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ORIGINAL ARTICLE

Preventive Measures and Risk Factors for Post-ERCP Pancreatitis: A Systematic Review and Individual Patient Data Meta-Analysis

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Abstract

Background Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most common complication of ERCP, with limited studies comparing combined prophylactic measures and their efficacy relative to individual patient risk profiles.

This study aims to perform an individual patient data meta-analysis (IPDMA) to evaluate the contribution of patient and ERCP-related risk factors to PEP development and to identify the best prophylaxis strategies according to the patient's risk profile.

Methods We systematically searched MEDLINE, Embase, and Cochrane databases until November 2022 for randomized controlled PEP prophylaxis trials. We invited authors to share individual patient data, including PEP risk profile and prophylaxes used. PEP incidence rates for different prophylaxis were calculated. Efficacy was compared using multilevel logistic regression and expressed as relative risk (RR). Subgroup analysis evaluated the role of patient and ERCP-related risk factors in developing PEP.

Results Data from 11 studies, including 6430 patients, were analyzed. After adjusting for risk factors, rectal NSAIDs (RR 0.69, 95%CI 0.54–0.88) and peri-procedural high-volume intravenous fluid (IVF) (RR 0.40, 95%CI 0.21–0.79) were effective in reducing PEP incidence, while no benefit was noted with pancreatic duct (PD) stents (RR 1.25, 95%CI 0.91–1.73). In patients receiving rectal NSAIDs ($n=2617$), difficult cannulation (RR 1.99, 1.45–2.73), contrast injection into the pancreatic duct (PD) (RR2.37, 1.68–3.32), and prior history of PEP (RR 1.90, 1.06–3.41) were associated with increased PEP risk.

Conclusion This IPDMA confirms that rectal NSAIDs and peri-procedural IVF are effective PEP prophylactic strategies. Further studies focusing on combination therapy or the development of personalized PEP risk calculators are needed to improve prophylactic strategies.

Keywords Pancreatitis · ERCP · Patient-level meta-analysis · PEP · Rectal indomethacin

Abbreviations

ASGE	American Society of Gastrointestinal Endoscopy
ESGE	European Society of Gastrointestinal Endoscopy
ERCP	Endoscopic retrograde cholangiopancreatography
IPDMA	Individual patient data meta-analysis
PROSPERO	International Prospective Register of Systematic Reviews
IVF	Intravenous fluid
NSAID	Non-steroidal anti-inflammatory drugs
PD	Pancreatic duct
PEP	Post-ERCP pancreatitis
PRISMA-IPD	Preferred Reporting Items for Systematic reviews and Meta-Analyses Individual Patient Data
RCT	Randomized controlled trial

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is performed to treat diseases of the pancreaticobiliary tract. Acute pancreatitis is the most frequent and serious adverse event related to an ERCP. The incidence of post-ERCP pancreatitis (PEP) varies between 3.5 and 14% [1, 2]. Considering that 700,000 ERCPs are performed annually in the USA alone, PEP is a critical iatrogenic burden for the healthcare system, with mortality ranging from 0.2 to 0.9% and healthcare expenditures of 200 million dollars yearly [1, 3, 4].

Over the past years, numerous prophylactic strategies have been studied to minimize the risk of PEP. Three prophylactic strategies produce the most robust evidence and are included as options in the guidelines [5, 6]. Measures include endoscopic strategies, such as pancreatic duct (PD) stent placement, and non-endoscopic strategies, such as rectal non-steroidal anti-inflammatory drugs (NSAIDs) and peri-procedural high-volume intravenous fluid administration (IVF).

There have been limited comparisons of prophylactic strategies using a head-to-head randomized controlled trial (RCT) design [7–9]. The patient population's diversity, potential undisclosed co-medication, and variations in PD stent placement might introduce confounding factors and biased outcomes across these RCTs. Subgroup analyses of combined prophylaxis strategies in individual trials are often underpowered. Therefore, international guidelines often provide contradictory recommendations regarding routine prophylaxis [5, 6].

Patient- and procedure-related risk factors contribute to the development of PEP. These risk factors, described in the European Society of Gastrointestinal Endoscopy (ESGE) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines were derived from studies performed in patients who did not receive PEP prophylaxis, which is not current practice [5, 6]. In a recent survey, a notable increase in PEP prophylaxis utilization was observed between 2013 and 2020. The usage of NSAIDs in over 80% of the ERCPs by gastroenterologists rose from 62 to 93% [10]. However, it remains uncertain whether the risk factors for developing PEP change in the patient population receiving prophylaxis.

An individual patient data meta-analysis (IPDMA) is a powerful tool for synthesizing evidence from multiple studies, providing more precise and reliable estimates of prophylaxis effects while reducing the risk of bias and improving our understanding of the effects of interventions across different patients [11].

We performed an IPDMA of RCTs on PEP prophylaxis. Our primary aim was to evaluate the incidence of PEP among groups receiving different types PEP prophylaxis and, secondary, to evaluate the contribution of patient- and procedure-related risk factors for the development of PEP in groups of interest.

Methods

The study was conducted per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Individual Patient Data (PRISMA-IPD) guidelines (see Supplementary Appendix Table S1) [12, 13] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO: registration number CRD42021231197). The Medical Ethical Review Committee of the Johns Hopkins University School of Medicine in Baltimore, the USA, approved this study and waived the need for informed consent (IRB00181902).

