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High Burden of Pancreatic Surgery for Intraductal Papillary Mucinous Neoplasia With Low-Grade Dysplasia and Benign Cysts: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Intraductal papillary mucinous neoplasms with low-grade dysplasia (IPMNs w/LGD) and benign cysts, including serous cystadenomas (SCAs), are common pancreatic cystic lesions (PCLs) that are better managed conservatively. The burden of patients who undergo surgical resection for these cysts is unknown. Our study aims to estimate the global prevalence of surgical resections for IPMNs w/LGD and benign cysts, as well as the pre-operative misclassification rate among all resected PCLs.

Methods: We searched the literature through September 2023 to identify full-text articles that reported the surgical histopathology of resected PCLs. A proportional meta-analysis was performed using a random-effects model, with prevalence estimates reported as pooled proportions. Subgroup analysis and meta-regression were performed based on use of endoscopic ultrasound (EUS), years of enrollment, and geographic location.

Results: Sixteen studies (n = 5830) were identified. Among all surgically resected PCLs, 24% were IPMNs w/LGD (95% CI: 18%–32%), 16% were SCAs (95% CI 13%–19%), 4% were other benign cysts (95% CI: 3%–6%), and 24% were pre-operatively misclassified (95% CI: 16%–34%). Of the resected IPMNs, 62% had LGD (95% CI: 51%–71%). An increasing use of pre-operative EUS is associated with a lower prevalence of resected SCAs ($p < 0.05$) but has not impacted the rate of resections for IPMNs w/LGD. The pre-operative misclassification of PCLs has significantly decreased over time ($p < 0.01$), although not significantly influenced by increasing EUS utilization or geographic location.

Conclusion: One quarter of PCLs are pre-operatively misclassified and ~44% are surgically resected for benign cysts or IPMNs w/LGD. Implementation of advanced diagnostic tools might improve pre-operative classification and reduce overtreatment of PCLs.

1 | Introduction

Pancreatic cystic lesions (PCLs) are common with a global prevalence ranging between 13% and 18% [1]. Each PCL type is characterized by a different biological behavior, which ranges from benign (*serous cystadenoma [SCA], pseudocyst*), premalignant (*intraductal papillary mucinous neoplasms [IPMNs] with low-grade dysplasia (LGD), mucinous cystic neoplasms [MCNs]*), and malignant (*IPMN with high-grade dysplasia/adenocarcinoma [HGD/Ca], cystic neuroendocrine tumor [cNET], solid pseudopapillary tumor [SPN]*). Current standards of care rely on a combination of clinical history, imaging, endoscopic ultrasound (EUS) features, and cyst fluid analysis to identify the lesions that would benefit the most from surgical resection [2–6]. However, these diagnostic approaches remain suboptimal, resulting in a subset of patients who undergo surgical resections for SCAs and IPMN with LGD with an unjustified high risk of post-operative morbidity (~30%) and mortality (~2%) [7].

Several studies have reported the rate of pre-operative misclassifications of PCLs and the prevalence of surgical resections for benign cysts and IPMN with LGD [8–10]. However, each individual estimate is not representative of the global population with PCLs, given the variations across studies in geographic location, pre-operative use of EUS, and years that the study was conducted. Such global estimates are necessary to understand the burden of patients who could avoid surgery if more accurate diagnostic methods are available. Within this framework, we conducted a systematic review and meta-analysis to estimate the global prevalence of surgical resections for benign cysts and IPMNs with LGD, as well as the pre-operative misclassification rate among resected PCLs. In addition, we hypothesized that more recent cohorts and increasing use of EUS have significantly decreased the rate of surgical resections for SCAs, IPMNs with LGD, and pre-operative misclassification rate. Therefore, we also conducted a meta-regression to assess the impact of temporal trends, pre-operative use of EUS, and geographic location on our estimates.

