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The Incidence of Acute Pancreatitis After Device Assisted Enteroscopy: a Systematic Review and Meta-analysis

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ABSTRACT

Background: The diagnosis of small bowel diseases is challenging and device assisted enteroscopy (DAE) is a technique for visualizing the entire small bowel. DAE is considered as a safe procedure and the reported rate of adverse events associated with DAE in the literature is low. **Objective:** The present study tried to investigate the actual incidence of AP after DAE with a systematic review and meta-analysis of available relevant studies. **Methods:** Studies were searched through the PubMed, EMBASE, and Cochrane library databases. The following data were extracted from all eligible studies: author, country, publication year, publication type, study design, type of DAE used, route of DAE, number of patients with AP after DAE, and number of patients with hyperamylasemia after DAE. A random-effects model with RStudio version 4.2.0 was performed in all analyses. Heterogeneity was assessed using the I^2 test. The risk of bias was assessed by the Newcastle-Ottawa Scale criteria and the publication bias was assessed by the Egger test. **Results:** Twenty three studies involving a total of 11145 patients were included in the analysis. The overall, pooled AP rate after DAE was 1% (95% CI:0-1%). There was significant heterogeneity among the studies ($I^2 = 65\%$; $P < 0.01$). The pooled AP rate was 1% (95% CI:0-2%) in peroral route group. The pooled proportion of patients having hyperamylasemia after DAE was 29% (95% CI: 16-46%). Among the patients who had hyperamylasemia AP were identified in 2% (95% CI: 0-6%) of patients. **Conclusion:** The incidence of AP after DAE is about 1%. Hyperamylasemia is a common change in the patients undergoing DAE and only 2% of the patients with hyperamylasemia present with AP.

Key words: acute pancreatitis; small bowel; enteroscopy; hyperamylasemia; complication

1. BACKGROUND

The diagnosis of small bowel diseases is challenging due to the complex configuration of small bowel. Device assisted enteroscopy (DAE) is a technique for visualizing the entire small bowel, including double balloon enteroscopy (DBE), single balloon enteroscopy (SBE) and spiral enteroscopy (SE). All three systems present comparable insertion depth, diagnostic and therapeutic yield and adverse event rate. The European Society of Gastrointestinal Endoscopy (ESGE) had published guidelines suggesting that the diagnostic yield and safety profile of DBE, SBE and SE were comparable and deemed all three modalities suitable for routine clinical use (1). DAE is mainly used for the investigation of patients with obscure gastrointestinal bleeding (OGIB) or iron deficiency anemia without definite causes after conventional upper endoscopy and colonoscopy.

DAE is considered as a safe procedure and the reported adverse event rate associated with DAE in the literature is low (2-5). In a prospective multicenter survey from Germany including 2245 DBE procedures, the overall complication rate was 1.2% (6). Minor complications are more common, which include abdominal discomfort and minimal trauma to the intestinal mucosa. The most prevalent major complications are perforation, bleeding, acute pancreatitis (AP) and enteritis. The reported incidence of hyperamylasemia and pancreatitis after peroral SBE seems comparable to that after DBE (7). Abdominal pain and hyperamylasemia after DAE need not mean pancreatitis. It is usually easy to recognize severe pancreatitis, but the mild form may pose a problem. A lot of mild pancreatitis could be missed in patients with