Search Strategy and Selection Criteria

We searched the literature for RCTs using the following electronic databases: MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials, with a combination of MeSH terms, Emtree terms, and keywords that describe ERCP. The search had no language restrictions and included the period from the inception of each database till November 2022. A medical librarian with expertise in systematic reviews assisted with a comprehensive and iterative literature search syntax. The search strategy for each database is provided in the appendix (see Supplementary Appendix).

We used a systematic approach for reviewing the search results in accordance with Cochrane guidelines [14] and the Agency for Healthcare Research and Quality Methods Guide [15]. All studies were screened based on title and abstract to ensure they reported the number of PEP cases. Duplicates were identified and removed. The remaining studies were assessed by examining the full-text papers for adherence to our inclusion criteria. Our inclusion criteria included: RCTs that included adults (aged ≥ 18 years) who underwent ERCP, tested prophylaxis of our interests (e.g., rectal diclofenac or indomethacin, peri-procedural high-volume IVF, or PD stenting) and reported the incidence of PEP. Conference proceedings and abstracts were excluded, except when complete RCT information was available from the authors. We used forward citation and backward citation searches on all eligible articles, including scanning and tracking citations and references in footnotes and bibliographies. Two researchers (CJSW and VSA) independently performed title and abstract screening. Any discrepancies were resolved after discussion with a third reviewer (EJMvG and VKS).

Authors of all eligible studies were contacted to collect individual participants' data. We used several strategies to establish communication with the authors. The first and last authors were contacted initially. In case of no response, co-authors were contacted.

Data Analysis

A standardized database was sent to the authors who agreed to collaborate. All collected databases were cleaned and checked for completeness and internal consistency. The collaborators were directly contacted for missing data, and omissions were corrected. If individual patient data were not provided, the full-text article and supplementary files were screened for aggregated data. The contributed databases were then all converted into the same reporting format and combined into one final database by two authors (CJSW and VSA). The one-stage approach was used in this IPDMA [16].

The primary outcome was the incidence of PEP. The definition of PEP considered in this IPDMA included either consensus criteria as clinical pancreatitis with serum amylase (or lipase) at least three times the upper limit of normal at more than 24 h after the procedure, requiring hospitalization or prolongation of planned admission; or revised Atlanta criteria; or an adaptation of these criteria [17]. Patients were divided into seven different groups depending on the type of PEP prophylaxis they received: placebo, peri-procedural high-volume IVF, peri-procedural high-volume IVF + PD stent, peri-procedural high-volume IVF + rectal NSAID 100/200 mg, peri-procedural high-volume IVF + rectal NSAID 100/200 mg + PD stent, rectal NSAID 100/200 mg, rectal NSAID 100/200 mg + PD stent, and PD stent group.

The meta-analysis of aggregated data of all eligible papers can be found in our recently published network meta-analysis [18]. Differences between studies that did and did not provide IPD were compared in SPSS version 26.0 (IBM Corp., New York, USA). Descriptive statistics were applied to determine baseline characteristics. Differences in baseline characteristics between the different prophylaxis and control groups were analyzed using chi-square for categorical and the Kruskal–Wallis test for continuous variables.

Analyses with IPD were performed in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *P* value of 0.05 or less was considered significant in all statistical analyses. We thoroughly evaluated the frequencies, patterns, and reasons for missing data. The final missing rates for key variables were below the threshold of 5% and would, therefore, only have a minor influence on the analyses when imputed and introducing bias.

We performed two predefined multivariable analyses to evaluate for patient- and ERCP-related procedural PEP risk factors (age, sex, sphincter of Oddi dysfunction, history of PEP, recurrent pancreatitis, pancreatic sphincterotomy, precut sphincterotomy, biliary sphincterotomy, difficult cannulation, pancreatic contrast injection, trainee involvement), among subgroup of patients receiving rectal NSAIDs monotherapy and patients receiving peri-procedural high-volume IVF. These two prophylaxis categories were considered for such an analysis based on the recommendations for PEP prophylaxis per the ESGE and ASGE guidelines [5, 6].

Multilevel logistic regression was used to correct potential confounders while considering the dataset's hierarchical structure (patients nested within studies). We performed a model with a random intercept and all other variables fixed. All variables with $P < 0.20$ in univariate analysis were considered potential confounders and included in the multilevel logistic regression analysis. The outcome of this model was expressed as a risk ratio (RR) with 95% confidence intervals (CI).

We assessed the risk of bias in terms of random sequence generation, allocation concealment, blinding of the patients and investigators, and a summary of the assessment of bias across the study using the Cochrane Collaboration tool for assessing the risk of bias in RCTs [19]. Two researchers (CJSW and VSA) did the critical appraisal independently. Disagreements were resolved after a discussion with a third researcher (EJMvG). The certainty of evidence per outcome was evaluated with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [20]. A study-level pooled proportion meta-analysis was done using a random-effects model. Between-study heterogeneity was assessed by constructing a forest plot and determining the I^2 statistic using a random-effects model. I^2 statistic was used to define heterogeneity, with 30% being considered moderate, 60% considered substantial, and 90% considered considerable [21].

Results

Search Results and Study Characteristics

Our search yielded 1503 articles, resulting in 900 unique publications after removing duplications. 786 articles were excluded based on screening of the title and abstract. Of the 115 remaining studies, 71 were excluded based on the evaluation of the full text. Our final dataset comprises 44 articles (Fig. 1, Supplementary Appendix Table S2) [8, 9, 22–30]. We identified one additional article with citation snowballing that had not been indexed in the searched databases [8].

