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**Is endoscopic papillary balloon dilatation really a risk factor for post-ERCP pancreatitis?**

Fujisawa T *et al.* Is EPBD risky for post-ERCP pancreatitis?

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**Abstract**

Endoscopic papillary balloon dilatation (EPBD) is useful for decreasing early complications of endoscopic retrograde cholangio-pancreatography (ERCP), including bleeding, biliary infection, and perforation, but it is generally avoided in Western countries because of a relatively high reported incidence of post-ERCP pancreatitis (PEP). However, as the efficacy of endoscopic papillary large-balloon dilatation (EPLBD) becomes widely recognized, EPBD is attracting attention. Here we investigate whether EPBD is truly a risk factor for PEP, and seek safer and more effective EPBD procedures by reviewing past studies. We reviewed thirteen randomised control trials comparing EPBD and endoscopic sphincterotomy (EST) and ten studies comparing direct EPLBD and EST. Three randomized controlled trials of EPBD showed significantly higher incidence of PEP than EST, but no study of EPLBD did. Careful analysis of these studies suggested that longer and higher-pressure inflation of balloons might decrease PEP incidence. The paradoxical result that EPBD with small-calibre balloons increases PEP incidence while EPLBD does not may be due to insufficient papillary dilatation in the former. Insufficient dilatation could cause the high incidence of PEP through the use of mechanical lithotripsy and stress on the papilla at the time of stone removal. Sufficient dilation of the papilla may be useful in preventing PEP.

**Key words**: Endoscopic papillary balloon dilatation; Post-endoscopic retrograde cholangio-pancreatography pancreatitis; Endoscopic papillary large-balloon dilatation; Endoscopic sphincterotomy; Randomized controlled trial

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**Core tip:** Some recent studies suggest that Endoscopic papillary balloon dilatation (EPBD) itself does not increase post-endoscopic retrograde cholangio-pancreatography (ERCP) pancreatitis (PEP) incidence. Theoretically, endoscopic papillary large-balloon dilatation (EPLBD) can damage the papilla more than EPBD does, but even direct EPLBD without preceding sphincterotomy does not increase PEP rate. An explanation for this paradox is that procedures following EPBD, but not EPBD itself, induce PEP. Since the EPBD stress is limited around the papilla, a prophylactic pancreatic stent could protect against the damage related to EPBD. EPBD has many advantages that endoscopic sphincterotomy does not. Therefore, it is time to re-evaluate the risks and efficacy of EPBD, and to utilize it suitably instead of shelving it.

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**INTRODUCTION**

Stariz *et al*[[1](#_ENREF_1)] originally introduced endoscopic papillary balloon dilatation (EPBD) in 1983. It was developed to avoid complications of endoscopic sphincterotomy (EST) such as bleeding, perforation, and biliary infection. EPBD became popular because it was easier to perform than EST and had a possibility of preserving the function of the Oddi sphincter. However, one complication of EPBD caused anxiety: an increase in post-endoscopic retrograde cholangio-pancreatography (ERCP) pancreatitis (PEP). Many researchers studied the efficacy and safety of EPBD and found it to be feasible and acceptable, with the exception of one study. Disario *et al*[[2](#_ENREF_2)] performed an international multicentre study in 2004 and reported that the incidence of severe complications in the EPBD group was significantly higher than the EST group, and that two patients in the EPBD group died due to PEP. This result frightened many endoscopists, and EPBD has since been regarded as a risky procedure. EPBD has been avoided in Western countries, although it is still popular in Asian countries. On the other hand, EPBD using a large-calibre balloon (10 – 20 mm in diameter, endoscopic papillary large balloon dilatation; EPLBD) was recently developed for retrieving large and/or piled biliary stones, and the efficacy and safety of EPBD were also re-evaluated[[3-7](#_ENREF_3)].

Here, we review past studies of EPBD/EPLBD, and re-evaluate the incidence of PEP following EPBD. In addition, we discuss a safer EPBD protocol for decreasing complications.

**REPORTED PROS AND CONS OF EPBD AND EST**

The characteristics of EPBD are briefly summarized in Table 1. The pros and cons of EPBD have been often compared to those of EST First, EPBD is technically easier and more beginner-friendly than EST. It can be adopted even in cases in which the ampulla is in a large diverticulum or cases with limited endoscopic views.