2 | Methods

2.1 | Search Strategy

A comprehensive literature search was designed and carried out by an experienced health science librarian using PubMed (including MEDLINE), Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews, from inception of each database through September 28, 2023. Searches included the following concepts: "pancreatic cyst", "surgical intervention", and "unnecessary surgery". Filters were applied to the search in PubMed and Embase to remove articles discussing only children and animal studies. Search results were exported from the individual databases and imported into EndNote. Results were then exported in XML format from EndNote and uploaded into Covidence. Items were automatically deduplicated by Covidence as they were imported [11]. The complete search strategy is available in Supporting Information S1. Findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. The study protocol was registered at the OSF registry (osf.io/zksuy).

2.2 | Study Selection

Two authors (P.D. and E.Q.) screened individual titles and abstracts of the identified studies and excluded studies that did not address the research question of interest. The full texts of the remaining studies were assessed to determine whether they met the inclusion and exclusion criteria. Any disagreements were resolved through consensus with the corresponding author (J.D.M.). Inclusion criteria involved randomized controlled trials and observational studies (prospective, retrospective, or cross-sectional design) of at least 50 patients who underwent surgical resection for PCLs and who provided final surgical histopathology. Case reports, editorials, review articles, letters to the editor, guidelines, meta-analyses, conference abstracts, and those not written in the English language were excluded. A manual search of the list of references of included studies and of the selected articles proposed by content experts was performed to complement the search.

2.3 | Data Extraction and Risk of Bias Assessment

Data extraction was conducted by two investigators (S.T. and P.D.) using a standardized form created in Microsoft Excel (Microsoft Corporation, Redmond, WA). For each of the studies, results of final surgical histopathology of the resected cysts were collected (IPMNs, MCNs, SPN, cNET, SCAs, other benign cysts, other cyst types). For IPMNs and MCNs, the degree of dysplasia was also recorded (either LGD or HGD/Ca). The number of cysts that were misclassified pre-operatively in comparison to final surgical histopathology was also recorded. Other variables extracted from each of the studies included study characteristics (years of enrollment, geographic location), demographics (age, sex), and proportion of patients who had preoperative EUS. Methodological quality of the studies was independently assessed by two investigators (S.T. and P.D.) using the Newcastle-Ottawa scale [13]. Based on a score from 0 to 9, the quality of studies was rated as low (0–3), intermediate (4–6), and high (7–9).

2.4 | Study Outcomes

Our study evaluated: (A) prevalence of resected benign cysts; (B) prevalence of resected IPMNs with LGD; (C) proportion of resected IPMNs that had LGD; and (D) pre-operative PCL misclassification rates. For resected benign cysts, the prevalence of resected SCAs and other benign cysts was recorded and reported separately. The category of other benign cysts included pseudocysts, lymphoepithelial lesions, retention cysts, and other uncommon benign cysts. The prevalence of benign cysts and IPMNs with LGD was calculated using all the resected cysts as the denominator. The proportion of resected IPMNs with LGD was calculated using the number of cysts with IPMN histology as the denominator. Pre-operative PCL misclassification was defined as a mismatch between the presumed pre-operative cyst type (e.g., IPMN, MCN, SCA) using clinical, radiographic, EUS findings and/or cyst fluid analysis, and final surgical histopathology without considering the degree of dysplasia in mucinous cysts.

2.5 | Statistical Analysis

A proportional meta-analysis was performed using logit transformation [14]. The prevalence estimates were pooled using a random-effects model and reported as proportions with corresponding 95% confidence intervals (CIs). Heterogeneity was measured using the I^2 statistic, with $I^2 \geq 50\%$ considered as considerable heterogeneity. Cochran Q test was calculated and a p-value of < 0.05 was considered as an indicator of heterogeneity. Publication bias was assessed by screening funnel plots for any asymmetry and by using the Egger regression test.

