Does periampullary diverticulum affect ERCP cannulation and post-procedure complications? an up-to-date meta-analysis

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ABSTRACT

Research conclusions differ on the impact of periampullary diverticulum (PAD) on endoscopic retrograde cholangiopancreatography (ERCP). An up-to-date meta-analysis evaluated the role of PAD in ERCP, especially in terms of cannulation failure and early complications. A comprehensive literature search was performed. All statistical analyses were carried out with the Review Manager 5.3 software. Horizontal lines represented a 95% confidence interval (CI) and the area of each square in forest plots. Twenty-six studies including 23 826 patients with or without PAD who underwent ERCP were evaluated. PAD was associated with an increase in the overall cannulation failure rate (RR=1.46, 95% CI: 1.27-1.67; p<.00001), but in the subgroup of studies performed post-2000, PAD was irrelevant to cannulation failure (RR=1.16, 95% CI: 0.96–1.41; p=0.12). In overall analyses, PAD was also associated with a high risk of ERCP-related pancreatitis (RR=1.32, 95% CI: 1.10-1.59; p=0.003), perforation (RR=1.73, 95% CI: 1.06-2.82; p=0.030), and bleeding (RR=1.48, 95% CI: 1.13–1.93; p=0.005). The presence of PAD increased the overall cannulation failure rate, but not the rate post-2000. PAD also affected the occurrence of early pancreatitis, perforation, and bleeding.

Keywords: *Endoscopic retrograde cholangiopancreatography, diverticulum, complications, meta-analysis*

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is indispensable in the diagnosis and treatment of pancreaticobiliary diseases (1, 2). Periampullary diverticulum (PAD) is a condition in which pouches of mucosa and submucosa extend through the intestinal wall within a radius of 2–3 cm from the ampulla of Vater (3). The incidental appearance of PAD may cause concern in the operating endoscopist, because the impact of PAD on ERCP cannulation has been controversial (4-6). Until recently, two conference abstracts (7, 8) that used meta-analysis showed that PAD was associated with an increase in cannulation failure. However, the generally high success rate of cannulation reported in articles post-2000 was ignored. Baron et al. (9) believed that post-2000 is a new era in ERCP development that includes more advanced technology. Rossos et al. (10) reported a technique that used a sphincterotome for cannulation, and the first prospective study (11) in 1999 confirmed that the success rate of cannulation by sphincterotome was significantly greater than that of cannulation by the standard catheter (67% vs. 97%). Use of the sphincterotome gradually became the primary method of cannulation.

Does the effect of the presence of PAD on ERCP cannulation become smaller as the overall cannulation success rate increases? For the reasons mentioned, a new and reasonable analysis of studies was undertaken. These studies evaluated the effects of PAD on cannulation pre- and post-2000, respectively.

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METHODS

Literature Review
A search of the scientific literature (published up to September 8, 2018) was performed on the following databases: PubMed, EMBASE, and the Cochrane Library. It was restricted to articles published in English. The keywords used were: ("periampullary duodenal diverticula" OR "duodenal papilla diverticulum" OR "PAD") AND ("ERCP" OR "endoscopic retrograde cholangiopancreatography" or "Cholangiopancreatography, Endoscopic Retrograde"). The authors also physically searched the references of the original studies to avoid missing any information. The review was approved by the Ethics Committee for Human Experiments of the First Hospital of Lanzhou University.

Study Selection Criteria and Exclusion Criteria
Two investigators reviewed the material identified by the searches and included published studies that met the following criteria:

- observational design (retrospective or prospective cohort or case-control study);
- subjects with and without PAD who underwent ERCP;
- evaluation of ERCP-related adverse events (i.e., pancreatitis, bleeding, or perforation)
- Case reports, conference abstracts, letters, and animal studies were excluded. Studies with an enrollment period (years of study) that extended across 2000 were excluded. Disagreements was resolved through discussion and negotiation. A third reviewer made the final decision if there was still disagreement after the discussion.

Data Extraction
Data extraction was carried out by two independent investigators. The two investigators resolved discrepancies by forming a consensus. The information recorded included author, year of publication, country, number of patients in each group, mean age and age range, sex, cannulation failure rates, and incidences of post-ERCP-pancreatitis (PEP), perforation, hemorrhage, and other complications.

MAIN POINTS
- *Periampullary diverticulum is irrelevant to failed cannulation of ERCP.*
- *Periampullary diverticulum increases the incidence of early post-ERCP complications, including pancreatitis, bleeding, and perforation.*
- *Intradiverticular papilla may be associated with the rate of failed cannulation during ERCP.*

Definition of Outcomes
The primary endpoint of the meta-analysis was the cannulation failure rate. The secondary endpoint was the incidence of PEP, perforation, or bleeding. A failed cannulation was arbitrarily defined as having occurred if deep instrumentation of the desired duct, including the biliary tree or pancreatic duct, a cholangiogram, or pancreatic ductography could not obtained despite all techniques and efforts, including the pre-cut technique and so on. The author assessed early complications such as PEP (12, 13) and perforation based on consensus criteria (14). Procedure-related bleeding was defined as clinical (not just endoscopic) evidence of bleeding with a decrease in hemoglobin or the need for transfusion or intervention (angiographic or surgery) (14). According to the classification of Lobo et al. (15) and Boix et al. (16), PAD was classified into two types. The first, intradiverticular papilla (IDP), was defined as major papilla inside of the diverticulum or between two or more diverticula. The second, non-IDP, was defined as a diverticulum within (but not containing) a 2–3 cm radius of the major papilla. In addition, the major papilla in the margin of the diverticulum belonged to the non-IDP group, because the margin is thin (17).

Methodological Quality
The independent reviewers assessed the methodological quality of the observational studies using the Newcastle-Ottawa Scale (NOS) (18). A score of 0 to 9 was assigned to every study. The items evaluated included the exposure cohort's presentation, the choice of the unexposed cohorts, the exposure's resolution, the comparability of the results, and follow-up grounded on design or analysis.

