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**Pancreatic stents to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis: A meta-analysis**

Sugimoto M *et al*. Pancreatic stents to prevent PEP: A meta-analysis

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**Abstract**

***BACKGROUND***

Endoscopic retrograde cholangiopancreatography (ERCP) plays a major role in the investigation and treatment of pancreaticobiliary diseases. However, post-ERCP pancreatitis (PEP) is a severe adverse effect. Prior meta-analyses have shown that prophylactic PS was useful for preventing PEP. However, abstract reports and patients who underwent endoscopic ampullectomy were included in the previous analyses. In addition, two meta-analyses involved non-randomized controlled trials (RCTs). The efficacy of PS for preventing severe PEP was different in each meta-analysis. Therefore, we performed the current meta-analysis, which included only full-text articles, and added new findings.

***AIM***

To reveal the efficacy of prophylactic pancreatic stent (PS) placement for preventing PEP.

***METHODS***

We searched the MEDLINE, Cochrane Library and PubMed databases for related RCTs. Among the reports retrieved, 11 studies were included in this meta-analysis. All full-text articles were published between 1993 and 2016. A total of 1475 patients were enrolled in the included studies; of these patients, 734 had a PS inserted, and 741 did not have a PS inserted. PEP and severe PEP occurrence were evaluated in this meta-analysis.

***RESULTS***

PEP was observed in all studies and occurred in 39 (5.3%) patients who received a PS. On the other hand, PEP occurred in 141 (19%) patients who did not receive a PS. The occurrence of PEP was significantly lower in the patients who underwent PS placement than in the patients who did not receive a PS (OR = 0.32; 95%CI: 0.23-0.45; *P* < 0.001). In addition, the occurrence of severe PEP was evaluated. Notably, the occurrence of severe PEP was not observed in the stent group; however, the occurrence of severe PEP was observed in 8 (1.3%) patients who did not have a PS inserted. Severe PEP occurred significantly less often in the stent group than in the no stent group (OR = 0.24; 95%CI: 0.06-0.94; *P* = 0.04).

***CONCLUSION***

In conclusion, prophylactic PS placement is useful for preventing PEP and severe PEP.

**Key words:** Endoscopic retrograde cholangiopancreatography; Pancreatic stent; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Meta-analysis

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**Core tip:** Endoscopic retrograde cholangiopancreatography (ERCP) plays a major role in the investigation and treatment of pancreaticobiliary diseases. However, post-ERCP pancreatitis (PEP) is a severe adverse effect. To prevent PEP, prophylactic pancreatic stent (PS) placement was recommended in some randomized controlled trials (RCTs). We performed this meta-analysis that included only RCTs with full-text articles to evaluate the efficacy of prophylactic PS for preventing PEP. As a result, the rates of PEP and severe PEP occurrence were statistically lower in the stent group than in the no stent group. Prophylactic PS was efficient in preventing PEP.

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**INTRODUCTION**

Endoscopic retrograde cholangiopancreatography (ERCP) occupies an important place in the endoscopic treatment and investigation of pancreatic and biliary diseases. However, post-ERCP pancreatitis (PEP) is a severe adverse event. Several past studies have reported that the occurrence of PEP was observed in 0.4%–5.6% of patients[[1-8](#_ENREF_1)]. Additionally, the fatality rate of PEP was 0%–0.1%[[4](#_ENREF_4),[6-8](#_ENREF_6)].