To explore sources of heterogeneity, we carried out a priori determined subgroup analyses by geographic location (Europe, North America, or Asia), pre-operative EUS use (< 50 vs. ≥ 50%), and years of enrollment (prior to 2000, 2000–2010, 2011–2021). We also conducted different meta-regression models using geographic location, proportion of pre-operative EUS, and the average year of enrollment as co-variates. For the analysis of years of enrollment, the periods that the study reported were used to report one or more average years of enrollment, with their respective reported estimates (Supporting Information S1: Table 1). Additionally, if a study or study subgroup substantially overlapped between two or more predetermined time periods (i.e., a patient population from 2007 to 2016), then these patients were excluded from this subgroup analysis. Results were reported with 2-sided p-values. Sensitivity analyses were performed using the "leave-one-out" technique. Statistical analysis was performed using R Studio (version 4.3.0).

3 | Results

3.1 | Study Selection and Quality Assessment

A PRISMA diagram with details on study selection is provided in Figure 1. Of 4270 studies, 1031 duplicates were automatically removed, and 3239 study titles were screened. A total of 22 full-text articles were reviewed, of which 16 publications fulfilled eligibility criteria, encompassing 5830 subjects who were included in the meta-analysis [8–10, 15–27]. All studies were rated as high quality using the Newcastle- Ottawa scale (Supporting Information S1: Table 2). Visual inspection of the funnel plots and Egger's test showed no evidence of publication bias (Supporting Information S1: Figure 1).

3.2 | Study Characteristics

Table 1 summarizes the characteristics of the included studies. Nine studies were conducted in Europe (Germany, Italy, Netherlands, Italy, Spain, Sweden, Belgium, Serbia, Finland) [8, 9, 15, 17, 20, 22–24, 27], four in North America (all in the United States) [10, 18, 19, 25], two in Asia (India, Singapore) [16, 21] and one across multiple continents [26]. All studies were of retrospective cohort design, of which three enrolled subjects from multiple centers [16, 26, 27]. Enrollment in these studies ranged from 1983 to 2021.

Eleven studies reported the proportion of patients who had pre-operative EUS ($n = 4453$) [8–10, 16–18, 20–22, 24, 25]. Ten studies reported the pre-operative classification for all resected PCLs ($n = 2651$) [8–10, 15, 17–20, 22, 23]. All the studies provided a histopathologic diagnosis of IPMN from resected specimens ($n = 2659$), of which thirteen reported the degree of dysplasia (HGD/Ca [1177] vs. LGD [1226]) [8, 10, 16, 18–27]. One study included only IPMNs with dysplasia classification [27], while the other fifteen included a variety of the different cysts (MCNs: 1044; SCAs: 835; SPNs: 441; cNETs: 222, others: 629) [8, 16, 18, 19, 24–26].

3.3 | Prevalence of Benign Cysts

The pooled prevalence of resected SCAs was 16% (95% CI: 13%–19%; I^2 89%; Figure 2A). Using the "leave-one-out" technique, the pooled prevalence of resected SCAs ranged from 14% to 16% (Supporting Information S1: Figure 2). On subgroup analysis, the prevalence of resected SCAs was significantly reduced when ≥ 50% of patients had pre-operative EUS (12%) as compared to when EUS was used less frequently (19%, $p < 0.001$, Table 2). This was confirmed by meta-regression, showing an inverse correlation between the proportion of EUS procedures and surgical resection for SCAs ($p = 0.01$), with a higher proportion of EUS procedures resulting in a lower prevalence of surgical resection for SCAs (Figure 3A). On subgroup analysis by continent, the prevalence of resected SCAs was significantly higher in Asia (22%) compared to Europe (15%) and North America (13%) ($p < 0.001$; Table 2). However, this difference was not observed on meta-regression by continent ($p = 0.20$; Figure 3B). Surgical resection of other benign cysts represented 4% of all resections (95% CI: 3%–6%; I^2 86%; Figure 2B) and ranged from 4% to 5% using the "leave-one-out" technique (Supporting Information S1: Figure 3).