Individual Patient-Level Data

Individual patient data were successfully retrieved from the authors of 11 of the 44 studies (25%) [8, 9, 22–30]. We

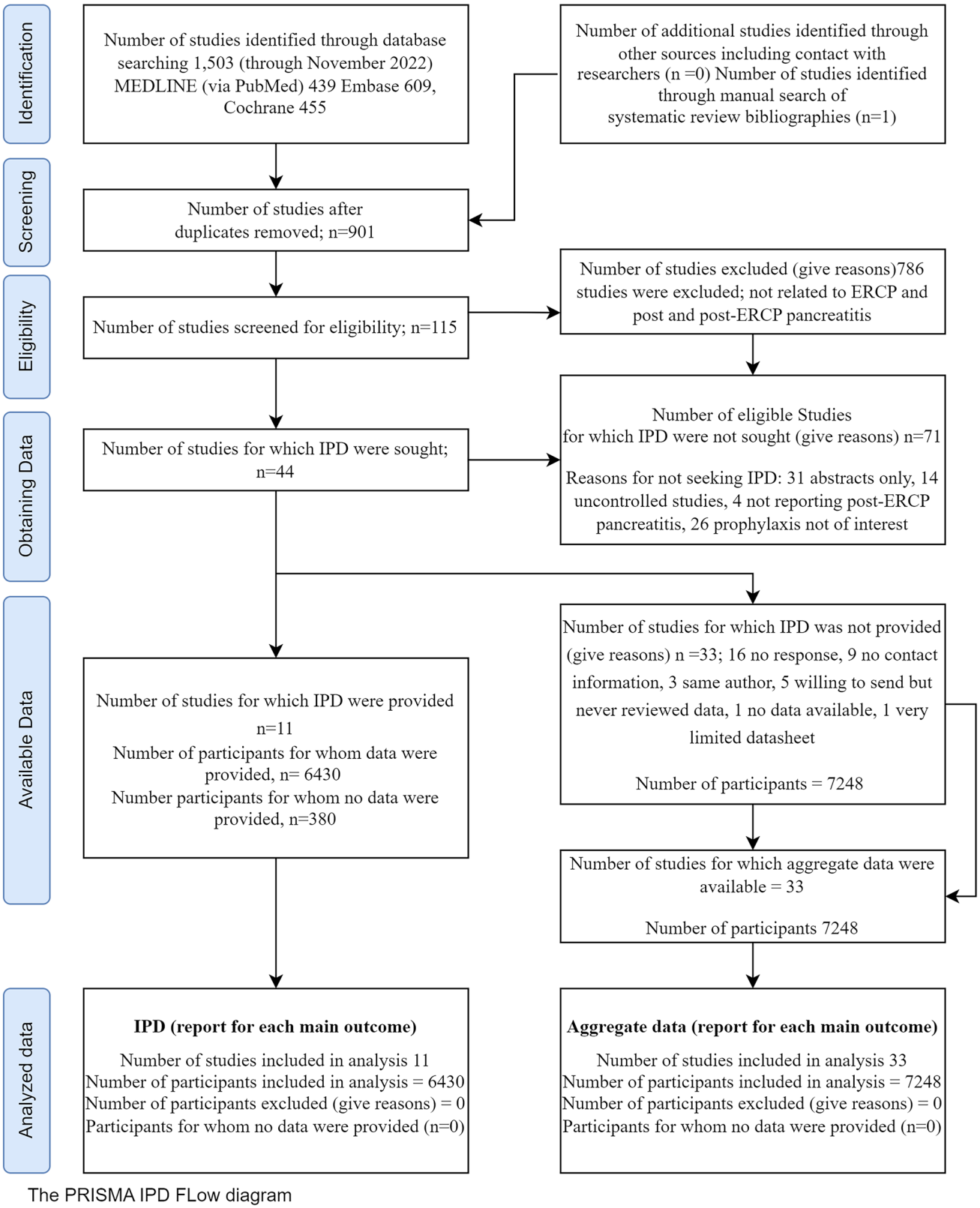

Fig. 1 The PRISMA IPDMA flow diagram. *IPD* individual patient data

found no inconsistencies concerning the data received when compared with the original manuscripts. One author sent patient-level data of 2292 (88%) of 2600 included individuals because one hospital in that multicenter study was not allowed to share individual patient data [9]. We were unable to establish contact with the authors of 25 articles. Individual patient data could not be retrieved from the authors of 33 articles. In total, we included 6430 patients from eleven studies in our analysis. Study characteristics of the eleven trials from which we received patient-level data are summarized in Table 1.

We compared design and publication characteristics between studies with (n = 11) and without ($n = 33$) available IPD (see Table 2 and Supplementary Appendix Figure S1a and S1b). Studies included in the IPDMA were newer and had more patients than those without available IPD. Among the eleven studies that provided IPD, four included all risk patients, four high-risk patients, and one moderate- to high-risk patient.

