429
Cystic duct injury, *n* (%)	0	1 (4)	0.429
ENBD self-removal, *n* (%)	0	0	–

EBS: endoscopic biliary stenting; EGBS: endoscopic gallbladder stenting; ENBD: endoscopic nasobiliary drainage; ENGBD: endoscopic nasogallbladder drainage; EPBD: endoscopic papillary balloon dilatation; EPLBD: endoscopic papillary large balloon dilatation; EPS: endoscopic pancreatic stenting; ERCP: endoscopic retrograde cholangiopancreatography; IQR, interquartile range; EST: endoscopic sphincterotomy.

30-day and 90-day mortality

The clinical outcomes are shown in Table 4. One patient in the elective group died on day 30; after ENGBD, he underwent elective stone removal, and cholangitis improved. Cerebral infarction developed, believed to be caused by discontinuation of antithrombotic drugs, and he exhibited organ dysfunction due to arteriosclerosis obliterans progression. The patient died without the desire for additional treatment. No patient died between 31 and 90 days. The 30-day and 90-day mortality rates were 2.7% each.

Table 3. Clinical outcome. First stone removal.

	Primary group ($n = 14$)	Elective group ($n = 23$)	*p* value
Endoscopic therapy when first stone removal			
EST for naïve papilla, *n* (%)	9 (90)	15 (100)	0.227
EPBD for naïve papilla, *n* (%)	1 (10)	0	0.161
EPLBD for naïve papilla, *n* (%)	4 (40)	3 (20)	0.324
ENBD, *n* (%)	7 (50)	2 (9)	0.014
EBS, *n* (%)	1 (7)	1 (4)	0.715
ENGBD, *n* (%)	1 (7)	0	0.194
EGBS, *n* (%)	1 (7)	0	0.194
EPS, *n* (%)	0	0	–
Balloon catheter, *n* (%)	14 (100)	23 (100)	–
Mechanical lithotripsy, *n* (%)	2 (14)	2 (9)	0.595
Sedation			
Flunitrazepam, median (IQR), mg	0.6 (0.3–1)	0.6 (0.5–0.8)	0.987
pentazocine, median (IQR), mg	0 (0–7.5)	0 (0–15)	0.687
pethidine hydrochloride, median (IQR), mg	0 (0–0)	0 (0–0)	0.435
Procedure time of ERCP, median (IQR), min	30 (21–43)	25 (18–35)	0.389
Complete stone removal when first bile duct stone removal, *n* (%)	13 (93)	22 (96)	0.779
Adverse event			
Pancreatitis, *n* (%)	0	0	–
Bleeding, *n* (%)	1 (7)	0	0.194
Perforation, *n* (%)	0	0	–
Re-intervention, *n* (%)	0	0	–
Cystic duct injury, *n* (%)	0	0	–
ENBD self-removal, *n* (%)	0	0	–

EBS: endoscopic biliary stenting; EGBS: endoscopic gallbladder stenting; ENBD: endoscopic nasobiliary drainage; ENGBD: endoscopic nasogallbladder drainage; EPBD: endoscopic papillary balloon dilatation; EPLBD: endoscopic papillary large balloon dilatation; ERCP: endoscopic retrograde cholangiopancreatography; EPS: endoscopic pancreatic stenting; EST: endoscopic sphincterotomy.

Hospitalization period and costs

In the primary group, the duration from the first ERCP to the common bile duct (CBD) stone removal (0 (0–0) days vs 12 (9–17) days; $p < 0.001$) and hospitalization period (12 days vs 26 days; $p = 0.012$) were significantly shorter, and hospitalization costs ($7731 (5379–8762) vs $18,758 (11,147–54,320); $p < 0.001$) were significantly lower than those in the elective group.

Table 4. Clinical outcome.

	Primary group ($n = 14$)	Elective group ($n = 23$)	*p* value
Hospitalization period, median (IQR), day	12 (10–17)	26 (19–35)	0.002
Duration of ICU stay, median (IQR), day	0 (0–3)	3 (0–4)	0.07
Duration from the first ERCP to the first CBD stone removal, median (IQR), day	0	12 (9-17)	<0.001
Duration of antibiotic treatment, median (IQR), day	9 (5–11)	9 (7–13)	0.264
Hospital costs, median (IQR), $	7731 (5379–8762)	18,758 (11,147–54,320)	<0.001
30-day mortality, %	0	4	0.194
90-day mortality, %	0	4	0.194

IQR, interquartile range; ICU: intensive care unit; ERCP: endoscopic retrograde cholangiopancreatography; CBD: common bile duct.

Discussion

A systematic review and meta-analysis reported in-hospital acute cholangitis mortality rates of 1.9% or 4.4%, respectively, without US administrative data.[8] Although not observed in this study, an increase in 90-day mortality was reported. Singapore's propensity score–matched analysis reported an overall in-hospital mortality rate of 4.6%, a 30-day mortality rate of 7.4%, and a 90-day mortality rate of 8.5%.[9] The mortality rate of SAC using the currently revised TG13/18 severity assessment was 5.1% in a joint study between Japan and Taiwan. There is no dispute that the mortality rate of SAC is high;[10] however, problems with the diagnostic criteria for SAC have also been highlighted. Each organ dysfunction in the severity assessment was equally assessed. In the study, multivariate analysis also showed that organ failure (other than liver dysfunction) was significantly associated with acute cholangitis mortality.[10] Acute cholangitis has different weights for each organ dysfunction in the severity assessment, and overlapping may result in higher mortality; however, it is not clear which organ dysfunction in the severity assessment of SAC is capable of primary stone removal.