3.4 | Prevalence of Resected IPMNs With LGD

The pooled prevalence of resected IPMNs with LGD among all resected PCLs was 24% (95% CI: 18%–32%; I^2 93%; Figure 2B). The pooled prevalence estimate ranged from 22% to 27% on sensitivity analysis with the "leave-one-out" technique (Supporting Information S1: Figure 4). There was no impact on the proportion of EUS procedures performed or geographic location on the prevalence of resected IPMNs with LGD (Table 2).

Of the resected IPMNs, the proportion of IPMNs with LGD was 62% (95% CI: 51%–71%; I^2 91%; Figure 2C). Using the "leave-one-out" technique, the proportion of resected IPMNs with LGD among resected IPMNs ranged from 59% to 64% (Supporting Information S1: Figure 5). Similarly, subgroup analysis and meta-regression showed no association of this proportion with either proportion of pre-operative EUS or continent (Table 2).

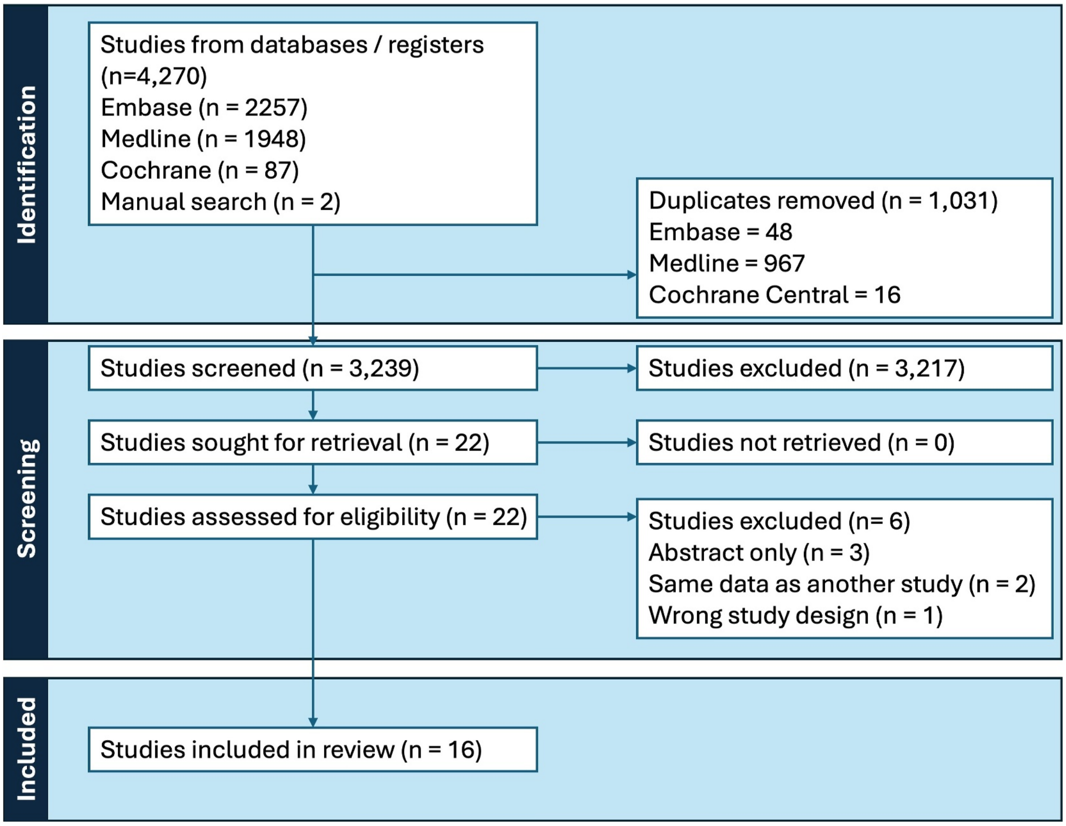

FIGURE 1 | PRISMA diagram summarizing the search and review strategy.