PEP Prophylaxis Groups

We re-labeled the 6430 patients into eight groups: placebo ($n = 1555$), peri-procedural high-volume IVF ($n = 259$), peri-procedural high-volume IVF + PD stent ($n = 41$), peri-procedural high-volume IVF + rectal NSAID 100/200 mg ($n = 344$), peri-procedural high-volume IVF + rectal NSAID + PD stent ($n = 21$), rectal NSAID ($n = 2617$), rectal NSAID + PD stent ($n = 1118$), and PD stent group ($n = 475$) (Table 3). We combined patients who had received rectal NSAID 100 mg and 200 mg in this study to limit the number of different prophylaxis groups given no differences were seen in the efficacy of PEP prophylaxis among the individual studies that compared these doses [29, 30]. Missing data at an individual patient level was limited, i.e., for age (< 1%), recurrent pancreatitis (3.6%), difficult cannulation (< 1%), and pancreatic contrast injection (< 1%). The variable difficult cannulation was missing in 39% of the patients (two complete studies) and biliary cannulation in 38.4% of the patients, therefore imputation could not be performed. All other variables did not have significant levels of missing data.

Patient Characteristics

Patients had a median age of 58 years (Q1 45-Q3 70) and the majority were female (59.5%). A majority of the patients underwent biliary sphincterotomy (69.0%) and fewer patients pancreatic (17.4%) or pre-cut (10.6%) sphincterotomy. A trainee was involved in a quarter of all the ERCP procedures. The PEP rate of the total cohort was 8.8%. All the baseline variables differed significantly between the PEP prophylaxis groups. Baseline characteristics are shown in Table 3.

Risk Factors for PEP in Predefined Subgroups

In a subgroup of patients that received rectal NSAIDs monotherapy as prophylaxis, difficult cannulation (RR 1.99: 95% CI 1.45–2.73), pancreatic contrast injection (RR 2.37: 95% CI 1.68–3.32), and history of PEP (RR 1.90: 95% CI 1.06–3.41) were found to significantly increase the risk for developing PEP (Table 4). In a subgroup of patients that received peri-procedural high-volume IVF, difficult cannulation appears to have a significant impact on the development of PEP (RR 8.47: 95% CI 2.34–30.71—Table 4).

Prophylaxis for Post-ERCP Pancreatitis

Figure 2 lists the effect of different prophylaxis groups on PEP incidence using individual patient-level data. On re-categorizing the patients, the placebo group had a PEP incidence of 10.2% (95% CI 6.4–15.9), while the highest PEP incidence was noted in the group receiving PD stent alone 15.5% (95% CI 12.5–19.1) followed by the group receiving both rectal NSAIDs and PD stent 11.1% (95% CI 7.2–16.8). On multivariate analysis (Table 5) and adjusting for the PEP risk factors using patient-level data, peri-procedural high-volume IVF (RR 0.40: 95% CI 0.21–0.79; $P = 0.008$) and rectal NSAIDs (RR 0.69: 95% CI 0.54–0.88; $P = 0.003$) were found to reduce the risk of PEP significantly. The PEP prophylaxis efficacy of the other groups was not significant in the multivariate analysis.

Quality of Evidence, Bias, and Heterogeneity

On assessing the quality of RCTs using the revised Cochrane risk of bias (RoB2) tool, 10 RCTs had a low risk of bias due to confounding, 100% of RCTs had no deviations from the intended interventions, and no missing data (Supplementary Appendix Fig. S2). However, 18% of the RCTs had a high risk of bias in the measurement of outcomes and 45% of the RCTs had a risk of bias due to the selection of participants and the classification of the outcomes. According to the GRADE approach, the certainty of the evidence of all outcomes was considered low to moderate (Supplementary Appendix Table S3). Assuming a random-effects model, heterogeneity across studies was substantial ($I^2 = 79\%$, $P < 0.01$), as seen in the forest plot (Fig. 2).

Discussion

Our study utilizing individual patient data of 6430 patients from 11 studies validates the efficacy of rectal NSAIDs and peri-procedural high-volume IVF in reducing the

Table 1 Study characteristics in the individual patient data cohort

Author, year (reference)	Population	Mean age (years)	Female %	Definition of PEP	PEP prophylaxis evaluated	Number of patients	PEP (%)
Buxbaum 2014 [22]	All risk	44	52	Consensus criteria	IV high volume lactated Ringer's solution at a rate of 3.0 mL/kg/h during the procedure, a bolus of 20 mL/kg immediately after the procedure, followed by a post-procedure rate of 3 mL/kg/h for 8 h	39	0
					IV standard volume lactated Ringer's solution at a rate of 1.5 mL/kg/h during the procedure and for 8 h after the procedure without a bolus	23	4 (17)
Choi 2017 [23]	Average to high risk	58	46	Consensus criteria	IV high volume lactated Ringer's solution in an initial bolus of 10 mL/kg before procedure, 3 mL/kg/h during and for 8 h after procedure, and a post-procedure bolus of 10 ml/kg	255	11 (4)
					IV standard volume lactated Ringer's solution at a rate of 1.5 mL/kg/h during and for eight hours after the procedure	255	25 (10)
Elmu nzer 2012 [31]	High risk	45	79	Consensus criteria	Rectal indomethacin 100 mg	295	27 (9)
					Placebo	307	52 (17)
Fogel 2019 [30]	High risk	50	78	Consensus criteria	Rectal indomethacin 100 mg	515	76 (15)
					Rectal indomethacin 200 mg	522	65 (12)
Lai 2019 [29]	All risk	60	38	Consensus criteria	Rectal indomethacin 100 mg	87	3 (3)
					Rectal indomethacin 200 mg	75	6 (8)
Levenick 2016 [25]	All risk	65	53	Consensus criteria	Rectal indomethacin 100 mg	223	16 (7)
					Placebo	226	11 (5)
Lua 2015 [26]	High-risk	50	59	Consensus criteria	Rectal diclofenac 100 mg	69	7 (10)
					No prophylaxis	75	4 (5)
Luo 2016 [9]	All risk	63	52	Consensus criteria	All types of risk patients: rectal indomethacin 100 mg	1297	47 (4)
					High-risk patients: rectal indomethacin 100 mg	281	35 (12)
					Average risk patients: no prophylaxis	1022	65 (6)