The risk factors shown to influence PEP occurrence in past reports were previous history of pancreatitis or PEP, two or more pancreatography procedures, sphincter of Oddi dysfunction (SOD), age younger than fifty years, female sex, difficulty of biliary cannulation, biliary sphincter balloon dilation, and precut sphincterotomy[[7-15](#_ENREF_7)]. However, the usefulness of pancreatic stent (PS) placement for PEP has been reported in these high-risk patients[[16-55](#_ENREF_16)]. Several prospective randomized controlled trials (RCTs) were discussed in these reports. Some RCTs showed the efficacy of PS placement in preventing PEP[[19](#_ENREF_19),[20](#_ENREF_20),[22](#_ENREF_22),[26](#_ENREF_26),[27](#_ENREF_27),[30](#_ENREF_30),[45](#_ENREF_45),[51-53](#_ENREF_51),[55](#_ENREF_55)]. In addition, six meta-analyses were performed on this topic. The insertion of a PS was recommended in all of the meta-analyses[[35](#_ENREF_35),[38](#_ENREF_38),[56-59](#_ENREF_56)]. However, the RCTs involved in these meta-analyses were varied. In addition, two meta-analyses involved non-RCTs[[38](#_ENREF_38),[59](#_ENREF_59)]. In a study included in the two meta-analyses, the no stent group was not randomized[[31](#_ENREF_31)]. Therefore, we performed a meta-analysis limited to full-text articles and excluding any RCTs of special cases (for example, ampullectomy cases, only abstracts, *etc.*). In addition, we included new RCTs in this meta-analysis.

**MATERIALS AND METHODS**

***Literature search***

We conducted a meta-analysis data search according to PRISMA statement guidelines[[60](#_ENREF_60)]. MS and TT performed literature retrieval using the MEDLINE, PubMed, Cochrane Library databases. The retrieval was limited to reports written in English. The following keywords were used for the search: “pancreatic stent” and “post-ERCP pancreatitis”.

***Study selection***

The studies that met the following criteria were selected: (1) RCTs comparing patients who received a PS for the prevention PEP and patients who did not receive a PS during ERCP; (2) full-length articles; and (3) articles written in English. We excluded studies that met the following criteria: (1) case reports; (2) case series; (3) retrospective case control studies; and (4) studies on endoscopic ampullectomy, because the procedure considerably changes the form of the Vater papilla. Moreover, we performed a manual search of reports cited in the extracted articles to discover any additional reports.

***Data extraction***

The data extracted were as follows (Tables 1 and 2): (1) study data (first author, year of publication, country); (2) patient characteristics (age, sex, number of patients who received a PS, number of patients who did not receive a PS); and (3) factors related to ERCP procedures (type of PS, success rate of PS insertion, occurrence of PEP, severity of PEP, severity criteria of PEP).

***Evaluation of bias***

The publication bias for the obtained data was assessed using funnel plots.

***Statistical analysis***

The meta-analysis was performed using The EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[[61](#_ENREF_61)]. The homogeneity of each study was judged by determining the *I*2 value. An *I*2 value ≤ 25% was considered to have no statistical heterogeneity. An *I*2 value of 25%-50% was treated as low statistical heterogeneity, and an *I*2 value of 50%-75% was treated as moderate statistical heterogeneity. An *I*2 value > 75% was considered to have high statistical heterogeneity. A fixed-effects model was used if extracted studies had low heterogeneity. A random-effects model was used if the extracted studies were heterogeneous. A *P* value < 0.05 indicated a significant difference.

**RESULTS**

***Selection of eligible studies***

A total of 369 articles were identified by searching MEDLINE, Cochrane Library and PubMed. Of these reports, 80 studies were excluded because of duplication. In addition, 279 studies were excluded according to the selection criteria described above, as determined from the title and abstract. Finally, 11 studies were included in this meta-analysis (Figure 1).

All of these studies were RCTs published between 1993 and 2016. A total of 1475 patients were included in the studies, and of whom, 734 patients underwent insertion of PS, and 741 patients did not have a PS inserted. In some studies, proteinase inhibitors or antibiotics were administered as other prophylaxis; however, rectal indomethacin was not used in any study. All patient characteristics are shown in Table 1, and ERCP-related procedures are shown in Table 2.

***The definition of PEP and severity of PEP***

In the RCTs, with the exception of two studies by Smithline *et al*[55] and Fazel *et al*[52], PEP was defined according to Cotton’s criteria[[62](#_ENREF_62)]. In these RCTs, new abdominal pain after ERCP with elevated serum amylase no less than three times the normal upper limit in 24 h was diagnosed as PEP. In the study by Smithline *et al*[55], abdominal pain with elevated serum lipase or amylase no less than two times the normal upper limit was diagnosed as PEP. In the study by Fazel *et al*[52], epigastric and umbilical pain with elevated serum amylase no less than two times the normal upper limit was diagnosed as PEP.