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Author	Year	Country	Study type	Publication type	No. of cases	Entero-scope used in study	Peroral cases	Peranal cases
Honda et al(9)	2006	Japan	Retrospective	fulltext	13	DBE	13	0
Heine et al(10)	2006	Netherlands	Retrospective	fulltext	275	DBE	NA	NA
Mensink et al(11)	2007	Netherlands	Prospective	fulltext	2362	DBE	1207	412
Kopáčová et al(12)	2007	Czech	Prospective	fulltext	35	DBE	35	0
Gerson et al(13)	2009	USA	Retrospective	fulltext	2413	DBE	1691	722
Aktas et al(14)	2009	Netherlands	Prospective	fulltext	135	DBE	135	0
Pata et al(15)	2010	Turkey	Retrospective	fulltext	56	DBE	48	8
Aktas et al(7)	2010	Netherlands	Prospective	fulltext	166	SBE	44	61
Nishimura et al(16)	2010	Japan	Retrospective	fulltext	92	DBE	25	10
Zepeda-Gómez et al(17)	2011	Mexico	Prospective	fulltext	92	DBE	92	0
Möschler et al(6)	2011	Germany	Prospective	fulltext	2245	DBE	1052	277
Teshima et al(18)	2012	Netherlands	Prospective	fulltext	32	SE	32	0
Shibuya et al(19)	2012	Japan	Retrospective	fulltext	202	DBE	202	0
Itaba et al(20)	2013	Japan	Prospective	fulltext	44	DBE	44	0
Feng et al(21)	2014	China	Prospective	fulltext	20	DBE	12	8
Nakayama et al(22)	2014	Japan	Retrospective	fulltext	538	DBE	295	243
Tsujikawa et al(23)	2015	Japan	Retrospective	fulltext	84	SBE	84	0
Kopáčová et al(24)	2016	Czech	Prospective	fulltext	117	DBE	117	0
Matsushita et al(25)	2016	Japan	Retrospective	fulltext	96	DBE	96	0
Ivano et al(26)	2017	Brozil	Retrospective	fulltext	65	DBE	NA	NA
Hagiwara et al(27)	2019	Japan	Prospective	fulltext	96	DBE and SBE	20	76
Goenka et al(28)	2020	India	Retrospective	fulltext	180	SBE	114	66
Noujaim et al(29)	2020	USA	Retrospective	fulltext	1787	DBE, SBE and SE	1514	270

Table 1. Study characteristics

DAE performed on an outpatient basis because of inadequate follow-up. As the differentiation between clinically mild pancreatitis and hyperamylasemia with transient abdominal discomfort is difficult, it seems likely that an under estimate of post-DAE pancreatitis might have occurred. Understanding the potential endoscopic adverse events, their expected frequency, and the risk factors associated with their occurrence may help to minimize the incidence of adverse events.

2. OBJECTIVE

The present study tried to investigate the actual incidence of AP after DAE with a systematic review and meta-analysis of available relevant studies.

3. MATERIAL AND METHODS

Literature search

Relevant studies were identified by searching in the PubMed, EMBASE, and Cochrane Library databases from January 2001 to December 2021. Search items were listed as follows: “acute pancreatitis” or “pancreatitis” or “AP” or “SAP” and “device assisted enteroscopy” or “double balloon enteroscopy” or “single balloon enteroscopy” or “spiralenteroscopy”. The search was limited to studies in humans published in English. References of eligible articles and review articles were manually searched.

Selection of articles

The selection criteria were studies in (1) patients undergoing DAE including DBE, SBE and SE; (2) the AP

Author	No. of cases	Peroral cases	Peranal cases	AP after DAE	Hyperamylasemia after DAE
Honda et al(9)	13	13	0	1(7.7%)	6
Heine et al(10)	275	NA	NA	3(1.1%)	NA
Mensink et al(11)	2362	1207	412	7(0.3%)	NA
Kopáčová et al(12)	35	35	0	1(2.9%)	18
Gerson et al(13)	2413	1691	722	6(0.2%)	NA
Aktas et al(14)	135	135	0	1(0.7%)	22
Pata et al(15)	56	48	8	6(10.7%)	NA
Aktas et al(7)	166	44	61	0(0%)	13
Nishimura et al(16)	92	25	10	0(0%)	0
Zepeda-Gómez et al(17)	92	92	0	3(3.3%)	36
Möschler et al(6)	2245	1052	277	4(0.2%)	NA
Teshima et al(18)	32	32	0	0(0%)	6
Shibuya et al(19)	202	202	0	0(0%)	140
Itaba et al(20)	44	44	0	1(2.3%)	14
Feng et al(21)	20	12	8	0(0%)	9
Nakayama et al(22)	538	295	243	5(09%)	NA
Tsujikawa et al(23)	84	84	0	3(3.6%)	NA
Kopáčová et al(24)	117	117	0	0(0%)	NA
Matsushita et al(25)	96	96	0	1(1.0%)	38
Ivano et al(26)	65	NA	NA	1(1.5%)	NA
Hagiwara et al(27)	96	20	76	1(1.0%)	NA
Goenka et al(28)	180	114	66	2(1.1%)	NA
Noujaim et al(29)	1787	1514	270	1(0.1%)	NA

Table 2. Outcomes of the individual studies

rates after DAE were presented; (3) the number of patients was more than 10. Exclusion criteria were abstracts, reviews and meta-analyses, editorials, case reports, studies that did not report the A Prate after DAE. Each eligible article was reviewed in full text. Literature search was performed independently by 2 reviewers (SHT and ZYG) and thencross-checking search results was completed by the same reviewers. Two authors (SHT and ZYG) fulfilled study selection and data extraction and a third reviewer (SXD) was involved if there was any conflict.