Table 1 (continued)

Author, year (reference)	Population	Mean age (years)	Female %	Definition of PEP	PEP prophylaxis evaluated	Number of patients	PEP (%)
Mok 2016 [27]	High risk	60	63	Consensus criteria	Normal Saline + rectal indomethacin 100 mg	48	6 (13)
					Normal Saline + placebo (Placebo)	48	10 (21)
					Lactated Ringer's + rectal indomethacin 100 mg	48	3 (6)
					Lactated Ringer's + placebo (Placebo)	48	9 (19)
Phillip 2019 [28]	All risk	61	57	Atlanta Classification	PD stent	87	11 (13)
					No stent	80	20 (25)
Sperna Weiland 2021 [8]	Average to high-risk	58	59	Consensus criteria	IV high volume lactated Ringer's solution a bolus of 20 mL/kg immediately after the procedure, followed by a post-procedure rate of 3 mL/kg/h for 8 h + rectal diclofenac 100 mg	388	30 (8)
					Rectal diclofenac 100 mg	425	39 (9)

PD pancreatic duct, *PEP* post-ERCP pancreatitis, *IV* intravenous

Table 2 Comparison of Studies providing and not providing individual patient data

Variable	IPD unavailable $N = 33$ studies	IPD available $N = 11$ studies	*P* value
Year of publication, median (IQR)	2015 (2007–2016)	2016 (2015–2019)	0.017
Geographical location			
Asia	20	4	
Europe	6	2	
Americas	7	5	
Sample size, median (IQR)	166 (101–299)	449 (162–813)	0.033
PEP prophylaxis/interventions*			
NSAID	17	8	
IVF high volume	4	2	
PD stent	12	1	
IVF high volume + NSAID	1	1	
PEP incidence % and 95% CI from weighted mean	11.2 (9.4–13.3)	9.1 (7.0–11.7)	0.53

CI confidence interval, *IPD* individual patient data, *IQR* interquartile range, *IVF* intravenous fluid, *PD* pancreatic duct, *PEP* post-ERCP pancreatitis, *NS* not significant

The non-parametric test that was used for scale variables with a skewed distribution was the Mann–Whitney *U* test

*Does not add up to the total of included studies due to multiple comparisons in one trial

Forest plots available in Supplementary Appendix as Fig. S1a and S1b

risk of PEP after adjusting for the patient-level PEP risk factors. Societal guidelines recommend the use of rectal NSAIDs for PEP prophylaxis among all ERCP procedures, however, we have identified the risk factors for PEP development despite the use of rectal NSAIDs, where additional prophylaxis may be required.

IPDMA allows the re-categorizing of patients according to the specific combinations of PEP prophylaxis across

Table 3 Baseline characteristics of patients in individual patient data cohort

	Total ($n=6430$)	Placebo* ($n=1555$)	Prophylaxis group 1 ($n=259$)	Prophylaxis group 2 ($n=41$)	Prophylaxis group 3 ($n=344$)	Prophylaxis group 4 ($n=21$)	Prophylaxis group 5 ($n=2617$)	Prophylaxis group 6 ($n=1118$)	Prophylaxis group 7 ($n=475$)	*P* value**
Patient characteristics										
Sex (Female)	3829/6430 (59.5%)	820 (52.7%)	124 (47.9%)	15 (36.6%)	203 (59.0%)	15 (71.4%)	1481 (56.6%)	833 (74.5%)	338 (71.2%)	< 0.0001
Age (Median years, [IQR]) ($n=6421$)	58 [45–70]	63 [50–72] (3 missing)	60 [50–67]	55 [48.5–68]	56 [44–70]	61 [42–72.5]	60 [48–71] (5 missing)	49 [38–61] (1 missing)	50 [40–64]	< 0.0001
SOD ($n=6430$)	1292 (20.1%)	52 (3.3%)	5 (1.9%)	0 (0%)	2 (0.6%)	0 (0%)	306 (11.7%)	702 (62.8%)	225 (47.4%)	< 0.0001
History of PEP ($n=6430$)	313 (4.9%)	23 (1.5%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	98 (3.7%)	142 (12.7%)	48 (10.1%)	< 0.0001
Recurrent pancreatitis ($n=6201$)	707 (11.4%)	49 (3.4%)	4 (1.8%)	0 (0%)	2 (0.6%)	0 (0%)	194 (7.4%)	371 (33.2%)	86 (22.2%)	< 0.0001
ERCP characteristics										
Pancreatic sphincterotomy ($n=6430$)	1121/6430 (17.4%)	30 (1.9%)	5 (1.9%)	4 (9.8%)	1 (0.3%)	0 (0%)	215 (8.2%)	634 (56.7%)	232 (48.8%)	< 0.0001
Pre-cut sphincterotomy ($n=6430$)	684 (10.6%)	32 (2.1%)	7 (2.7%)	14 (34.1%)	58 (16.9%)	10 (47.6%)	364 (13.9%)	157 (14.0%)	42 (8.8%)	< 0.0001
Difficult cannulation ($n=6412$)	1341 (20.9%)	151 (9.7%)	18 (6.8%)	34 (82.9%)	60 (17.8%)	9 (42.9%)	633 (24.3%)	305 (27.3%)	131 (27.6%)	< 0.0001
Pancreatic contrast injection ($n=6429$)	1478 (23.0%)	74 (4.8%)	5 (1.9%)	4 (9.8%)	45 (13.1%)	9 (42.39)	401 (15.3%)	805 (72.0%)	135 (28.4%)	< 0.0001
Trainee involvement ($n=6430$)	1702 (26.5%)	432 (27.8%)	38 (14.7%)	2 (4.9%)	28 (8.1%)	1 (4.8%)	763 (29.2%)	277 (24.8%)	161 (33.9%)	< 0.0001
Biliary sphincterotomy ($n=3994$)	2757 (69.0%)	479 (74.6%)	231 (89.2%)	39 (95.1%)	296 (86.0%)	14 (66.7%)	825 (67.8%)	601 (58.1%)	272 (62.4%)	< 0.0001