Adequacy. Each high-quality study was given one or two stars according to comparability, a total of nine stars could be obtained. An appropriate selection criterion for the participants was considered to be a continuous series of controls derived from similar patients. In comparability, age- and sex-matched or matched for additional diagnosis or treatment before endoscopy could get one star. The follow-up time was at least 3 months. A star was given for follow-up performed in >80% of the initial cohort. The final scores determined the overall risk of a given level of bias. Seven to nine stars were a low-risk cohort, four to six stars were medium-risk, and three or fewer stars was high-risk. The differences in scoring were resolved by forming a consensus.

Subgroup Analysis and Statistical Analyses
The literature studies on cannulation were divided into two subgroups according to the years each study

was performed (pre- and post-2000). There were no subgroups studying the impact of PAD position or the effects of PAD on complications, because the conclusion was consistent in studies pre- and post-2000 and very few articles focused on adverse events pre-2000.

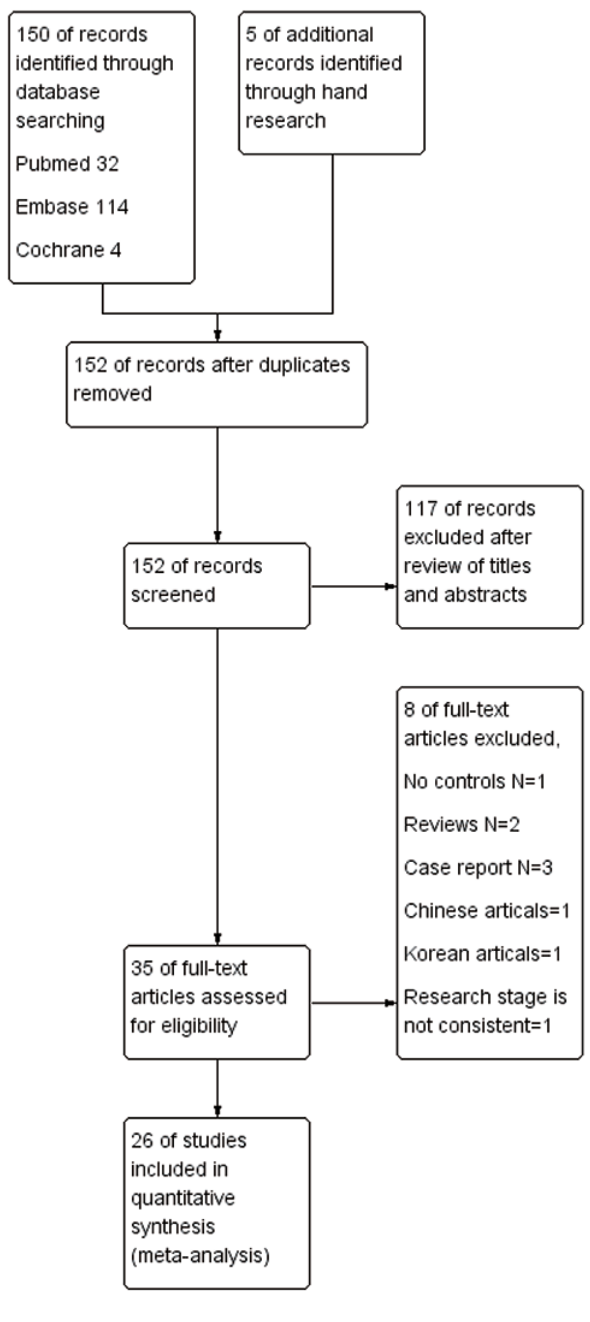

Figure 1. Search flow diagram.

Pooled analysis of data on clinical outcomes was performed with the Mantel-Haenszel method. Risk ratio (RR) analysis was used to produce an overall effect estimate of all outcomes. The fixed-effect model was used when there was low heterogeneity in the variables among the studies, and the random-effect model was used if there was significant heterogeneity. Intention-to-treat data were extracted from all studies.

The authors used the chi-square test to assess heterogeneity among the trials and the I^2 statistic to estimate the degree of the inconsistency. An I^2 statistic >50% suggested significant heterogeneity (19). Statistical heterogeneity was graded as low (<50%), moderate (51%–75%), or high (>75%) by the I^2 statistic according to the criteria (19). Standard techniques were used to generate forest plots to pool the included studies. Horizontal lines represented a 95% confidence interval (CI) and the area of each square. This indicated the RR point estimate. The overall summary estimate under fixed-effect or random-effect of 95% CI was shown. The vertical line was the null (RR=1.0). Publication bias for the failed cannulation analysis was estimated by the Egger test and funnel plot. An Egger test p<0.05 was considered a significant publication bias. All statistical analyses were achieved with the Review Manager 5.3 computer program (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2014).

RESULTS

Twenty-six articles (2, 3, 5, 6, 15-17, 20-38) were included in the meta-analysis. Eight prospective and 18 retrospective studies were eligible for inclusion in this systematic review and meta-analysis (Figure 1). Of them, one study just compared the perforation incidence in PAD and non-PAD groups. The remaining studies compared the cannulation failure rate and the ERCP-related adverse events between PAD and non-PAD groups.

Characteristics of the studies are outlined in Table 1, including details of cannulation failure and ERCP-related complications in patients with or without PAD. A total of 23,826 patients were included in the analysis. In 26 studies, the definitions of cannulation failure and ERCP-related adverse events were not the same in parts of the studies. The NOS scale assessed the quality of the studies included in the meta-analysis. Overall, there was an average medium quality of six of nine stars for all studies (range six to seven stars); however, we must point out that there were still confounding factors. First, there was uncertainty regarding the homogeneity with

Table 1. Characteristics, cannulation, and complications of the included studies.