Data extraction

The following data were extracted from all eligible studies: author, country, publication year, publication type, study design, type of DAE used, route of DAE, number of patients with AP after DAE, and number of patients with hyperamylasemia after DAE.

Definitions

AP is diagnosed on clinical, biochemical and radiological grounds according to revised Atlanta classification of AP (8).

AP after DAE: AP immediately after DAE; other than the instrumentation of the small bowel, no other cause of the AP could be identified in the patients.

Hyperamylasemia after DAE: Increased serum amylase level of patients is found after DAE without abdominal pain and radiological pancreatic changes.

Author	Year	NO. of cases	AP after DAE
Honda et al(9)	2006	13	1(7.7%)
Kopáčová et al(12)	2007	35	1(2.9%)
Aktas et al(14)	2009	135	1(0.7%)
Zepeda-Gómez et al(17)	2011	92	3(3.3%)
Teshima et al(18)	2012	32	0(0%)
Shibuya et al(19)	2012	202	0(0%)
Itaba et al(20)	2013	44	1(2.3%)
Tsujikawa et al(23)	2015	84	3(3.6%)
Kopáčová et al(24)	2016	117	0(0%)
Matsushita et al(25)	2016	96	1(1.0%)

Table 3. AP incidence in patients after peroral DAE

Risk of bias and publication bias analysis

The risk of bias was assessed by the Newcastle-Ottawa Scale (NOS) criteria for cohort studies. There are three major parts assessed: 1) Selection (Score 0-4); 2) Comparability (Score 0-2); and 3) Outcome (Score 0-3). The maximum score is 9. A score of 0-3, 4-6, and 7-9 represents low, moderate, and high quality, respectively. The publication bias was assessed by the Egger test.

Statistical analysis

A random-effects model with RStudio version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria)

Author	Year	No. of cases	Hyperamylase-mia after DAE
Honda et al(9)	2006	13	6(46.2%)
Kopáčová et al(12)	2007	35	18(51.4%)
Aktas et al(14)	2009	135	22(16.3%)
Aktas et al(7)	2010	166	13(7.8%)
Nishimura et al(16)	2010	92	0(0%)
Zepeda-Gómez et al(17)	2011	92	36(39.1%)
Teshima et al(18)	2012	32	6(18.8%)
Shibuya et al(19)	2012	202	140(69.3%)
Itaba et al(20)	2013	44	14(31.8%)
Feng et al(21)	2014	20	9(45%)
Matsushita et al(25)	2016	96	38(39.6%)

Table 4. Hyperamylasemia incidence after DAE

was performed in all analyses to generate a more conservative estimate. We pooled proportions with 95% confidence intervals (CIs), which are presented as forest plots. The heterogeneity between studies was estimated by the Cochran Q test and the I^2 statistics. $P < 0.1$ and $I^2 > 50\%$ were considered to be significantly heterogeneous. Categorical variables are presented as absolute numbers and percentage. Statistically significant differences were evaluated using the Results were considered as significant at $p < 0.05$.

4. RESULTS

Literature search results

Twenty three studies involving a total of 11145 patients were included in the analysis. All studies were published between 2006 and 2020 including 12 retrospective and 11 prospective studies. The results of the literature search are summarized in Figure 1. The characteristics of the 23 eligible studies are summarized in Table 1.

Characteristics of study

In the 23 studies, a total of 11145 patients underwent DAE procedures. All studies were conducted between 2006 and 2020. There were 11 prospective studies and 12 retrospective studies. Eight studies were performed in Japan, followed by Netherland (5/23), Czech (2/23), USA (2/23), China (1/23), Germany (1/23), Mexico (1/23), Turkey (1/23), Brazil (1/23) and India (1/23). The number of patients in each eligible study was more than 10 and the largest one included 2413 patients. DBE was the most common enteroscopy in the included studies which was used in 19 studies and SE was performed only in 2 studies. About 64% (6872/10805) of DAE were performed through peroral route. The results of the various outcomes of the individual studies are showed in Table 2.

Risk of bias and publication bias analysis

The NOS score ranged from 4 to 8 points. Twenty studies were considered to be of moderate quality, and 3 were of high quality (12, 20, 25). Publication bias (Egger test): $t = 2.63$; $P = 0.0155$.