The severity of PEP was classified according to Cotton’s criteria in almost all RCTs[[62](#_ENREF_62)] (Table 2). In the criteria, mild pancreatitis was defined as an extension of planned hospitalization of two to three days. Moderate pancreatitis was defined as an extension of planned hospitalization of four to ten days. Severe pancreatitis was defined as an extension of planned hospitalization of more than ten days with or without bleeding or a pseudocyst requiring intervention.

***Meta-analysis***

PEP was observed in all studies; it occurred in 39 (5.3%) patients who underwent PS insertion, and on the other hand, it occurred in 141 (19%) patients who did not have a PS inserted. The heterogeneity among the included studies was low (*I*2 = 31%, *P* = 0.15); therefore, we selected a fixed-effects model. The occurrence of PEP was significantly lower in patients who received a PS than in the patients who did not receive a PS (OR = 0.32; 95%CI: 0.23-0.45; *P* < 0.001; Figure 2).

We also evaluated severe PEP between the stent group and the no stent group. The occurrence of severe PEP was not observed in the stent group; however, the occurrence of severe PEP was observed in 8 (1.3%) patients who did not undergo PS insertion. Statistical heterogeneity was not seen in the included studies (*I*2 = 0%, *P* = 0.99); therefore, a fixed-effects model was chosen. The occurrence of severe PEP was significantly lower in the stent group than in the no stent group (OR = 0.24; 95%CI: 0.06-0.94; *P* = 0.04; Figure 3).

***Publication bias***

Egger’s test of funnel plot asymmetry showed publication bias (*P* = 0.009; Figure 4). The funnel plot was asymmetric, and we found that negative studies with a smaller number of subjects were missing.

**DISCUSSION**

In this meta-analysis, prophylactic PS placement was efficient for preventing PEP. This result is the same as that in each previous RCT that was included in this meta-analysis. In addition, this meta-analysis proved that prophylactic PS placement prevented the occurrence of severe PEP.

In the eleven RCTs in this meta-analysis, ten RCTs indicated that prophylactic PS placement decreased the occurrence of PEP[[19](#_ENREF_19),[20](#_ENREF_20),[22](#_ENREF_22),[26](#_ENREF_26),[27](#_ENREF_27),[30](#_ENREF_30),[45](#_ENREF_45),[51-53](#_ENREF_51)]. However, Smithline *et al*[55] reported that prophylactic main pancreatic duct stenting is not recommended for the prevention of PEP[[55](#_ENREF_55)]. The different results among the RCTs was influenced by the small sample size. In addition, there were far fewer patients with severe PEP. Therefore, the occurrence of severe PEP was not significantly different between the stent group and the no stent group in any of the included studies. On the other hand, severe PEP was not observed in the no stent group in the included RCTs. These results indicated that prophylactic PS might prevent not only total PEP but also severe PEP.

The efficacy of prophylactic PS for preventing severe PEP was not statistically proven in any RCT. However, six meta-analyses were previously performed on prophylactic PS to prevent PEP. Additionally, two of the six meta-analyses also reported that prophylactic PS did not significantly prevent severe PEP[[56](#_ENREF_56),[58](#_ENREF_58)]. As more cases about prophylactic PS were reported, two meta-analyses performed by Mazaki *et al*[[57](#_ENREF_57),[59](#_ENREF_59)] proved that prophylactic PS was efficient for preventing severe PEP. The second recent meta-analysis was carried out by Shi *et al*[35] and involved only full-text articles and excluded reports with only abstracts. However, the efficacy of prophylactic PS for preventing severe PEP was not shown in the meta-analysis. In the current meta-analysis, we included only full-text articles. As a result, PS was found to be efficient for preventing severe PEP. The addition of new RCTs and exclusion of RCTs on special cases such as ampullectomy[[63](#_ENREF_63)] may have contributed to the definitive results of this meta-analysis.

This study has some limitations. First, all RCTs involved in this meta-analysis were written in English. Second, the type of PS was different in each RCT. Third, publication bias existed in this study. In the future, we hope that the accumulation of a greater number of relevant RCTs will overcome this bias.