IPD individual patient data, *SOD* Sphincter of Oddi, *ERCP* endoscopic retrograde cholangiopancreatography, *NSAID* non-steroidal anti-inflammatory drugs, *IVF* intravenous fluid

*Reference group. Prophylaxis Group 1: peri-procedural high-volume IVF, Prophylaxis Group 2: peri-procedural high-volume IVF + PD stent. Prophylaxis Group 3: peri-procedural high-volume IVF + rectal NSAID 100/200 mg. Prophylaxis Group 4: peri-procedural high-volume IVF + rectal NSAID + PD stent. Prophylaxis Group 5: Rectal NSAID. Prophylaxis Group 6: Rectal NSAID + PD stent. Prophylaxis Group 7: PD stent

**All variables tested by Chi-squared except Age (Kruskal–Wallis test)

Table 4 Contribution of risk factors for development of post-ERCP pancreatitis in subgroups (=multivariate)

Risk factor	Rectal NSAID ($n=2617$)	Peri-procedural high-volume IVF ($n=259$)
	RR (95% CI)	RR (95% CI)
Difficult cannulation	**1.99 (1.45–2.73)**	**8.47 (2.34–30.71)**
Age	0.99 (0.98–1.00)	1.00 (0.95–1.05)
Pancreatic contrast injection	**2.37 (1.68–3.32)**	NA
Male sex	0.76 (0.56–1.04)	0.60 (0.18–2.04)
Sphincter of Oddi	1.04 (0.67–1.61)	NA
History of post-ERCP pancreatitis	**1.90 (1.06–3.41)**	NA
Pancreatic sphincterotomy	1.29 (0.82–2.05)	NA
Pre-cut sphincterotomy	1.48 (0.98–2.24)	1.40 (0.22–9.02)
Trainee involvement	0.88 (0.63–1.24)	NA

CI confidence interval, *ERCP* endoscopic retrograde cholangiopancreatography, *NSAID* non-steroidal anti-inflammatory drugs, *IVF* intravenous fluid, *RR* relative risk, *NA* not applicable

Bold values indicate intervals that it is statistically significant

multiple RCTs while adjusting for their PEP risk profile based on patient- and procedure-related factors. It also adjusts for any unreported additional PEP prophylaxis that the patient has received. For example, in the landmark RCT by Elmunzer et al., in which the primary aim of the RCT was to evaluate the efficacy of rectal NSAIDs, over 80% of the patients also received a PD stent, thereby confounding the results [23]. Conventional meta-analyses or network meta-analyses are unable to adjust for these nuances and may result in erroneous conclusions.

Though patient-level data were obtained from only 11 of 44 suitable RCTs in our study, the PEP incidence was not significantly different between the included studies and those that were not (11.2% vs. 9.1%, P value = 0.53). When categorizing patients based on the specific PEP prophylaxis they had received, all PEP prophylaxis groups had at least 250 patients, except for the patients receiving a combination of peri-procedural high-volume IVF + PD stent and peri-procedural high-volume IVF + rectal NSAID + PD stent. The limited number of cases is attributed to the recent adoption of combination prophylaxis.

As noted in Table 3, on review of the patient-level data, a notable difference in the PEP risk profile was observed among patients in the various RCTs, and this disparity persisted even after categorizing them based on the PEP prophylaxis they had received. The variation in risk profiles could have influenced the outcomes while evaluating PEP prophylaxis in each study. In the current IPDMA, multivariate analyses were conducted to account for differences in the risk profiles using patient-level data. Even after this adjustment for PEP risk factors, the peri-procedural high-volume IVF and rectal NSAID groups continued to show significant benefits for PEP prophylaxis.