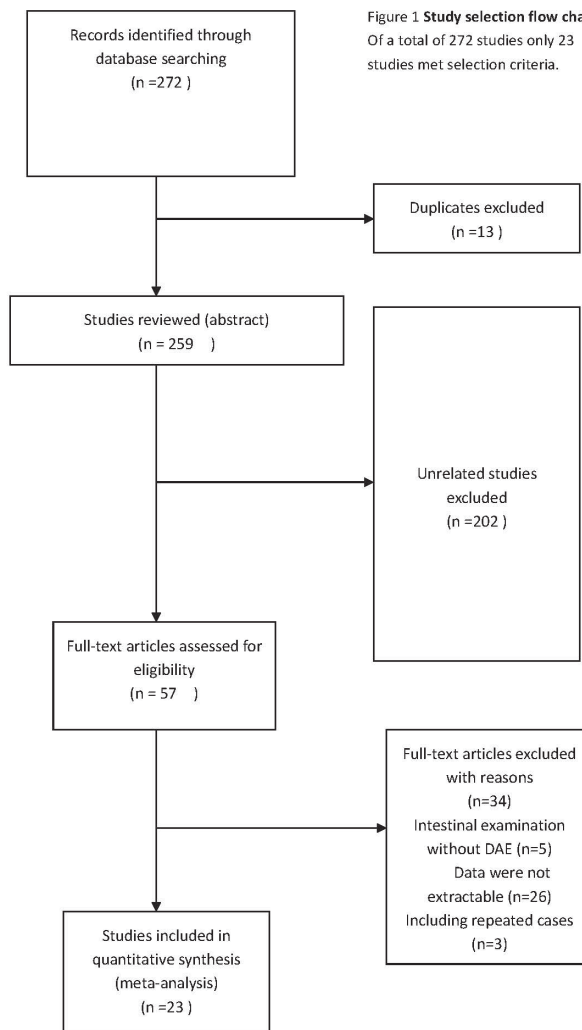


Figure 1 Study selection flow chart. Of a total of 272 studies only 23 studies met selection criteria.

Figure 1. Study selection flow chart. Of a total of 272 studies only 23 studies met selection criteria.

AP rate after DAE

The AP rates of all included studies ranged from 0% to 11%. The overall, pooled AP rate after DAE was 1% (95% CI: 0-1%) (Figure 2). There was significant heterogeneity among the studies ($I^2 = 65\%$; $P < 0.01$).

AP rate after DAE through peroral route

In 10 studies, all patients underwent only peroral DAE. As shown in Table 3, the AP rates in peroral route group ranged from 0% to 8%. The pooled AP rate was 1% (95% CI: 0-2%) in this group. Significant heterogeneity was found among the studies ($I^2 = 57\%$; $P = 0.01$) (Figure 3).

Hyperamylasemia rate after DAE

Eleven studies provided the data of patients who had hyperamylasemia after DAE (Table 4). The pooled proportion of patients having hyperamylasemia after DAE was 29% (95% CI: 16-46%) (Figure 4). Among the patients who had hyperamylasemia AP was identified in 2% (95% CI: 0-6%) of patients.

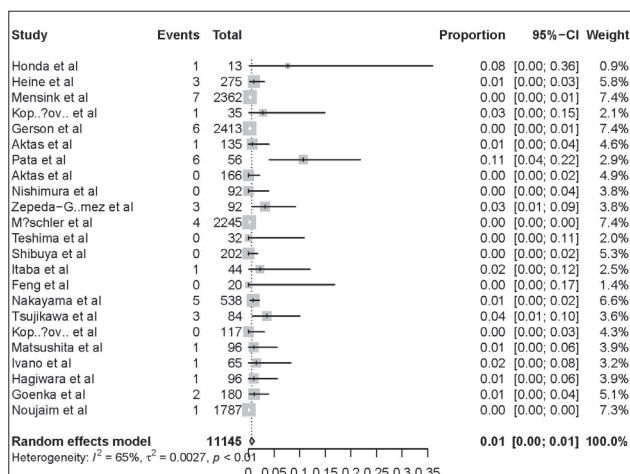


Figure 2. AP rate after DAE-approximately 1% AP in patients after DAE. Cases with AP after DAE were reported in 1% (95% CI:0-1%) of the 11145 patients in the 23 studies. There was significant heterogeneity among the studies (P<0.01).