Author	Year	Study type	Country	Years of study	study group (No.		Mean age, y	Male/female	Score (NOS)	unsuccessful cannuation	pancreatitis	perforation	bleeding	cholangitis	pre-cut technique
Corral et al. (6)	2018	R	America	2000–2012	PAD	1089	68.4±14.3	600/489	6	37	NA	NA	NA	NA	NA
					non-PAD	3267	68.4±14.3	1800/1467		72	NA	NA	NA	NA	NA
Karaahmet et al. (21)	2018	R	Turkey	2015¬–2016	PAD	164	69.7±14.4	63/101	6	2	29	1	11	NA	7
					non-PAD	663	60.2±17.5	259/404		9	77	1	17	NA	49
Chen L et al. (22)	2016	R	China	2009–2015	PAD	1489	67.52±13.51	828/661	6	21	35	1	8	NA	22
					non-PAD	1500	57.98±14.89	843/657		14	22	0	8	NA	18
Takano et al. (38)	2016	R	Japan	2010–2014	PAD	48	NA	NA	6	NA	NA	6	NA	NA	NA
					non-PAD	160	NA	NA		NA	NA	1	NA	NA	NA
Sun et al. (31)	2016	R	China	2008–2012	PAD	161	62(23–90)	83/78	6	8	26	2	NA	NA	NA
					non-PAD	483	61(26–87)	249/234		39	61	12	NA	NA	NA
Örmeci et al. (5)	2016	R	Turkey	2009–2014	PAD	130	69.9	65/65	6	1	4	1	0	2	NA
					non-PAD	260	62.3	121/139		19	6	0	2	4	NA
Lobo et al. (15)	1998	R	England	NA	PAD	109	76(37–93)	44/65	6	41	NA	NA	NA	NA	NA
					non-PAD	1102	65	441/661		80	NA	NA	NA	NA	NA
Chang-Chie et al. (35)	1987	p	China	1980–1986	PAD	153	58.45(32–84)	86/67	7	13	NA	NA	NA	NA	NA
					non-PAD	1090	NA	576/536		98	NA	NA	NA	NA	NA
Parlak et al. (37)	2015	P	Turker	NA	PAD	222	68.9±10.1	99/123	7	12	3	1	NA	1	64
					non-PAD	979	57.5±16.6	460/521		32	7	4	NA	3	410
Omar et al. (3)	2015	P	Egypt	2010–2015	PAD	114	52±8.1	55/59	7	11	9	2	1	1	12
					non-PAD	908	41.4±9.5	420/488		37	45	1	10	8	121
Boga et al. (30)	2016	R	Turkey	2011–2014	PAD	112	72.7±12.2	31/81	6	8	10	1	7	NA	NA
					non-PAD	836	56.8±16.4	383/453		54	69	5	43	NA	NA
Akin et al(20)	2015	R	Turkey	NA	PAD	40	72.9±9.9	21/19	6	5	7	NA	NA	NA	7
					non-PAD	40	68.1±12	20/20		2	4	NA	NA	NA	5
Geraci et al. (27)	2013	R	Italy	2008–2012	PAD	81	69.5	36/45	6	0	2	0	1	NA	NA
					non-PAD	419	49.7	182/237		7	12	2	15	NA	NA
Mohammad et al. (2)	2013	R	Iran	2009–2012	PAD	44	65.9±16	18/26	6	16	1	0	0	0	NA
					non-PAD	736	57±17.1	375/361		75	2	4	2	4	NA
Kim et al. (29)	2013	R	South Korea	2006–2011	PAD	93	75.2±8.8	46/47	6	3	7	0	5	NA	9

Table 1. Characteristics, cannulation, and complications of the included studies (continued).

Author	Year	Study type	Country	Years of study	study group (No.		Mean age, y	Male/female	Score (NOS)	unsuccessful cannuation	pancreatitis	perforation	bleeding	cholangitis	pre-cut technique
					non-PAD	130	69.7±10.9	76/54		4	12	1	11	NA	16
Katsinelos et al. (28)	2013	p	Greece	2008–2010	PAD	107	77.36±8.36	43/64	7	3	10	0	6	NA	10
					non-PAD	321	68.06±14.69	146/175		1	21	0	14	NA	44
Aslan. (25)	2012	P	Turkey	2008–2010	PAD	108	74±11	41/67	7	5	NA	NA	8	NA	2
					non-PAD	478	62±17	193/285		11	NA	NA	20	NA	7
Park et al. (26)	2012	R	Korea	2005–2010	PAD	33	73.8±9.1	14/19	6	2	2	0	1	NA	NA
					non-PAD	121	68.8±14.3	66/55		11	13	1	2	NA	NA
Tyaji et al. (17)	2009	R	India	2006–2007	PAD	46	51±15	12/34	6	1	2	NA	1	NA	6
					non-PAD	100	39±17	24/76		7	3	NA	1	NA	36
Panteris et al. (16)	2008	p	Greece	2001–2006	PAD	117	72.7	54/63	7	6	1	2	0	1	NA
					non-PAD	484	67	241/243		25	7	8	9	3	NA
Tham et al. (32)	2004	p	England	NA	PAD	83	73(26–89)	34/49	7	5	4	0	NA	NA	NA
					non-PAD	261	72(51–93)	106/155		16	10	1	NA	NA	NA
Zoepf et al. (24)	2001	R	Germany	1991–1996	PAD	350	71(23–98)	141/209	6	16	0	3	31	NA	NA
					non-PAD	350	62(11–100)	156/194		14	3	3	17	NA	NA
Boix et al. (23)	2006	R	Spain	2000–2002	PAD	131	74.7±14.9	63/68	6	13	4	NA	4	1	NA
					non-PAD	269	64.4±17.3	131/138		32	6	NA	2	1	NA
Vaira et al. (34)	1989	p	England	1983–1988	PAD	308	75(27–100)	103/124	7	18	1	1	9	1	NA
					non-PAD	2150	75(27–100)	203/244		72	3	1	14	1	NA
Kirk et al. (36)	1980	R	England	1973–1977	PAD	38	64(42–84)	54/46	6	15	NA	NA	NA	NA	NA
					non-PAD	717	51(18–92)	51/49		143	NA	NA	NA	NA	NA
Hall et al. (33)	1990	R	America	1984–1988	PAD	95	NA	NA	6	5	NA	NA	NA	NA	NA
					non-PAD	546	NA	NA		21	NA	NA	NA	NA	NA

※ The data was not reported in the original literature and was replaced by the overall cannulation failure rate of this center. NA: not available. P: prospective. R: retrospective respect to the risk factors for the endpoints between the two groups. Second, PAD was the independent risk factor for cannulation failure in four of the studies included (2, 3, 24, 31), and Zoepf et al. (24) regarded PAD as an independent risk factor associated with significant bleeding.