Second, EPBD has lower rates of bleeding. Indeed, one of the greatest aims of developing EPBD was to avoid post-procedural bleeding. A meta-analysis of 15 randomized clinical trials and 1768 participants showed that EPBD had significantly lower rates of bleeding than EST[[8](#_ENREF_8)]. Indeed, the claim of lower incidence of bleeding after EPBD is supported by most meta-analyses[[9-11](#_ENREF_9)]. Effects on the rates of perforation and biliary infection, however, are not consistent among the reports[[9-12](#_ENREF_9)].

Third, EPBD has advantages in patients with surgically altered anatomy after gastrectomy or gastric bypass surgery. In patients with Billroth II anastomoses, EPBD is associated with a significantly lower rate of bleeding, but not a higher rate of pancreatitis compared to EST[[13](#_ENREF_13)]. Only large biliary stone size and repeated ERCP procedures are suggested as risk factors for complications in Billroth II anastomosis cases[[14](#_ENREF_14)]. In patients with Roux-en-Y anastomoses, EPBD combined with balloon-assisted enteroscopy is also useful[[15](#_ENREF_15)].

Finally, EPBD can preserve the function of papillary sphincter even after papillary manipulation[[16](#_ENREF_16)]. EST destroys the function of the sphincter, often permanently. The elimination of sphincter function may allow duodenobiliary reflux and lead to recurrence of biliary stones and biliary infection. Animal studies reveal that long-lasting exposure to digestive enzymes and bacteria in the bile duct induces epithelial hyperplasia and dysplasia[[17](#_ENREF_17),[18](#_ENREF_18)]. In an animal study using live pigs, EPBD caused no architectural distortion or smooth muscle disruption, although EST caused transmural haemorrhage, smooth muscle disruption, and mucosal necrosis in the papillary structure[[19](#_ENREF_19)]. In a histological study of humans, EPBD mostly preserved the papillary architecture and smooth muscle[[20](#_ENREF_20)]. In a study using a quantitative cholescintigraphy, hilum-duodenum transit time after EST was significantly shorter than in controls, but EPBD preserved hilum-duodenum transit time[[21](#_ENREF_21)]. Moreover, studies using manometry or MRI reveal that EPBD can preserve papillary function better than EST[[16](#_ENREF_16),[22](#_ENREF_22),[23](#_ENREF_23)]. Some studies also examined long-term outcomes. Over several years of follow-up, fewer patients develop biliary infections and recurring biliary stones after EPBD compared to EST[[24-27](#_ENREF_24)]. However, the effects of EPBD/EST on bile duct carcinogenesis have not been elucidated yet[[28](#_ENREF_28)].

In contrast to the multiple advantages of EPBD over EST, disadvantages of EPBD are few. Some studies suggest that EST is superior to EPBD in terms of success rate of stone removal. EPBD has also been associated with a higher incidence of PEP than EST. In this review we will try to elucidate whether these two disadvantages of EPBD really exist.

**FACTORS IN CONVENTIONAL EPBD**

An EPBD procedure consists of several variable factors: balloon size, pressure of inflation, duration of balloon dilation (ballooning time), frequency of inflation, and inflation speed. There is no standard technique dictating these factors, although guidelines for EPBD have been published[[29-32](#_ENREF_29)]. We summarized EPBD procedures used in past randomized controlled trials (RCTs), compared EST and conventional EPBD using small calibre balloons, and evaluated the methods in terms of PEP rate and therapeutic efficacy (Table 2)[[2](#_ENREF_2),[13](#_ENREF_13),[22](#_ENREF_22),[25](#_ENREF_25),[33-41](#_ENREF_33)]. A total of 13 RCTs were included in the analysis[[2](#_ENREF_2),[13](#_ENREF_13),[22](#_ENREF_22),[25](#_ENREF_25),[33-41](#_ENREF_33)]. Simple comparisons of PEP rate were difficult, because they varied widely among the RCTs. Therefore, we divided the studies into two groups: one group that showed significant differences in the PEP rate between EPBD and EST (significant group)[[2](#_ENREF_2),[33](#_ENREF_33),[34](#_ENREF_34)], and another group that did not (non-significant group)[[13](#_ENREF_13),[22](#_ENREF_22),[25](#_ENREF_25),[35-41](#_ENREF_35)]. There was no study that showed a higher PEP rate in EST than in EPBD. Three RCTs[[2](#_ENREF_2),[33](#_ENREF_33),[34](#_ENREF_34)] reported that the PEP rate of EPBD was significantly higher than EST, but the remaining 10 RCTs[[13](#_ENREF_13),[22](#_ENREF_22),[25](#_ENREF_25),[35-41](#_ENREF_35)] did not show a significant difference. Three RCTs[[34](#_ENREF_34),[37](#_ENREF_37),[38](#_ENREF_38)] reported that the rate of therapeutic success in the first session was significantly lower in the EPBD group than in the EST group, and three other RCTs[[22](#_ENREF_22),[34](#_ENREF_34),[36](#_ENREF_36)] revealed that frequency of mechanical lithotripsy (ML) use in the EPBD group was higher than that in the EST group.