3.5 | Prevalence of Pre-operative Misclassification Rate

The pooled prevalence of pre-operatively misclassifying a PCL was 24% (95% CI: 16%–34%; I^2 95%; Figure 2D). A sensitivity analysis was conducted excluding patients with an unspecified pre-operative cyst diagnosis, resulting in similar estimates (25%; 95% CI: 17%–35%; I^2 94%) (Supporting Information S1: Figure 6). On sensitivity analysis using the "leave-one-out" technique, pre-operative misclassification ranged from 21% to 26% (Supporting Information S1: Figure 7).

On subgroup analyses by years of enrollment, there was a progressive reduction in PCL misclassification over time from 50% prior to 2000, 35% between 2000 and 2010%, and 22% between 2011 and 2021 ($p = 0.01$; Table 2). This trend was confirmed in meta-regression, with a lower risk of PCL misclassification in contemporary cohorts ($p < 0.01$; Figure 3C). A higher proportion of pre-operative EUS was not associated with reduction in cyst misclassification (Figure 3D). Similarly, there was no significant difference in cyst misclassification across continents (Figure 3E).

4 | Discussion

Of all surgical resections for pancreatic cysts, nearly half are performed for benign cysts or IPMNs with LGD. Although surgical resections for SCAs seem to be dropping with increasing use of EUS, the rate of surgical resections for IPMNs with LGD remains stagnant regardless of EUS utilization. The risk of cyst misclassification prior to surgical resection occurred in a quarter of patients and seems to be dropping in contemporary cohorts, but this effect does not appear to be related to increasing use of EUS. Our findings portray the need for better diagnostic tools that can differentiate PCLs more accurately prior to surgical decisions.

Surgical resection of PCLs is currently driven using society guidelines and multidisciplinary discussions between surgeons, radiologists, and gastroenterologists [2–6]. In the absence of histopathology, these decisions rely on cross-sectional imaging, EUS and cyst fluid analysis (carcinoembryonic antigen [CEA], glucose, amylase, and cytology), which predict cyst type and the degree of dysplasia/neoplasia with suboptimal accuracy [23, 28, 29]. This explains why pre-operative diagnosis and gold-standard surgical histopathology did not correlate with 24% of PCLs in our study. Importantly, this estimate has declined over time, with individuals who underwent a surgical resection after 2010 having a one-in-five chance of misclassification. This cohort effect is likely explained by improvements in MRI technologies and refinements of evidence-based guidelines. However, we found that increasing EUS utilization has not improved the pre-operative classification of PCLs on meta-regression. This may be explained by variability in EUS learning curves and substantial interobserver variability across endosonographers in differentiating PCLs based on cyst morphology, particularly in unilocular cysts [30, 31]. Even with fine needle aspiration, both CEA and cytology offer limited diagnostic value with sensitivity < 60% and

TABLE 1 | Characteristics of the studies included in the systematic review.