Primary Endpoint: Failed Cannulation Rate in PAD Groups vs. Non-PAD Groups

Twenty-five studies (2, 3, 5, 6, 15-17, 20-37) involving 23,618 patients reported the cannulation rate in PAD and non-PAD groups. The RR and 95% CI for each study and the pooled RR are shown in Figure 2. The overall summary estimated that RR was 1.46 (95% CI: 1.27-1.67; p<0.001); heterogeneity testing resulted in I^2=76% and p<0.001. In the subgroup (see Figure 2) of post-2000 studies, the summary estimated that RR was 1.16 (95% CI: 0.96-1.41; p=0.12) and heterogeneity testing resulted in I^2=35% and P =0.07 using a fixed-effect model. In addition, in the subgroup of pre-2000 studies, the summary estimated that RR was 2.05 (95% CI: 1.68-2.51; p<0.001), and heterogeneity testing resulted in I2=89% and p<0.001. The cannulation rates in IDP and non-IDP groups were reported in 12 studies (n=3005 patients). The overall summary estimated that RR was 2.32 (95% CI: 1.65-3.24; p<.001), and heterogeneity testing resulted in I2=0% and p=0.630.

Study or Subgroup	PAD Events	PAD Total	non-PAD Events	non-PAD Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.1 Post-2000							
Tham 2004	5	83	16	261	2.9%	0.98 [0.37, 2.60]	2004
Boix 2006	13	131	32	269	7.9%	0.83 [0.45, 1.54]	2006
Panteris2008	6	117	25	484	3.7%	0.99 [0.42, 2.36]	2008
Tyaji 2009	1	46	7	100	1.7%	0.31 [0.04, 2.45]	2009
Park 2012	2	33	11	121	1.8%	0.67 [0.16, 2.86]	2012
Aslan 2012	5	108	11	478	1.5%	2.01 [0.71, 5.67]	2012
Kim 2013	3	93	4	130	1.3%	1.05 [0.24, 4.57]	2013
Mohammad 2013	0	44	0	736		Not estimable	2013
Greaci 2013	0	81	7	419	0.9%	0.34 [0.02, 5.92]	2013
Katsinelos 2013	3	107	1	321	0.2%	9.00 [0.95, 85.61]	2013
Akin 2015	5	40	2	40	0.8%	2.50 [0.51, 12.14]	2015
Parlak 2015	12	222	32	979	4.5%	1.65 [0.87, 3.16]	2015
Omar 2015	11	114	37	908	3.1%	2.37 [1.24, 4.51]	2015
Örmeci 2016	1	130	19	260	4.8%	0.11 [0.01, 0.78]	2016
ChenL 2017	21	1489	14	1500	5.3%	1.51 [0.77, 2.96]	2016
Boga 2016	8	112	54	836	4.8%	1.11 [0.54, 2.26]	2016
Sun 2016	8	161	39	483	7.3%	0.62 [0.29, 1.29]	2016
Corral 2018	37	1089	72	3267	13.6%	1.54 [1.04, 2.28]	2018
Karaahmet 2018	2	164	9	663	1.3%	0.90 [0.20, 4.12]	2018
Subtotal (95% CI)		**4364**		**12255**	**67.2%**	**1.16 [0.96, 1.41]**	
Total events	143		392				
Heterogeneity: Chi² = 26.30, df = 17 (P = 0.07); I² = 35%							
Test for overall effect: Z = 1.55 (P = 0.12)							
1.1.2 Pre-2000							
Kirk 1980	15	38	143	717	5.4%	1.98 [1.30, 3.01]	1980
Chang-Chie1987	13	153	98	1090	9.1%	0.95 [0.54, 1.64]	1987
Vaira 1989	18	308	72	2150	6.8%	1.75 [1.06, 2.88]	1989
Hall1990	5	95	11	546	1.2%	2.61 [0.93, 7.35]	1990
Lobo 1998	39	100	80	1102	5.0%	5.37 [3.89, 7.42]	1998
Zoepf 2001	16	350	14	350	5.3%	1.14 [0.57, 2.31]	2001
Subtotal (95% CI)		**1044**		**5955**	**32.8%**	**2.05 [1.68, 2.51]**	
Total events	106		418				
Heterogeneity: Chi² = 44.87, df = 5 (P < 0.00001); I² = 89%							
Test for overall effect: Z = 7.04 (P < 0.00001)							
Total (95% CI)		**5408**		**18210**	**100.0%**	**1.46 [1.27, 1.67]**	
Total events	249		810				
Heterogeneity: Chi² = 96.79, df = 23 (P < 0.00001); I² = 76%							
Test for overall effect: Z = 5.30 (P < 0.00001)							
Test for subgroup differences: Chi² = 16.17, df = 1 (P < 0.0001), I² = 93.8%							