In conclusion, prophylactic PS was useful for preventing not only PEP but also severe PEP.

**ARTICLE HIGHLIGHTS**

***Research background***

Endoscopic retrograde cholangiopancreatography (ERCP) occupies an important place in the endoscopic treatment and investigation of pancreatic and biliary diseases. However, post-ERCP pancreatitis (PEP) is a severe adverse effect. To prevent PEP, prophylactic pancreatic stent (PS) placement has been recommended based on the results of several randomized controlled trials (RCTs).

***Research motivation***

Prior meta-analyses have shown that prophylactic PS was useful for preventing PEP. However, abstract reports and patients who underwent endoscopic ampullectomy were included in the previous analyses. The efficacy of PS for preventing severe PEP was different in each meta-analysis. Therefore, we performed the current meta-analysis, which included only full-text articles, and added new findings.

***Research objectives***

In this meta-analysis, we evaluated the efficacy of prophylactic PS for the prevention of PEP.

***Research methods***

We identified the included RCTs by searching MEDLINE, Cochrane Library and PubMed. Among the retrieved reports, 11 studies were included in this meta-analysis. The occurrence of PEP and severe PEP was evaluated.

***Research results***

The rates of PEP and severe PEP occurrence were significantly lower in patients who received a PS than in patients who did not receive a PS.

***Research conclusions***

Prophylactic PS was useful not only for preventing PEP but also for preventing severe PEP.

***Research perspectives***

This meta-analysis proved that prophylactic PS prevented severe PEP. This result will contribute to a reduction in PEP and severe PEP in patients undergoing ERCP.

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**P-Reviewer:** Chawla S, Ljubicic N, Lv XP, Sperti C **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Medicine, research and experimental

**Country of origin:** Japan

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): D

Grade E (Poor): E

All searched literature databases: MEDLINE, PubMed, Cochrane library

(*n* = 370)

Literature after duplicates removed

(*n* = 290)

Literature excluded on selection criteria, title and abstract

(*n* = 279)

Studies included in meta-analysis

(*n* = 11)

**Figure 1 The flowchart of the article selection process.**

**Odds Ratio**

**Control**

Fazel *et al*, 2003

Smithline *et al*, 1993

Tarnasky et al, 1998

Kawaguchi *et al*, 2012

Yin *et al*, 2016

**Study**

**Fixed effect model**

**Random effects model**

Heterogeneity:

*I*

2

= 31%

,

*P*

= 0.15

Sofuni *et al*, 2007

Tsuchiya *et al*, 2007

Ito *et al*, 2010

Sofuni *et al*, 2011

Pan *et al*, 2011

Lee *et al*, 2012

**Events**

6

1

2

3

1

1

20

4

1

6

8

**Total**

**734**

43

41

38

98

32

35

213

20

60

50

104

**Experimental**

**Events**

9

10

10

14

4

8

31

14

8

15

18

**Total**

**741**

50

39

36

103

32

35

213

20

60

51

102

0.01

0.1

1

10

100

**OR**

**0.32**

**0.29**

0.74

0.07

0.14

0.20

0.23

0.10

0.61

0.11

0.11

0.33

0.39

**95%-CI**

**[0.23; 0.45]**

**[0.18; 0.47]**

[0.24; 2.27]

[0.01; 0.60]

[0.03; 0.72]

[0.06; 0.72]

[0.02; 2.14]

[0.01; 0.84]

[0.33; 1.11]

[0.03; 0.46]

[0.01; 0.91]

[0.12; 0.93]

[0.16; 0.94]

**(fixed)**

**100.0%**

**--**

5.6%

7.8%

7.6%

10.3%

3.0%

6.0%

21.8%

8.7%

6.1%

10.1%

13.0%

**Weight**

**(random)**

**--**

**100.0%**

11.2%

4.2%

6.7%

9.4%

3.8%

4.1%

21.2%

7.8%

4.2%

12.3%

15.0%

**Weight**

**Figure 2 Forest plot of post-endoscopic retrograde cholangiopancreatography pancreatitis.**

Smithline *et al*, 1993

= 0.99

**Study**

**Fixed effect model**

**Random effects model**

Heterogeneity:

*I*

2

= 0%

,

*P*

Tarnasky *et al*, 1998

Fazel *et al*, 2003

Sofuni *et al,* 2007

Tsuchiya *et al*, 2007

Ito *et al*, 2010

Sofuni *et al*, 2011

Kawaguchi *et al*, 2012

Lee *et al*, 2012

**Events**

0

0

0

0

0

0

0

0

0

**Total**

**610**

43

41

38

98

32

35

213

60

50

**Experimental**

**Events**

2

0

3

0

1

0

1

0

1

**Total**

**619**

50

39

36

103

32

35

213

60

51

**Control**

0.01

0.1

1

10

100

**Odds Ratio**

**OR**

**0.23**

**0.25**

0.22

0.12

0.32

0.33

0.33

**95%-CI**

**[0.06; 0.94]**

**[0.06; 1.00]**

[0.01; 4.77]

[0.01; 2.49]

[0.01; 8.23]

[0.01; 8.19]

[0.01; 8.38]

**(fixed)**

**100.0%**

**--**

22.3%

0.0%

34.5%

0.0%

14.4%

0.0%

14.6%

0.0%

14.3%

**Weight**

**(random)**

**--**

**100.0%**

21.0%

0.0%

21.9%

0.0%

18.8%

0.0%

19.2%

0.0%

19.0%

**Weight**

**Figure 3 Forest plot of severe** post-endoscopic retrograde cholangiopancreatography pancreatitis**.**

Standard Error

0.05

0.10

0.20

0.50

1.00

2.00

1.0

0.8

0.6

0.4

0.2

0.0

Odds Ratio

**Figure 4 Funnel plot of post-endoscopic retrograde cholangiopancreatography pancreatitis occurrence.**

**Table 1 Patient characteristics of selected studies**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Sample number** | | **Mean age** | | **Sex (male/female)** | | **Patients** |
| **Stent** | **No stent** | **Stent** | **No stent** | **Stent** | **No stent** |
| Smithline *et al*[[55](#_ENREF_55)], 1993 | UnitedStates | 43 | 50 | 46 | 47 | 19/81 | 22/78 | SOD, CBD < 10 mm |
| Tarnasky *et al*[[51](#_ENREF_55)], 1998 | UnitedStates | 41 | 39 | 45.7 | 46.4 | NA | NA | SOD |
| Fazel *et al*[[52](#_ENREF_55)], 2003 | UnitedStates | 38 | 36 | 45.8 | 43.6 | 4/32 | 6/32 | SOD, difficult cannulation |
| Sofuni *et al*[19, 2007 | Japan | 98 | 103 | 67.0 | 66.0 | 60/38 | 64/38 | NA |
| Tsuchiya *et al*[[20](#_ENREF_55)], 2007 | Japan | 32 | 32 | 65.0 | 69.0 | 19/13 | 22/10 | NA |
| Ito *et al*[[22](#_ENREF_55)], 2010 | Japan | 35 | 35 | 68 | 70 | 19/16 | 20/15 | Difficult cannulation |
| Sofuni *et al*[[27](#_ENREF_55)], 2011 | Japan | 213 | 213 | NA | NA | NA | NA | Risk factors, such as SOD, history of pancreatitis |
| Pan *et al*[[26](#_ENREF_55)], 2011 | China | 20 | 20 | 61.0 | 57.0 | 9/11 | 10/10 | High-risk patients |
| Kawaguchi *et al*[[30](#_ENREF_55)], 2012 | Japan | 60 | 60 | 66.0 | 68.0 | 27/33 | 25/35 | SOD, previous PEP |
| Lee *et al*[[53](#_ENREF_55)], 2012 | SouthKorea | 50 | 51 | 57.3 | 57.9 | 17/33 | 21/30 | Difficult cannulation |
| Yin *et al*[[45](#_ENREF_55)], 2016 | China | 104 | 102 | 57.2 | 57.4 | 59/45 | 55/47 | High-risk patients |

SOD: Sphincter of Oddi dysfunction; CBD: Central bile duct; NA: Not available; PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis.