5. DISCUSSION

Besides choledocholithiasis and alcohol, many other factors, such as iatrogenic factors, may lead to the development of AP (30). Hyperamylasemia may occur after endoscopic retrograde cholangiopancreatography (ERCP), which is predictive of the post-ERCP pancreatitis (PEP), the most common complication of ERCP (31). AP may be a major complication not only of ERCP but also of DAE. A study showed that after peroral DBE patients were more likely to have hyperamylasemia than peranal route and hyperamylasemia appeared to be associated with subsequent AP. (9). The actual incidence of AP after DAE may be under estimated because mild pancreatitis cases may not be recognized due to slight symptoms (32). The rate of AP after DAE has been reported to be between 0.3% and 1% (10, 33, 11, 22, 6, 32). Our study showed that the AP rates of all included studies ranged from 0% to 11% and the pooled AP rate after DAE was 1% (95% CI:0-1%). This result is similar with previous reports. AP after DAE is usually not severe and most patients resolved with supportive care, although there were few cases of necrotizing pancreatitis and death have been reported (32).

DAE can be inserted in two opposite ways: peroral or peranal route. The choice of the insertion way depends on the possible location of the lesion. In the cases where the location of the lesion is unpredictable the peroral route is preferred, since the procedure through peranal route is more complex and has higher failure rates. Some studies suggested that the risk of AP after DBE through peroral route may be greater compared with peranal way. DBE is manipulated by alternately inflating and deflating two balloons that are attached to the enteroscope end and the overtube. One hypothesis suggested that an inflated balloon in the duodenum might cause reflux of duodenal fluids into the pancreatic duct (34). An animal model study demonstrated that the inflated balloon could cause duodenal papillary damage and increased biochemical markers associated with pancreatitis (35). When an inflated balloon is in the duodenal bulb and

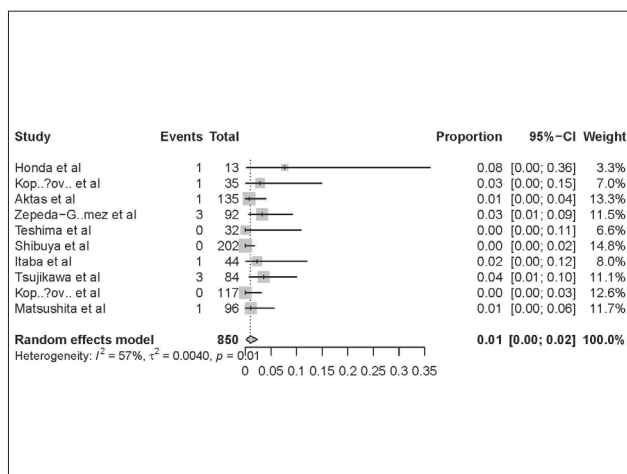


Figure 3. AP rate of patients in peroral DAE group-approximately 1% AP in patients undergoing peroral DAE. Forest plot shows that 1% (95% CI: 0-2%) of the patients who underwent peroral DAE experienced AP. There was evidence of heterogeneity among the studies (P=0.01).

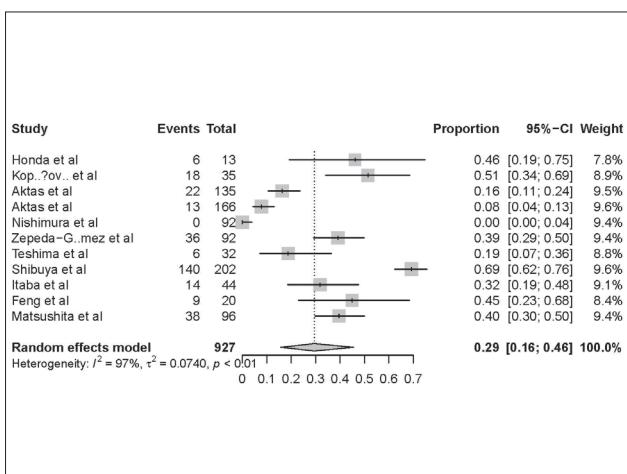


Figure 4. Hyperamylasemia rate of patients undergoing DAE -approximately 29% Hyperamylasemia in patients undergoing DAE. Forest plot shows that 29% (95% CI: 16-46%) of the patients who underwent DAE presented with hyperamylasemia. There was evidence of heterogeneity among the studies (P<0.01).