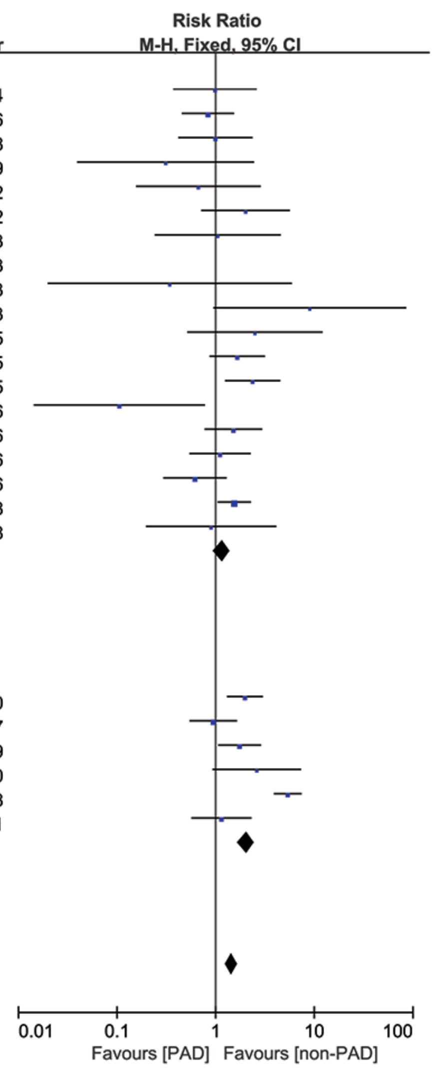

Figure 2. Forest plot for the failure rate of cannulation (PAD vs non-PAD).

Secondary Endpoints: Incidence of PEP, Perforation, Bleeding, and Cholangitis

Nineteen studies involving 14,835 patients provided data on the incidence of PEP. The overall summary estimated that RR was 1.32 (95% CI:1.10-1.59; p=0.003), heterogeneity testing resulted in I^2=0% and p=0.92 (see Figure 3a) using a fixed-effect model. Five studies provided data about the PEP incidence in IDP and non-IDP groups. RR and 95% CI for each study and the pooled RR are shown in Figure 3b. The overall summary estimated that RR was 1.14 (95% CI: 0.64-2.02; p=0.660). Heterogeneity testing resulted in I^2=0% and p=0.730. Perforation rates for each study are shown in Figure 4. The overall summary estimated that RR was 1.73 (95% CI: 1.06-2.82; p=0.030). Heterogeneity testing resulted in I^2=2% and p=0.430. Bleeding rates for each study are shown in Figure 5. The overall summary estimated that RR was 1.48 (95% CI: 1.13-1.93; p=0.005). Heterogeneity testing resulted in I^2=30% and p=0.130. Cholangitis rates for each study are shown in Figure 6. The overall summary estimated that RR was 1.44 (95% CI: 0.62-3.32; p=0.390). Heterogeneity testing resulted in I^2=0% and p=0.950.

Additional analyses: the use of a pre-cut technique for cannulation

Data regarding the use of a pre-cut technique for cannulation was acquired from nine studies (7502 patients); the pooled RR was 0.72 (95% CI: 0.61-0.85; p<0.001).