	Study design/Population								Final histopathology (*n*, %)										
	Years of enrollment	Continent	Country	Number of centers	Number of patients	Mean/Median age (± SD or IQR)	Female (*n*, %)	Pre-op EUS (*n*, %)	IPMN	IPMN (HGD/Ca)	IPMN (LGD)	MCN	MCN (HGD)	MCN (LGD)	SPN	cNET	SCA	Other[a]	Pre-op mis-classification (*n*, %)
Aleksandric 2020	1983–2013	Europe	Serbia	1	66	54 ± 17	54 (82)	NR	0 (0)	NR	NR	37 (56)	NR	NR	0 (0)	0 (0)	29 (44)	0 (0)	5 (8)
Chaudhari 2019	2007–2016	Asia	India	7	423	41 (NR)	328 (78)	70 (17)	34 (8)	12 (3)	22 (5)	128 (30)	15 (4)	113 (27)	121 (29)	16 (4)	98 (23)	26 (6)	NR
Cho 2013	1999–2011	North America	USA	1	74	59 ± NR	56 (76)	48 (65)	20 (27)	4 (5)	16 (22)	34 (46)	9 (12)	25 (34)	2 (3)	1 (1)	14 (19)	3 (4)	NR
Correa-Gallego 2010	2000–2008	North America	USA	1	136	61 ± 15	82 (60)	NR	61 (45)	13 (10)	48 (35)	25 (18)	1 (1)	24 (18)	9 (7)	8 (6)	22 (16)	11 (8)	41 (30)
De Pretis 2017	2000–2012	North America	USA	1	174	NR	NR	111 (64)	88 (51)	57 (33)	31 (18)	24 (14)	NR	NR	NR	NR	17 (10)	45 (26)	52 (30)
Del Chiaro 2013	2004–2012	Europe	Sweden	1	141	60 (NR)	81 (57)	31 (22)	73 (52)	NR	NR	25 (18)	NR	NR	8 (6)	0 (0)	33 (23)	2 (1)	54 (38)
Giannone 2022	2009–2019	Europe	Italy	1	585	64 (15)	341 (58)	393 (67)	364 (62)	213 (36)	151 (26)	78 (13)	NR	NR	45 (8)	3 (1)	62 (11)	33 (6)	83 (14)
Goh 2020	1998–2018	Asia	Singapore	1	462	59 (NR)	58.7 (13)	123 (27)	131 (28)	26 (6)	105 (23)	61 (13)	NR	NR	42 (9)	23 (5)	100 (22)	105 (23)	NR
Honselmann 2016	2001–2011	Europe	Germany	1	141	64 (53–73)	106 (75)	17 (12)	55 (39)	20 (14)	35 (25)	9 (6)	NR	NR	6 (4)	7 (5)	23 (16)	41 (29)	77 (55)
Kleeff 2015	2007–2014	Europe	Germany	1	86	68 (NR)	50 (58)	54 (63)	53 (62)	6 (7)	47 (55)	13 (15)	2 (2)	11 (13)	3 (3)	0 (0)	14 (16)	3 (3)	16 (19)
Roldan 2023	1990–2020	North America	United States	1	1290	60 (NR)	774 (60)	805 (62)	658 (51)	352 (27)	306 (24)	203 (16)	25 (2)	178 (14)	54 (4)	100 (8)	168 (13)	107 (8)	NR
Salvia 2012	2000–2010	Europe	Italy	1	476	53 ± 15	311 (65)	70 (15)	183 (38)	NR	NR	101 (21)	NR	NR	36 (8)	14 (3)	64 (13)	78 (16)	92 (19)
Salvia 2023	2011–2020	Europe	Italy	1	601	61 (NR)	385 (64)	301 (50)	278 (46)	160 (27)	118 (20)	117 (19)	22 (4)	95 (16)	79 (13)	17 (3)	55 (9)	55 (9)	81 (13)
Springer 2019	2012–2016	[b]	USA, Italy, South Korea, Japan	16	862	64 (52–72)	560 (65)	NR	447 (52)	236 (27)	211 (24)	153 (18)	15 (2)	138 (16)	23 (3)	29 (3)	115 (13)	95 (11)	NR
Tamburrino 2023	2006–2015	Europe	Italy, Finland, Belgium, Spain	7	66	66 (NR)	NR	NR	66 (100)	26 (39)	40 (61)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR

(Continues)

TABLE 1 | (Continued)