There was no obvious difference in EPBD procedures between the significant group[[2](#_ENREF_2),[33](#_ENREF_33),[34](#_ENREF_34)] and the non-significant group[[13](#_ENREF_13),[22](#_ENREF_22),[25](#_ENREF_25),[35-41](#_ENREF_35)]; however, the maximum pressure and ballooning time in the significant group tended to be lower and shorter, respectively, than in the non-significant group. Balloon size and dilatation speed were similar between the two groups. Thus, higher pressure (> 8 atm) and longer inflation (> 60 s) might be associated with lower PEP incidence in EPBD.

**EPLBD WITHOUT PRECEDING EST**

In addition to EPBD analysis, we compared the same parameters between reported studies comparing EPLBD and EST (Table 3)[[42-51](#_ENREF_42)]. EPLBD following EST was excluded, because preceding EST may affect the incidence of PEP. We sorted a total of 10 studies in descending order of the PEP rate. Seven of the 10 studies compared EST groups and EPLBD with preceding EST groups[[42-46](#_ENREF_42),[48](#_ENREF_48),[51](#_ENREF_51)]. In all seven studies, the rates of therapeutic success, ML use, and PEP were not significantly different between the EPLBD and control groups. EPLBD without preceding EST removed large stones as easily and safely as EST. In EPLBD cases, there was no association between balloon size and PEP incidence. The dilatation speed was described as “gradual” in most studies. There were two methods to determine the maximum pressure of ballooning: one was stopping at the pressure of balloon waist disappearance, and the other was ballooning up to the size of stones. When ballooning up to the size of large stones, the waist usually disappeared before the balloon reached the target size. In the two studies[[50](#_ENREF_50),[51](#_ENREF_51)] with the lowest PEP incidence, longer (> 4 min) and higher-pressure (dilation up to the size of stones) inflation methods were adopted compared to the other eight studies[[42-49](#_ENREF_42)]. As with conventional EPBD with smaller calibre balloons, longer and higher-pressure inflation might also decrease PEP incidence in EPLBD.

Thus, the data imply that conventional EPBD might be associated with an increased rate of PEP, but EPLBD without preceding EST is not (Tables 2 and 3). How should we interpret these paradoxical results? In the past reports, three reasons were suggested[[4](#_ENREF_4)]. First, frequency of MLT use is decreased in EPLBD. Second, the patients who receive EPLBD are relatively older. Younger age is supposed to be a risk factor of PEP[[52](#_ENREF_52)]. Third, EPLBD makes selective cannulation into the bile duct easier and decreases incorrect cannulation and injection into the pancreatic duct. If factors other than the balloon size are not different, EPLBD theoretically could damage the papilla more than EPBD. Therefore, it seems that papillary damage itself does not cause PEP, but rather, other procedures accompanying EPBD could cause PEP.

**BALLOON SIZE, INFLATION TIME, AND INFLATION PRESSURE**

Then, what is the best method of EPBD? There have been few studies evaluating the details of EPBD procedures. Concerning balloon size, Akiyama *et al*[[53](#_ENREF_53)] compared efficacy and safety between 10-mm-wide and 8-mm-wide balloons. The rate of complete stone removal within a single session was higher and use of lithotripsy was lower with a 10-mm-wide balloon than with an 8-mm-wide balloon. PEP and other complication rates were similar between the two balloon sizes. Li *et al*[[54](#_ENREF_54)] also studied the PEP rate for different balloon sizes and reported no difference. However, interpreting their study is difficult because of the small numbers of patients in each group (a total of 208 cases in five groups).