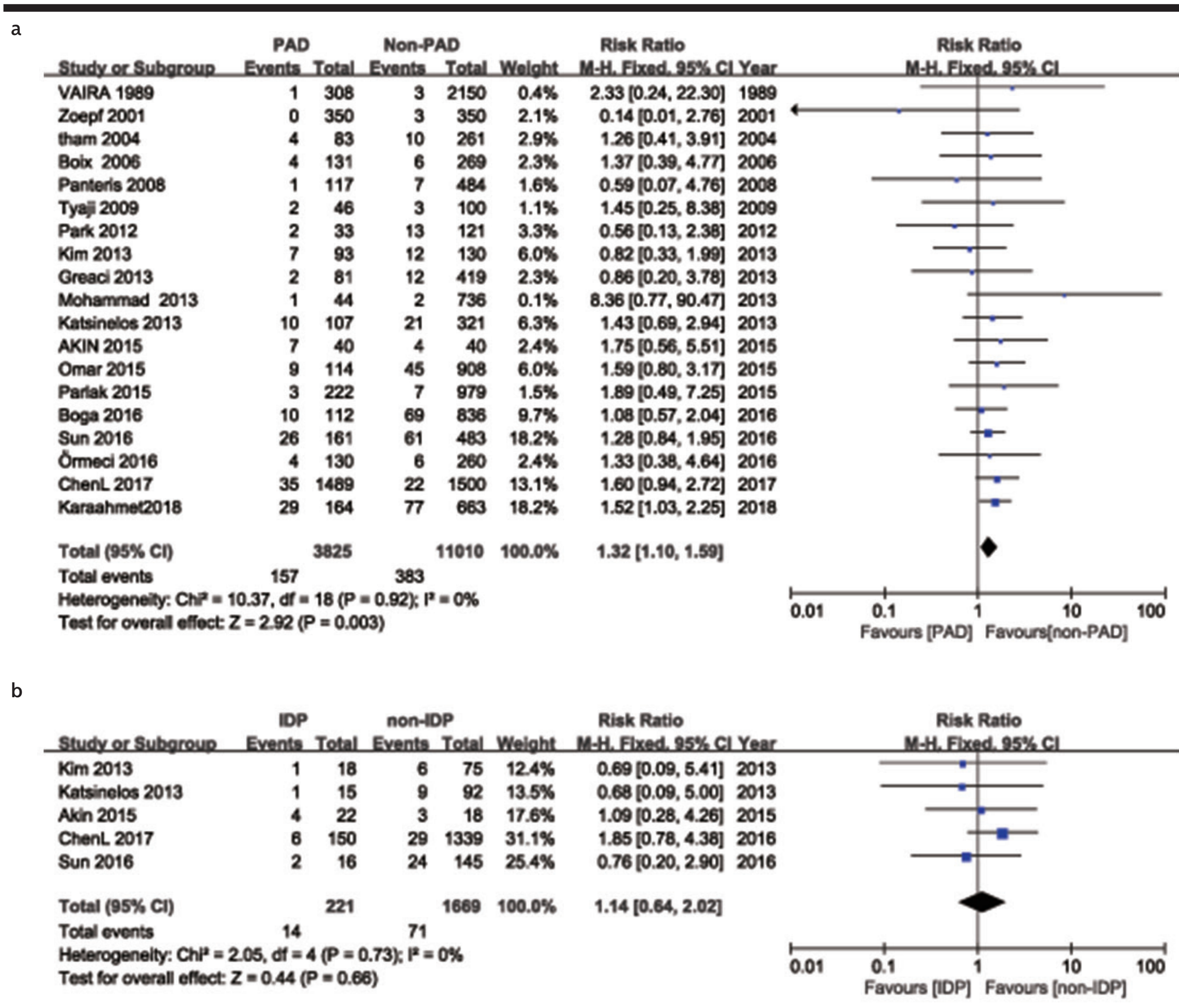

Figure 3. a, b. a) Forest plot for the rate of PEP (PAD vs non-PAD). b) Forest plot for the rate of PEP (IDP vs non-IPD).

Heterogeneity testing revealed that I^2=5% and p=0.39 (Figure 7).

Publication Bias

The funnel plot showed no evidence of noticeable asymmetry. The Egger test also showed no publication bias (Egger t value=−0.96, p=0.347, 95%CI: -1.50 to 0.54).

Limitations

There were many retrospective observational studies whose definitions of cannulation failure and ERCP-related complications were not homogenous. Also, we could not analyze the association of PAD and ERCP-related later complications and evaluate what technology and equipment had the lowest rates of failed cannulation and complications.

Study or Subgroup	PAD Events	PAD Total	Non-PAD Events	Non-PAD Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Vaira 1989	1	308	1	2150	1.2%	6.98 [0.44, 111.31]	1989
Zoepf 2001	3	350	3	350	14.3%	1.00 [0.20, 4.92]	2001
Tham 2004	0	83	1	261	3.5%	1.04 [0.04, 25.28]	2004
Panteris2008	2	117	8	484	14.9%	1.03 [0.22, 4.81]	2008
Park 2012	0	33	1	121	3.1%	1.20 [0.05, 28.70]	2012
Mohammad 2013	0	44	4	736	2.5%	1.82 [0.10, 33.28]	2013
Kim 2013	0	93	1	130	6.0%	0.46 [0.02, 11.28]	2013
Greaci 2013	0	81	2	419	3.9%	1.02 [0.05, 21.14]	2013
Parlak 2015	1	222	4	979	7.1%	1.10 [0.12, 9.82]	2015
Omar 2015	2	114	1	908	1.1%	15.93 [1.46, 174.29]	2015
Boga 2016	1	112	5	836	5.7%	1.49 [0.18, 12.66]	2016
ChenL 2017	1	1489	0	1500	2.4%	3.02 [0.12, 74.13]	2016
Takano 2016	6	48	1	160	2.2%	20.00 [2.47, 162.07]	2016
Örmeci 2016	1	130	0	260	1.6%	5.98 [0.25, 145.72]	2016
Sun 2016	2	161	12	483	28.7%	0.50 [0.11, 2.21]	2016
Karaahmet 2018	1	164	1	663	1.9%	4.04 [0.25, 64.29]	2018
Total (95% CI)		**3549**		**10440**	**100.0%**	**1.73 [1.06, 2.82]**	
Total events	21		45				

Heterogeneity: Chi² = 15.26, df = 15 (P = 0.43); I² = 2%
Test for overall effect: Z = 2.19 (P = 0.03)

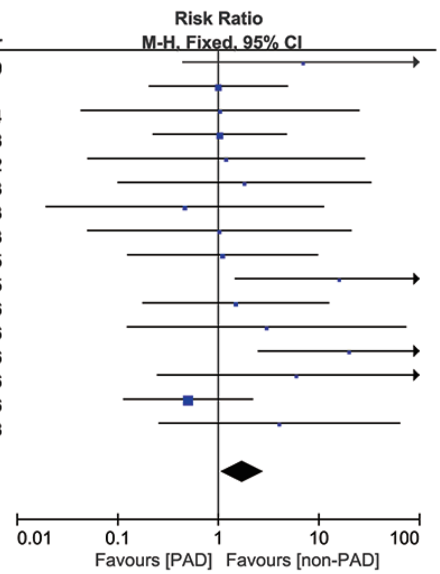

Figure 4. Forest plot for the rate of perforation (PAD vs non-PAD).

Study or Subgroup	PAD Events	PAD Total	Non-PAD Events	Non-PAD Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Vaira 1989	9	308	14	2150	4.5%	4.49 [1.96, 10.28]	1989
Zoepf 2001	31	350	17	350	22.0%	1.82 [1.03, 3.23]	2001
Boix 2006	4	131	2	269	1.7%	4.11 [0.76, 22.13]	2006
Panteris2008	0	117	9	484	4.8%	0.22 [0.01, 3.69]	2008
Tyaji 2009	1	46	1	100	0.8%	2.17 [0.14, 34.00]	2009
Park 2012	1	33	2	121	1.1%	1.83 [0.17, 19.60]	2012
Katsinelos 2013	6	107	14	321	9.1%	1.29 [0.51, 3.26]	2013
Greaci 2013	1	81	15	419	6.3%	0.34 [0.05, 2.57]	2013
Mohammad 2013	0	44	2	736	0.4%	3.28 [0.16, 67.22]	2013
Kim 2013	5	93	11	130	11.9%	0.64 [0.23, 1.77]	2013
Omar 2015	1	114	10	908	2.9%	0.80 [0.10, 6.16]	2015
ChenL 2017	8	1489	8	1500	10.3%	1.01 [0.38, 2.68]	2016
Örmeci 2016	0	130	2	260	2.2%	0.40 [0.02, 8.24]	2016
Boga 2016	7	112	43	836	13.2%	1.22 [0.56, 2.64]	2016
Karaahmet 2018	11	164	17	663	8.7%	2.62 [1.25, 5.48]	2018
Total (95% CI)		**3319**		**9247**	**100.0%**	**1.48 [1.13, 1.93]**	
Total events	85		167				