Patients in the PD stent group and rectal NSAIDs plus PD stent group had the highest incidence of PEP, which could likely be attributed to their risk profile, as noted in Table 3. A majority of the patients in this group had a suspicion of sphincter Oddi dysfunction (63%) and a history of pancreatitis. A significant proportion of patients from this group underwent pancreatic sphincterotomy (57%) and pancreatic contrast injection (72%), leading to additional manipulation of the papilla, trauma to the pancreas, and, therefore, an increased risk of PEP. Another caveat with the subgroups of patients receiving PD stent is that only 1 RCT randomized the patients to PD stent prophylaxis, while the other RCTs allowed the use of PD stent based on the endoscopist's discretion, likely the patients with a high risk of developing PEP. This may limit the interpretation of the PD stent results in our study.

Implications for Clinical Practice

The IPDMA confirms the efficacy of established PEP prophylaxis strategies analyzed through a robust dataset and guides the subgroups of patients with specific risk profiles who are likely to develop PEP despite the use of these prophylaxis strategies. These patients likely will benefit from additional or combinations of PEP prophylaxis or modifications to the ERCP procedural techniques.

Recognizing the risk factors that limit the efficacy of PEP prophylaxis based on our study allows endoscopists to modify the ERCP procedure to avoid such scenarios. For example, in the setting of difficult cannulation when initial cannulation attempts are unsuccessful, alternate techniques such as double-wire cannulation, needle-knife fistulotomy, transpancreatic septotomy, and pre-cut sphincterotomy should be considered [31]. While these maneuvers were previously suspected to be increasing the risk of PEP, it is now established that it is the preceding difficult cannulation, papillary edema that truly increases the PEP risk and each additional minute spent attempting cannulation increases the odds ratio (OR) for PEP by 1.072 [32].

Implications for Research

This IPDMA highlights key patient- and procedure-specific risk factors such as difficult cannulation, pancreatic contrast injection, and history of PEP, which lead to higher rates of PEP despite appropriate prophylaxis according to current guidelines. Future studies should focus on improving outcomes in these high-risk populations. Developing a personalized point-of-care PEP risk calculator, which incorporates these risk factors to guide prophylaxis selection, is needed to enhance clinical decision-making. Although our study did

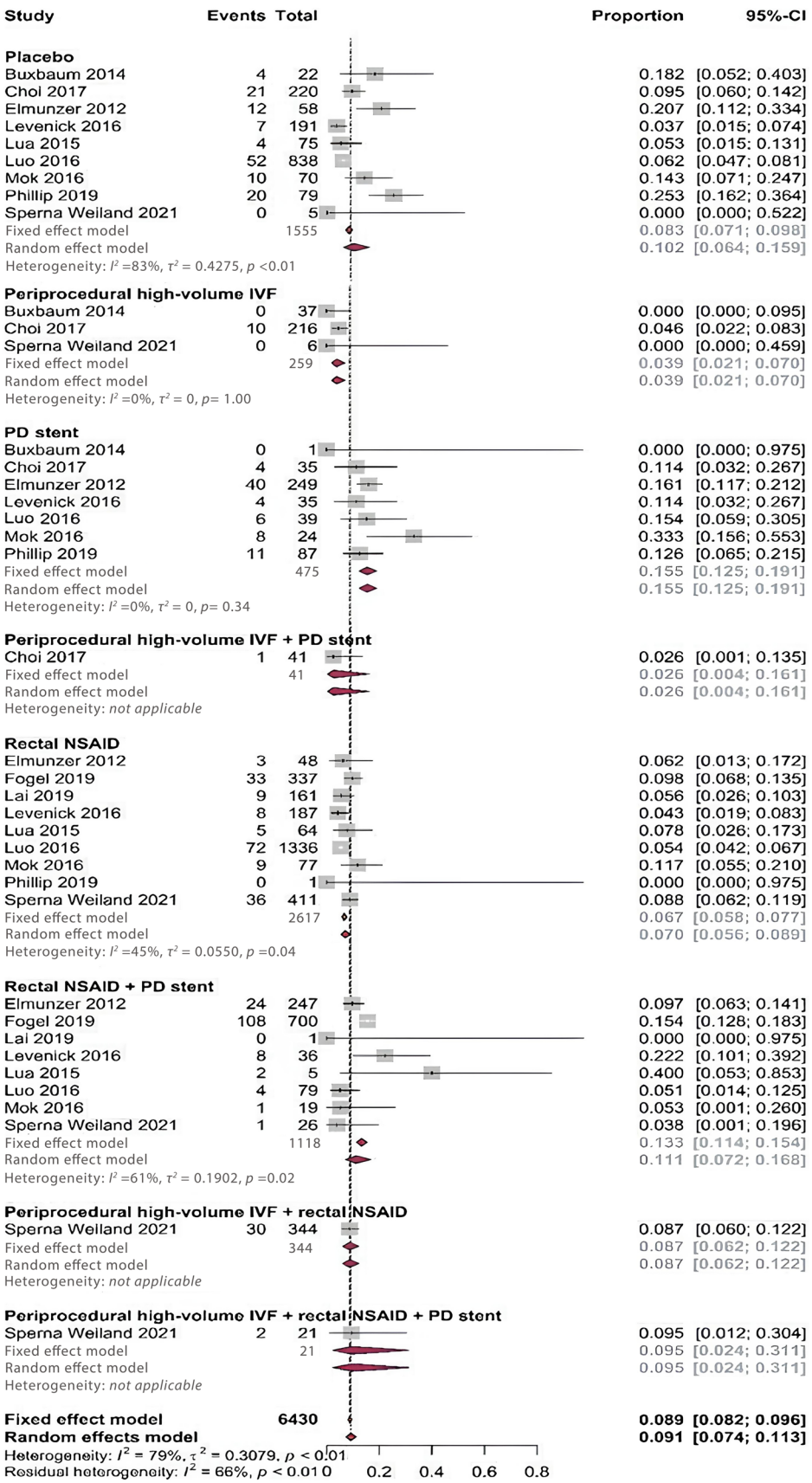

Fig. 2 The forest plot shows the effect of post-ERCP pancreatitis prophylaxis strategies at the study level and is summarized through meta-analyses