Liao *et al*[[55](#_ENREF_55)] studied the duration of balloon dilatation. The success rate of stone removal was higher and the PEP rate was lower with 5-minute dilatation than with 1-minute dilatation. In a meta-analysis reviewing randomized controlled trials, long EPBD (> 1 min) decreased not only PEP risk, but also the overall rate of complications. Conversely, short EPBD (≤ 1 min) had a higher risk of PEP than EST[[12](#_ENREF_12)]. Based on these results, ESGE guidelines for prophylaxis of post-ERCP pancreatitis recommend balloon dilatation for more than 1 minute[[31](#_ENREF_31)]. Bang *et al*[[56](#_ENREF_56)] however, reported that efficacy and safety are not significantly different between 20-second and 60-second dilatations. On the other hand, Kuo *et al* reported that papillary dilatation longer than 3 minutes increases the risk of recurrent biliary stones. Therefore, longer dilatation could decrease the PEP rate, but could damage the function of the papillary sphincter.

Concerning the dilatation pressure, Tsujino *et al*[[57](#_ENREF_57)] compared the PEP rate in EPBD methods between one group with EPBD at 8 atm maintained for 2 minutes and another with the pressure at disappearance of the balloon waist maintained for 15 s. The success rate and the PEP rate were not significantly different between the two groups. There is no study on the speed of balloon dilatation, but Japanese guidelines recommend gradual dilatation just until the waist of the balloon disappears[[29](#_ENREF_29)].

 Seo *et al*[[58](#_ENREF_58)] compared the PEP rate between EPBD (retrograde dilatation) and percutaneous transhepatic papillary balloon dilatation (anterograde dilatation). The PEP rate was significantly higher after retrograde dilatation compared to anterograde dilatation. The authors considered that PEP might be associated with procedures before or after balloon dilatation, including contrast medium injection into the pancreatic duct and mechanical lithotripsy, rather than balloon dilatation itself. Lastly, Tsujino *et al*[[59](#_ENREF_59)] examined risk factors for PEP after EPBD and identified only contrast medium injection into the pancreas as a risk factor.

**DISCUSSION**

The mechanism of EPBD-related PEP is still unclear. Damage to the pancreatic duct during papillary dilatation and papillary oedema or spasm after dilatation are potentially associated with induction of PEP. If the damage by EPBD is localized to the papilla, the placement of a prophylactic pancreatic stent could prevent EPBD-related PEP[[60](#_ENREF_60)]. Unfortunately, studies evaluating the efficacy of prophylactic pancreatic stents after EPBD have not been reported yet. However, the ESGE guidelines recommend placement of a prophylactic pancreatic stent when EPBD is performed, on the basis of this theoretical consideration[[31](#_ENREF_31)]. In addition to prophylactic pancreatic stents, endoscopic nasobiliary drainage (ENBD) attracts attention as a possible preventive measure for PEP after EPBD. ENBD has disadvantages of discomfort and cosmetic problem, and is rarely used in Western countries, although it is often used in Asian countries[[61](#_ENREF_61)]. Some studies show that ENBD is effective for PEP prevention after EPBD[[62-64](#_ENREF_62)]. It is speculated that ENBD reduces PEP rate by preventing pancreatic juice obstructions caused by residual stones or papillary oedema.

As mentioned above, the success rate of stone removal is significantly lower, and PEP rate is significantly higher in conventional EPBD than in EST. However, complication rates are not different between EPLBD and EST. This might be because papillary dilatation by EPBD with small calibre balloons is often insufficient for stone removal, and sufficient dilatation can increase success rate and decrease PEP rate. Insufficient dilatation by EPBD may also increase the rate of mechanical lithotripsy use and may place stress on the papilla at the time of stone removal. Insufficient dilatation could lead to entrapment of residual stones at the papilla and could impair pancreatic drainage[[65](#_ENREF_65),[66](#_ENREF_66)]. Insufficient dilatation of the papilla seems to be one of the reasons for the high PEP rate in conventional EPBD. Results showing that longer and larger dilatation is better for PEP prevention also support this insight[[12](#_ENREF_12),[53](#_ENREF_53),[55](#_ENREF_55)]. Therefore, the papilla should be dilated to a sufficient size with enough pressure.