Heterogeneity: Chi² = 19.90, df = 14 (P = 0.13); I² = 30%
Test for overall effect: Z = 2.82 (P = 0.005)

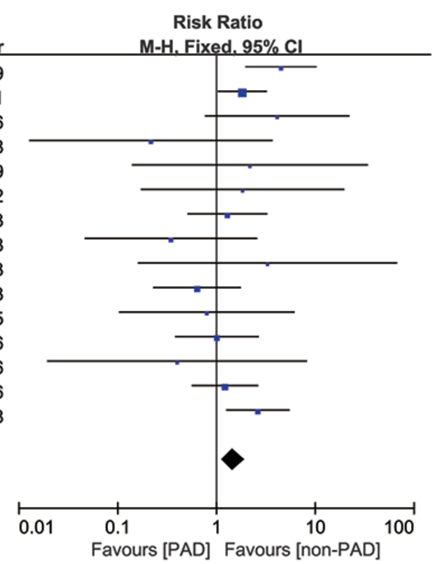

Figure 5. Forest plot for the rate of bleeding (PAD vs non-PAD).

DISCUSSION

PAD was initially described by Chomel et al. in 1710 (3). It has been observed in rates varying between 5% and 23% of patients in endoscopic evaluation (20). The incidence could be even higher in aging populations, possibly as high as 32% (21). PAD is associated with a higher incidence of common bile duct obstruction and biliary stone formation (22, 39, 40). In addition, it is caused by a defect during the fusion of the foregut and midget in embryonic life. This defect causes progressive weakening in the smooth muscles of the duodenum. Acquired factors (i.e., aging, sphincter of Oddi dysfunction, and increased intraduodenal pressure) also contribute to the development of PAD (5). ERCP, which was first reported by McCune et al. in 1968 (41), has been applied in the clinic and has gradually become an indispensable treatment for various biliary and pancreatic diseases (42, 43). However, the impact of the presence of PAD on ERCP cannulation has been controversial.

In this meta-analysis, the authors extracted and analyzed all published data comparing the rate of cannulation failure and the complications, especially pancreatitis, in patients with or without PAD who underwent ERCP. Moreover, the authors explored whether the effects of different types of PAD on ERCP were the same.

This analysis did not find solid evidences that PAD increases the cannulation failure rate in ERCP procedures in studies performed post-2000. Yet there was a strong relationship between PAD and the cannulation failure rate in ERCP procedures in studies performed pre-2000. This variation may be related to three aspects. First, endoscopists' understanding of PAD continues to deepen. Endoscopic operators in the initial period may have thought that PAD could result in serious complications. Therefore, they handled the operations gently, which led to a decreased cannulation success rate. Second, innovative techniques (i.e., sphincterotome for the cannula-

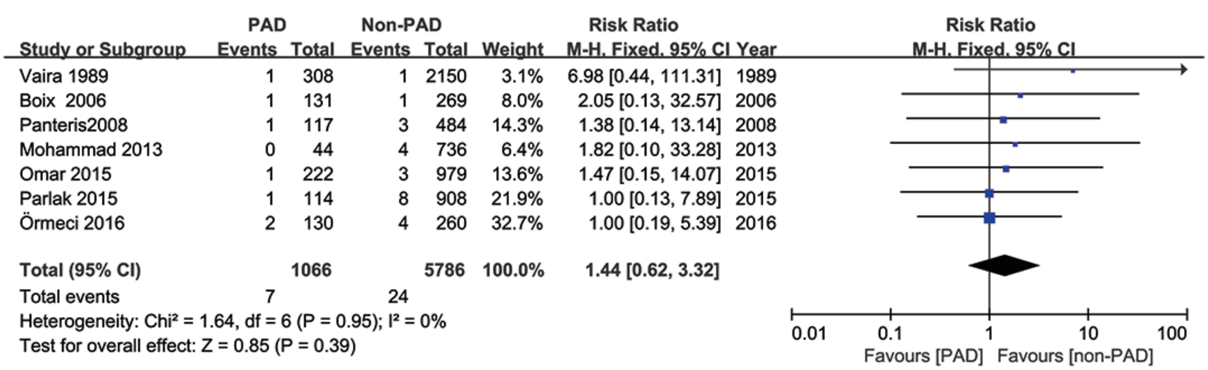

Figure 6. Forest plot for the rate of cholangitis (PAD vs non-PAD).

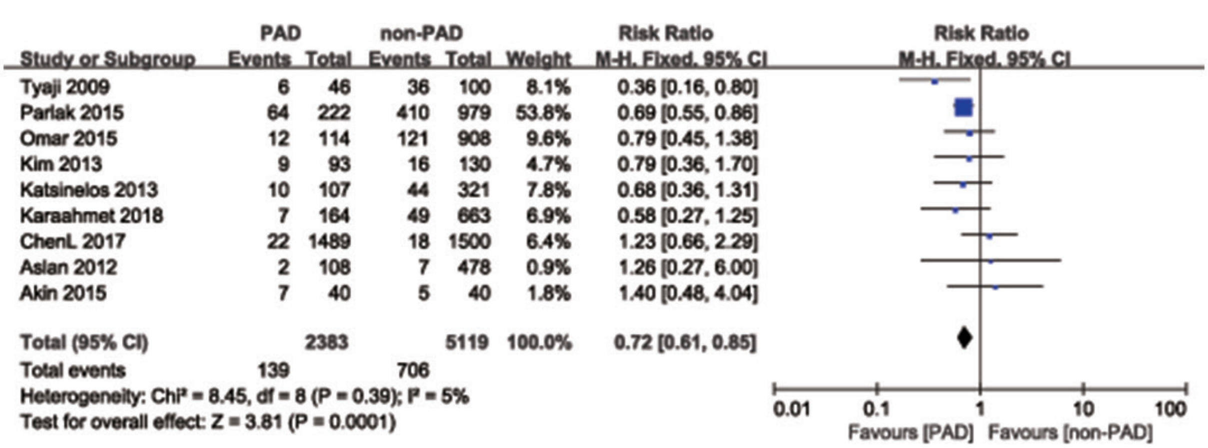

Figure 7. Forest plot for the rate of pre-cut techniques (PAD vs non-PAD).