Table 5 Uni- and multivariate model of risk factors for development of post-ERCP pancreatitis

	Sample size	Univariate analysis ($n=6430$) RR (95% CI)	Multivariate analysis* ($n=6430$) RR (95% CI)
Prophylaxis group 0	1555	Reference	Reference
Prophylaxis group 1	259	**0.40 (0.20–0.77)**	**0.40 (0.21–0.79)**
Prophylaxis group 2	41	0.25 (0.04–1.77)	0.23 (0.03–1.61)
Prophylaxis group 3	344	0.86 (0.53–1.38)	0.80 (0.49–1.29)
Prophylaxis group 4	21	0.94 (0.24–3.62)	0.72 (0.18–2.81)
Prophylaxis group 5	2617	**0.77 (0.61–0.98)**	**0.69 (0.54–0.88)**
Prophylaxis group 6	1118	1.18 (0.87–1.59)	0.87 (0.64–1.19)
Prophylaxis group 7	475	**1.60 (1.17–2.19)**	1.25 (0.91–1.73)

Prophylaxis Group 0: Placebo

Prophylaxis Group 1: Peri-procedural high-volume IVF

Prophylaxis Group 2: Peri-procedural high-volume IVF + PD stent

Prophylaxis Group 3: Peri-procedural high-volume IVF + rectal NSAID

Prophylaxis Group 4: Peri-procedural high-volume IVF + rectal NSAID + PD stent

Prophylaxis Group 5: Rectal NSAID

Prophylaxis Group 6: Rectal NSAID + PD stent

Prophylaxis Group 7: PD stent

ERCP endoscopic retrograde cholangiopancreatography, *NSAID* non-steroidal anti-inflammatory drugs, *IVF* intravenous fluid, *RR* relative risk

*Adjusted for Sex, Sphincter of Oddi dysfunction, History of post-ERCP pancreatitis, Pancreatic sphincterotomy, Pre-cut sphincterotomy, Trainee involvement

Bold values indicate intervals that it is statistically significant

not demonstrate a reduction in PEP risk with a combination of prophylaxis methods, a more robust clinical trial may be necessary to demonstrate a benefit. Additionally, exploring novel PEP prophylaxis methods, such as calcineurin inhibitors, which have shown promise in both clinical and experimental settings, is a critical area for future research.

Strengths

The strength of this IPDMA is mainly due to the size and quality of the included studies. The studies were scored on quality and evaluated with validated risk of bias tools. In addition, quality was improved by checking queries directly with the authors. The combined strength of this large dataset provides unique possibilities for subgroup analyses of PEP prophylaxis while maintaining sufficient power in the majority of groups and adjusting for their PEP risk profile. Lastly, this IPDMA approach provided a comprehensive perspective of PEP prophylaxis in clinical practice while understanding the patient's characteristics which unlikely can be obtained from conventional meta-analyses.

Limitations

Nonetheless, this study also has limitations. Not all approached authors were able or willing to share data on a patient level for varying reasons. This may have introduced some selection bias and limited the power in certain subgroups of PEP prophylaxis. While this IPDMA adjusts for the variations across patients by their risk profile, the definitions of the risk factors used in the included studies were sometimes different. For example, difficult cannulation was defined as anything from > 5 to > 10 cannulation attempts; however, these variations were not significant (see Supplementary Appendix Table S4) and unlikely to have contributed to patient-level variations in the PEP risk profile. Additionally, some subgroups, particularly those examining PD stents in combination with other prophylactic measures were small, diminishing the power to identify a statistically significant impact of the strategy. Identification of small incremental changes with combination therapy compared to established treatments may also require greater sample sizes.

Conclusion

Rectal NSAIDs and peri-procedural high-volume IVF are prophylactic strategies to reduce the risk for PEP. In patients receiving rectal NSAIDs, difficult cannulation, pancreatic contrast injection, and history of PEP contribute significantly to the development of PEP and may benefit from additional prophylaxis.

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Data availability The data supporting the results and analyses presented in this paper were shared for this specific purpose by the respective authors of the included original studies. The data are available via the corresponding author of the original papers at reasonable request.

Declarations

Conflict of interest JPHD has received research funding from Gilead and Abbvie. EJMvG has received research funding from Boston Scientific, Micro-Tech, Pentax, Tae Woong, Olympus, Viatris, and Zambon Medical and served as a consultant for MTW-Endoskopie. PS has received research funding from Pentax, Boston Scientific, Micro-Tech, and The Enose Company. VK reports personal fees from Abbvie, is an advisory board participant for Cook Medical, and receives grants from Orgensis and Theraly. VSA is co-founder and chief medical officer of Origin Endoscopy Inc., Solv Endotherapy Inc. and consultant for Olympus and has received educational grants from Boston Scientific, Medtronic, Abbvie, and Chirhoclin. All other authors declare no competing interests.

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