The maximal pressure applied in EPBD procedures may play an important role both in stone removal efficacy and safety. Among the 10 EPLBD studies in Table 3, six and four studies used the stone size[[42](#_ENREF_42),[44](#_ENREF_44),[45](#_ENREF_45),[47](#_ENREF_47),[50](#_ENREF_50),[51](#_ENREF_51)] and waist disappearance[[43](#_ENREF_43),[46](#_ENREF_46),[48](#_ENREF_48),[49](#_ENREF_49)] approaches, respectively. No significant differences in stone removal efficacy, ML use rate, and PEP rate were observed between the two approaches. Considering that EPBD with a 10-mm balloon achieved better efficacy and safety compared to that with an 8-mm balloon[[53](#_ENREF_53)], there is a possibility that adequate balloon size and pressure contribute to better efficacy and safety of EPBD procedures. In the waist-disappearance approach, the papilla dilatation effect with larger balloons may be greater than that with smaller balloons.

Ethnicity may have an impact on EPBD-related PEP rate. In a meta-analysis showing a higher PEP rate in EPBD groups than in EST groups, detailed analysis indicated that EPBD increased the PEP rate in Western patients (*P* < 0.0001), but not in Asian patients (*P* = 0.08)[[11](#_ENREF_11)]. In the study, only Western patients in the EPBD group experienced deadly pancreatitis[[2](#_ENREF_2)]. On the other hand, prospective studies of Asian patients show that results with EPBD and EST are both acceptable, although the PEP rate tends to be higher in the EPBD group[[9-12](#_ENREF_9)]. Sensitivity for EPBD-related PEP may have racial differences, just as the effects of drugs are different between different ethnic groups. In the future, endoscopic treatment procedures might be selected with consideration for the patient’s racial and genetic background.

**CONCLUSION**

At present, EPBD is generally recognized to be a risk factor of PEP. However, some studies suggested that balloon dilatation itself does not cause PEP, but procedures accompanying insufficient dilatation of the papilla can cause PEP. The mechanism of EPBD-related PEP should be further investigated. Until then, when EPBD is performed for stone removal, it seems to be better to dilate the papilla sufficiently (ballooning size > stone size, at least 8 mm with sufficient pressure for opening the waist; and ballooning time > 60 s) and to place a prophylactic pancreatic stent in order to prevent PEP.

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| --- |
| **Table 1 Pros and Cons of endoscopic papillary balloon dilatation** |
| 　 | **Pros** | **Cons** |
| EPBD1 | Beginner-friendly | More pancreatitis? |
| Less bleeding | Lower success rate of stone removal? |
| Less perforation? | 　 |
| Less biliary infection? | 　 |
| Adaptive to altered anatomy | 　 |
| Preserved sphincter function | 　 |

1Compared to endoscopic sphincterotomy (EST).