tion (10), wire-guided cannulation (44), pancreatic duct stent placement followed by precut sphincterotomy (45), double wire technique (46)) and novel equipment (i.e., cap-assisted forward-viewing endoscope (47), needle-knife (26)) have emerged up to the present time, and the issue of which technique or equipment was the best needs to be studied in depth. Third, endoscopic operators have become more skilled through large numbers of operations and tips attributed to successful cannulation (48). Contrary to expectations, the use rate of the precut technique in PAD patients was less than that in non-PAD patients; this should be considered in further extensive studies. Part of the explanation for this result may be that PAD, as reported in several articles (5, 16), was associated with a reduced rate of cannulation failure. The possible explanations for how PAD was associated with decreased cannulation failure were:

- Papilla sphincter dysfunction reduced cannulation resistance.
- The bile duct was more dilated in the PAD groups (3).
- There was a significant relation between undetectable or abnormal papilla and patients without PAD (16)

In addition, when IDP and non-IDP groups were compared, IDP was associated with cannulation failure. This could be because IDP was more common in cases of poorly detectable papilla, or because it was difficult to find the papillary orifice when it was deep inside the diverticulum. The direction of the bile duct was also harder to predict in this type of diverticulum (26). At the same time, several articles (2, 3, 5, 16, 24, 28, 30) in the review compared difficulties related to cannulation between PAD and non-PAD patients. This included more than five cannulation attempts or attempts that were longer than 10 minutes, accidental cannulation into the pancreatic duct, and the need for special technical tools and equipment, which was similar to the guideline and consensus (47, 49). In 2016, Boga et al. (30) reported that there was no statistically significant difference in terms of difficult cannulation between PAD and non-PAD groups. Ormeci et al. (5) reported that there was no statistical difference between the ERCP patients with and without PAD in terms of success rates for the first and second attempts. However, the other studies (2, 3, 16, 24, 28) noted that PAD increased the cannulation difficulty to varying degrees. In short, PAD was not a hindrance to successful cannulation in the new post-2000 era. If PAD was discovered during an operation, the endoscopists did not have to worry. In fact, they could be confident of successful cannulation and the completion of the subsequent operations, although the process of cannulation in patients with PAD may require more patience because of possible difficulties related to cannulation.

The second outcome showed that PAD was associated with an increase in the incidence of early complications, including PEP, bleeding, and perforation; the incidence of cholangitis was equivalent in the PAD and the non-PAD groups. A possible explanation for this may be that the PAD group needed more techniques, equipment, time, and follow-up operations after a successful cannulation. In addition, the definitions of complications were not exactly the same. For example, only five studies (3, 16, 22, 24, 29) clearly defined bleeding. Three studies (22, 24, 29) regarded bleeding as relevant, from the perspective of treatment, if injection therapy with epinephrine, blood transfusion, and/or endoscopic hemostasis were necessary; two studies (3, 16) regarded bleeding as relevant if there was clinical evidence (melena, hematochezia, or hematemesis associated with a hemoglobin decrease of ≥2 g/dL). The incidence of PEP in IDP patients was not more frequent than that in non-IDP patients. Unfortunately, we could not properly compare the rate of pancreatitis before and after 2000 because 18 of the 19 articles that provided data on pancreatitis were post-2000, though this is also an important area that requires further research. Also, our work has expanded upon the diverse results presented in a previous article (50). The present results are significant in at least two major respects. First, surgery in patients with PAD requires an experienced operator to perform delicate operations in order to prevent complications. Second, the postoperative management of patients with PAD requires greater attention so that doctors can efficiently discover pancreatitis, perforation, and/or bleeding. Finally, three studies (3, 24, 27) focused on the effect of PAD on later complications; biliary stones in patients with PAD were prone to recur.

Despite several encouraging data extractions, this meta-analysis has limitations. First, there were many retrospective observational studies. Some studies were based on a small sample of participants. Second, a few of the available studies did not report on complications or the definition of failed cannulation. ERCP-related complications (i.e., PEP, bleeding, perforation) were not uniform. Third, the authors could not assess the preferred techniques and devices related to lower incidences of cannulation failure and complications of ERCP. This is because the included literature spanned a long period and lacked clear comparisons. Fourth, the authors did not focus on the association of PAD and ERCP-related later complications because of the lack of effective data.

Despite the limitations listed, this study was a current systematic analysis assessing the influences of PAD on cannulation in ERCP. It reviewed studies with low heterogeneity. Highly significant results were obtained with minimal evidence of bias.

In conclusion, this systematic review and meta-analysis provided evidence that PAD is no longer an obstacle to successful cannulation, but that it has an impact on the early complications of ERCP, such as pancreatitis, perforation, and bleeding (not including cholangitis). IDP was associated with the cannulation failure rate, but was not associated with an increase in the incidence of PEP. With respect to these findings, there are three major suggestions. First, when skilled endoscopists from high-volume institutes find PAD during ERCP, there is no need to worry about cannulation failure. Second, every operator should perform delicate operations because of the increased rate of complications in patients with PAD. Last but not least, it is necessary to pay attention to adverse events, especially during and after the operation, as only in this way can the doctor find relevant complications as soon as possible in order to provide timely treatment. Further prospective trials with universal criteria for PAD and non-PAD, level of operator proficiency, choice of cannulation approach, and definition of cannulation failure and procedure-related adverse events should be performed for clear and more credible conclusions.

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