In this study, primary stone removal was performed, and no patients died of the primary disease. If no complications are observed and early discharge is possible, primary stone removal is preferable; however, the extent to which infection control and bleeding complications are tolerated is a concern. For infection control, the TG18 recommends emergency and early drainage for moderate and SAC. Usage of either EBS or ENBD is recommended for endoscopic drainage, and it is said that there is no need to place a drainage tube after stone removal;[11–13] however, poor drainage in SAC due to residual stones and edematous papilla can be fatal, and ENBD after primary removal for SAC may thus be useful.

ENBD was performed for 50% of primary stone removals, and it may be advantageous for infection control in the primary group. Advantages of ENBD include less concern regarding edematous papilla formation and poor drainage due to residual stones after endoscopic stone removal; in addition, because ENBD tube can be removed at the bedside, ERCP is not required. It is believed that reduction in ERCP would reduce the cost of hospitalization, as well as the burden on medical staff. There were many cases in which a large amount of contrast agent was not press-fitted; one case of the residual stone was confirmed on ENBD imaging. Disadvantages include nasopharyngeal discomfort and self-removal; however, since the stones may not be removed, self-removal is typically not a concern, even if ENBD is performed. EBS is more comfortable than ENBD for patients, but the disadvantages are occasional poor drainage. For all patients with stent placement, stent removal is required at a later date.

Regarding bleeding complications, a meta-analysis of controlled trials comparing biliary drainage

with and without EST for SAC reported a significantly higher risk of bleeding.[14] However, because there are no EST studies between moderate and SAC, comparison between EST and non-EST, as well as EST between moderate and SAC, is desired. In this study, APC was performed on the site suspected of bleeding after 2 days in one patient (platelet count: $6.9 \times 10^4/\mu L$; primary stone removal group) who underwent EST and EPLBD for progression of anemia. While it has been reported that EST for acute suppurative cholangitis—including decreased blood pressure and impaired consciousness—can be safely performed if the platelet count is not less than $5 \times 10^4/\mu L$ or there is not abnormal coagulation,[15] it has been reported that EPLBD with cholangitis causes bleeding.[16] For patients with SAC requiring EPLBD for CBD stone removal, EPLBD should not be performed during the first ERCP. Without EPLBD, the risk of bleeding is reduced, and primary stone removal can be safely performed.

Blood culture positive rate was reported to be 69% in septic shock.[17] In this study, the blood culture rate for the elective group patients was 91%, which was even higher than the bile culture rate of 81%. It is reported that bile culture is more sensitive than blood culture, but in this study, the positivity rate of bile culture was reversed compared to blood culture. The blood culture positives are due to gut microbiota, not contamination. The elective group had 91% blood culture and was expected to be a severe group. Blood culture is reported to be sterilized within minutes to hours after administration of antibacterial agents. At our hospital, blood culture is performed before administering antibacterial drugs. Antibacterial drugs are administered before ERCP, and bile culture is performed after administering antibacterial drugs. This could create a gap between blood and bile culture.

We did not observe deaths due to primary disease; however, patients without tracheal intubation who experienced respiratory dysfunction, and those who could not maintain blood pressure even—with vasopressor agents—could not undergo endoscopic treatment; instead, they underwent PTBD or PTGBD. Two of the 31 patients who underwent PTBD or PTGBD for SAC died. The SOFA score of the elective group was high, and primary bile duct stone removal was rarely performed in patients with cardiovascular dysfunction. Primary bile duct stone removal for SAC did not cause any major accidents, hospitalization periods were shortened, and hospitalization costs were significantly reduced. If ERCP specialists perform endoscopic treatment and select appropriate patients, the hospitalization period and hospitalization cost burden on the patient may be greatly reduced.

Limitations of this study include the small sample size, single facility, and retrospective design. In addition, in this study, patients with septic shock did not undergo primary stone removal. Thus, there was a selection bias regarding primary stone removal. However, it has been suggested that primary stone removal may be safe and effective for severe cholangitis without septic shock or extreme coagulation abnormalities. Even if randomized controlled trials (RCTs) are performed in the future, primary stone removal for septic shock is unknown, and it is desirable to limit it to primary stone removal for severe cholangitis without septic shock and/or extreme coagulation abnormalities.

Conclusion

Primary stone removal in SAC is rarely performed in patients with septic shock or cardiovascular dysfunction. Half of the primary group underwent ENBD, and no deaths occurred. In the primary group, the duration of hospitalization was significantly shorter, and hospitalization costs were significantly lower; thus, if patients are appropriately selected, bile duct stones may be safely removed for the treatment of SAC.

Conflict of interest statement

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