|  |  |
| --- | --- |
|  | **Table 2 Endoscopic retrograde cholangio-pancreatography** **pancreatitis rates in endoscopic papillary balloon dilatation and endoscopic sphincterotomy in ramdomized control trials** |
|  |  |  |  |  | **Significant difference from the control** |  | **Percentage of PEP** |  |  |  |  |  |
| 　 | **Ref.** | **Study design** | **Year**  | **Total patients** | **Therapuetic success** | **ML use** | **PEP rate** |  | **EPBD** | **EST** | **Balloon size (mm)** | **Maximum pressure (atm)** | **Ballooning time (seconds)** | Dilatation speed | Note |
| significant | Fujita *et al*[33] | RCT | 2003 | 282 | - | - | EPBD > EST | 　 | 10.9 | 2.8 | 8 | waist disappear | 15 | 3 minutes | 　 |
| Disario *et al*[2] | RCT | 2004 | 237 | - | - | EPBD > EST |  | 10.3 | 0.8 | 8 | maximum | 60 | NM | 2 deaths in EPBD |
| Watanabe *et al*[34] | RCT | 2007 | 180 | EST>EPBD | EPBD>EST | EPBD > EST | 　 | 16.7 | 6.7 | 8 | 7 | 120 | NM | 　 |
| non-significant | Minami *et al*[35] | RCT | 1995 | 40 | - | - | - |  | 10.0 | 10.0 | 8 | NM | 180 | NM | manometry |
| Bergman *et al*[36] | RCT | 1997 | 202 | - | EPBD>EST | - |  | 6.9 | 6.9 | 8 | 12 | 45-60 | 1-2 minutes | 1 death in EPBD |
| Ochi *et al*[37] | RCT | 1999 | 110 | EST>EPBD | - | - |  | 0 | 3.7 | 8 | 8 | 60 x 3 times | NM |  |
| Arnold *et al*[38] | RCT | 2001 | 60 | EST>EPBD | NM | - |  | 20 | 10.0 | 8 | 10 | 60 x 2 times | NM |  |
| Yasuda *et al*[22] | RCT | 2001 | 70 | - | EPBD>EST | - |  | 5.7 | 5.7 | 8 | 6 | 60 x 2 times | NM | manometry |
| Bergman *et al*[13] | RCT | 2001 | 34 | - | - | - |  | 6.2 | 0 | 8 | 10 | 45-60 | 1-2 minutes | Billroth II |
| Natsui *et al*[39] | RCT | 2002 | 140 | - | - | - |  | 5.7 | 4.3 | 8 | 8 | 120 | NM |  |
| Vlaviano *et al*[40] | RCT | 2003 | 202 | - | - | - |  | 4.8 | 1.0 | 10 | 12 | 30 | NM |  |
| Tanaka *et al*[41] | RCT | 2004 | 32 | - | - | - |  | 18.8 | 18.8 | 8 | 8 | 120 | NM | long-term outcome |
| Seo *et al*[25] | RCT | 2014 | 132 | - | - | - |  | 8.1 | 7.1 | 6-10 | stone size | 90-120 | gradually | age <40 years |

RCT: Randomized control trial; ML: Mechanical lithotripsy; NM: Not mentioned.

|  |
| --- |
| **Table 3 Post-endoscopic retrograde cholangio-pancreatography** **pancreatitis rates after endoscopic papillary large-balloon dilatation without preceding endoscopic sphincterotomy**  |
|  |  |  |  | **Significance compared to the control** |  | **Percentage of PEP**  |  |  |  |  |
| **Ref.** | **Study design** | **Year**  | **Total patients** | **Therapuetic success** | **ML use** | **PEP rate** |  | **EPLBD alone** | **EST alone** | **Mean balloon size (mm)** | **Maximum pressure** | **Mean ballooning time (seconds)** | dilatation speed |
| Minakari *et al*[42] | RCT | 2013 | 160 | - | NM | - |  | 11.2 | 8.7 | 15 | size of stones | 60 | NM |
| Kim *et al*[43] | R | 2013 | 223 | - | - | - |  | 10.9 | 6.8 | 15.6 | waist disappear | 38 | with caution |
| Hwang *et al*[44] | R | 2013 | 131 | - | - | - |  | 6.5 | 4.3 | 15.9 | size of stones | 60 | gradually |
| Li *et al*[45] | R | 2015 | 109 | - | - | - |  | 6.3 | 4.9 | 14.2 | size of stones | 60 | gradually |
| Oh *et al*[46] | RCT | 2012 | 83 | - | - | - |  | 5.0 | 7.0 | 11.8 | waist disappear | 31 | gradually |
| Omuta *et al*[47] | Pros | 2015 | 41 | N/A | N/A | N/A |  | 4.9 | N/A | 10-20 | size of stones | 0 | gradually |
| Kogure *et al*[48] | Pros | 2014 | 42 | - | - | - |  | 4.0 | 7.01 | 14.0 | waist disappear | 15-60 | gradually |
| Jeong *et al*[49] | R | 2009 | 38 | N/A | N/A | N/A |  | 2.6 | N/A | 15.5 | waist disappear | 53 | gradually |
| Chan *et al*[50] | R | 2011 | 247 | N/A | N/A | N/A |  | 0.8 | N/A | 13.2 | size of stones | 282 | NM |
| Lin *et al*[51] | RCT | 2004 | 104 | - | - | - |  | 0 | 0 | 8-12 | size of stones | 300 | NM |
| pplicable; NM: Not mentioned |

1Endoscopic papillary large-balloon dilatation (EPLBD) with preceding endoscopic sphincterotomy (EST). R: Retrospective; Pros: Prospective; RCT: Randomized controlled ttial; ML: Mechanical lithotripsy; N/A: Not applicable; NM: Not mentioned.