**Table 2 The factors related to the endoscopic retrograde cholangiopancreatography procedures of selected studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **ERCP procedure** | **Pancreatic stent** | **Success rate (%)** | **PEP *n* (%) stent/ no stent** | **Criteria of PEP severity** |
| Smithline *et al*[55], 1993 | Precut EST | Double-barbed 5 or 7fr, 2 or 2.5 cm | 90 | Total 6 (14)/9 (18)  Mild 5 (12)/5 (10)  Moderate 1 (2)/2 (4)  Severe 1 (2)/2 (4) | Cotton |
| Tarnasky *et al*[51], 1998 | EST | 5 or 7Fr, 2 or 2.5 cm | NA | Total 1 (2)/10 (26)  Mild 0 (0)/5 (13)  Moderate 0 (0)/5 (13)  Severe 0 (0)/ 0 (0) | Cotton |
| Fazel *et al*[52], 2003 | EST | 5fr nasopancreatic catheter or Double-barbed 5fr, 2 cm | 95 | Total 2 (5.3)/10 (28)  Mild 2 (5.3)/5 (14)  Moderate 0 (0)/2(6)  Severe 0 (0)/3 (8) | Cotton |
| Sofuni *et al*[19], 2007 | EST, EPBD, IDUS, biopsy, sphincter of Oddi manometry, POCS | 5Fr, 3 cm with 2 flanges on the duodenal side | 97 | Total 3 (3)/14 (13.6)  Mild 2 (2)/8 (7.8)  Moderate 1 (1)/6 (4.6)  Severe 0 (0)/0(0) | Cotton |
| Tsuchiya *et al*[20], 2007 | EST, IDUS, EPBD, sphincter of Oddi manometry | 5fr, 3 or 4 cm duodenal pig tail stent without inner flange | 100 | Total 1 (3.1)/4 (12.5)  Mild 1 (3.1)/2 (6.3)  Moderate 0 (0)/1 (3.1)  Severe 0 (0)/1 (3.1) | Cotton |
| Ito *et al*[22], 2010 | EST, IDUS, EPBD, biopsy | 5fr, 4 cm with a single duodenal pig tail | 97 | Total 1 (2.9)/8 (23)  Mild 1 (2.9)/8 (23)  Moderate and severe 0 | Cotton |
| Sofuni *et al*[27], 2011 | EST, EPBD, ENBD, IDUS, biopsy | 5Fr, 3 cm with 2 flanges on the duodenal side | 88 | Total 20 (9.4)/31 (15.2)  Mild 16 (7.5)/22 (14.6)  Moderate 4 (1.9)/8 (3.8)  Severe 0 (0)/1 (0.5) | Cotton |
| Pan *et al*[26], 2011 | ERCP | 5fr single pig tail | NA | Total 4 (20)/14 (70)  Mild, moderate, severe NA | Cotton |
| Kawaguchi *et al*[30], 2012 | Precut EST, pancreatic sphincterotomy, biopsy, IDUS | 5fr, 3 cm with two flanges on the duodenal side | 100 | Total 1 (1.7)/8 (13.3)  Mild 1 (1.7)/8 (13.3) | Modified Cotton |
| Lee *et al*[53], 2012 | EST, precut EST, IDUS, biopsy | Unflanged 3fr, 4, 6, or 8 cm duodenal pig tail stent | 96 | Total 6 (12)/15 (29.4)  Mild 5 (10)/12 (23.5)  Moderate 1 (2)/2 (3.9)  Severe 0 (0)/1 (2) | Cotton |
| Yin *et al*[45], 2016 | EST, EPBD | 5Fr, 5, 7, or 9 cm | NA | Total 8 (7.7)/18 (17.7)  Mild, Moderate, severe NA | NA |

PEP: Post-ERCP pancreatitis; EST: Endoscopic sphincterotomy; NA: Not available; EPBD: Endoscopic papillary balloon dilation; IDUS: Intraductal ultrasonography; POCS: Peroral cholangioscopy.