the other distal to the papilla, intraluminal hypertension in the occluded duodenal segment will develop, which may lead to the development of AP. As for SBE, an advantage is the prevention of hypertension in duodenum because of avoiding occlusion of a duodenum segment. But the tip of SBE is often angulated when the endoscope is pulled back and this hooking might lead to papillary damage and AP. Based on above mentioned theories, a possible preventive strategy is inflating the DBE balloons after the overtube has been passed distal to the ligament of Treitz (14). Pata et al have described that amylase levels after DBE are negatively correlated to the depth at which the balloons are first inflated (15). The inflation of the balloons after the duodenal papilla may diminish the iatrogenic effects on the pancreas. Some endoscopists prefer to inflate the balloons after passing the ligament of Treitz (36). However, in our study the incidence of AP (1%) after peroral route DAE did not significantly increase compared with overall incidence of

AP after DAE through mixed routes. This result indicated that there were various mechanisms of AP after DAE except duodenal or papillary damage by peroral route. It has been postulated that stretching of the small bowel or mesentery, mechanical stress on the pancreas by the endoscope, torsion of the pancreatic body and ischemia of the pancreas during DAE could induce AP after DAE (7). A case of AP after peranal SBE was reported and the author attributed the AP to the inflated balloon in the colon pressing against the pancreas (37). After enteroscopy in the porcine model, pancreatic necrotic foci are produced and this can be related to the possible ischemic etiopathogenesis of AP after DAE (38). Histological injuries found in this study are more likely related to an ischemic process in the vascular supply to the pancreas. The continuous pressure of the small intestine and the mesentery during the push and pull maneuvers could compromise the vascular supply to the pancreas, resulting in an increase in the pancreatic enzymes. Radiological studies showed that AP after DAE was mostly localized to the pancreas body and/or tail (25). Some investigators suspected that AP after DAE may occur as a result of traumatic injury and/or ischemia on the pancreas body and/or tail (39-41). And they pointed out that clockwise insertion is a significant risk factor of pancreatic hyperamylasemia and AP after DAE. Thus, shorter DAE time, fewer passes, and cautious insertion may be useful in reducing pancreatic injury.

Hyperamylasemia is frequently observed after DAE and an incidence of up to 51% has been reported. But most patients with hyperamylasemia do not progress to AP (17). The incidence of hyperamylasemia after DAE in our study was 29% and only 2% of the patients with hyperamylasemia presented with AP. Damage to the intestinal mucosa by local strain and friction during DAE may increase intestinal permeability and amylase absorption, which lead to the development of hyperamylasemia without severe pancreatic injury (14, 21). Hyperamylasemia may be related to papilla damage or pancreatic ischemia caused by DAE procedure, but this is not the main cause of hyperamylasemia after DAE because of the low incidence of AP among patients with hyperamylasemia. Factors predicting pancreatic hyperamylasemia were elderly patients, deeper insertion and clockwise insertion (23) and ulinastatin does not prevent hyperamylasemia following peroral DBE (20). On the basis of frequent hyperamylasemia after DAE, the factors affecting the outcome of the latent hyperamylasemia and the onset of AP need to be determined.

There are some limitations in the present study. The heterogeneity of the studies was significant. Much of the literature mixes patients undergoing DAE through peroral and peranal routes. These patients should be analyzed separately because they may have different incidence of AP. Most of the included studies adopted DBE, but three studies only used SBE and one study only used SE, respectively, which may influence the analyzing results. Risk factors for AP after DAE may include sex, age, previous abdominal surgery, duration of DAE, panenteroscopy, indication or endoscopic finding, type of endo-

scope, number of push-and-pull procedures, diagnostic or therapeutic procedure, and initial learning curve for DAE (32). However, the included studies did not report these details and we cannot perform systematic review and meta-analysis to estimate relevant risk factors.

6. CONCLUSION

In conclusion, the incidence of AP after DAE is about 1% and all patients undergoing DAE should be warned of the risk of AP prior to the exam. Hyperamylasemia is a common change after DAE which does not necessarily mean AP after DAE.

- **Author contributions:** (I) Conception and design: Xiao-Dong Shao, (II) Administrative support: Xiao-Dong Shao, (III) Provision of study materials or patients: Ye Tian, Cheng-Kun Li, Le Wang and Xiao-Dong Shao, (IV) Collection and assembly of data: Hao-Tian Shao, Yong-Guo Zhang, Le Wang and Xiao-Dong Shao, (V) Data analysis and interpretation: Hao-Tian Shao, Yong-Guo Zhang, Le Wang and Xiao-Dong Shao, (VI) Manuscript writing: Hao-Tian Shao, Yong-Guo Zhang, Le Wang, Ye Tian and Xiao-Dong Shao, (VII) Final approval of manuscript: Hao-Tian Shao, Yong-Guo Zhang, Le Wang, Ye Tian, Cheng-Kun Li and Xiao-Dong Shao
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