	Study design/Population								Final histopathology (n, %)										
	Years of enrollment	Continent	Country	Number of centers	Number of patients	Mean/Median age (± SD or IQR)	Female (n, %)	Pre-op EUS (n, %)	IPMN	IPMN (HGD/Ca)	IPMN (LGD)	MCN	MCN (HGD)	MCN (LGD)	SPN	cNET	SCA	Other[a]	Pre-op mis-classification (n, %)
Van Huijgevoort 2023	2006–2021	Europe	Netherlands	1	247	60 ± 14	142 (57)	NR	148 (60)	52 (21)	96 (39)	36 (15)	NR	NR	13 (5)	4 (2)	21 (9)	25 (10)	71 (29)

Abbreviations: Ca = carcinoma, cNET = cystic neuroendocrine tumor, HGD = high-grade dysplasia, IPMN = intrapapillary mucinous neoplasm, LGD = low-grade dysplasia, MCN = mucinous cystic neoplasm, NR = not reported, SCA = serous cystadenoma, SPN = solid pseudopapillary neoplasm.
[a]Other cysts include ductal adenocarcinoma, acinar cell adenoma, acinar cell carcinoma, anaplastic carcinoma, hepatoid carcinoma, pancreatoblastoma, granular cell tumor, leiomyoma, mixoid tumor, pseudocysts, lymphoepithelial cysts, retention cyst, simple cyst, lymphangioma, gastrointestinal stromal tumor, duplication cyst.
[b]Multiple continents (Asia, Europe, and North America).

may not significantly improve the classification of cysts with EUS [32]. While emerging evidence shows that glucose can distinguish mucinous from non-mucinous cysts with greater accuracy, this test was not standard practice when the studies were conducted and does not allow diagnosis of cyst type or degree of dysplasia [32]. This underscores the need to adopt more accurate and reliable tools in clinical practice such as through the needle biopsies, molecular analysis, and confocal laser endomicroscopy to improve pre-operative classification of PCLs [33–35].

Our meta-analysis found that 20% of resected cysts are benign cysts. Symptomatic benign cysts may represent a subset of this estimate, and in those settings, surgical resection may be justified. However, a surgical resection of benign cysts, especially SCAs, is often performed when the cyst is pre-operatively suspected to be malignant. Some SCAs with oligocystic morphology or presumed ductal communication can be misclassified as IPMNs or other cyst types [36]. The strong fibrotic component of SCAs, especially when microcystic, may mimic a mural nodule, a solid component, or cyst wall enhancement, which may precipitate surgical resection [37, 38]. Our study also showed that the prevalence of surgical resections for SCAs has declined with increasing implementation of EUS, which can show typical microcystic lesions with a honeycomb pattern. However, even in studies where EUS was performed in most of the cohort, the prevalence of SCA resection was still 12%. This supports the use of advanced modalities to more accurately diagnose SCAs and prevent unnecessary surgical resections for this type of cyst. For example, cyst fluid analysis for VHL mutations has been shown to diagnose SCAs with 99% specificity and 56% sensitivity [32]. Confocal laser endomicroscopy revealing a typical fern-pattern of vascularity allows diagnosing SCAs with similar specificity to molecular analysis, but with higher sensitivity (95%) [39]. Additionally, histological diagnosis may be possible for a subset of SCAs with fine needle biopsies or through the needle biopsy forceps [40, 41]. The prevalence of other resected benign cysts was rare and only reported in 4% of surgical resections.

The diagnosis of mucinous cysts can be made highly accurately with conventional diagnostic modalities. However, the stratification of dysplasia among IPMNs remains a major challenge. In our study, IPMNs with LGD represented a quarter of all cyst resections and near two thirds of IPMN resections, which exemplifies the real-world issues with current standards of care to distinguish HGD/Ca from LGD. Although EUS has become a mainstay in the evaluation of IPMNs and is recommended by all major guidelines prior to surgical decisions, we found that the increasing use of EUS has not impacted the rate of surgical resections for IPMN with LGD. To reduce this gap, the recent Kyoto guidelines support testing for TP53, SMAD4, CDKN2A and PIK3CA mutations, which have been shown to differentiate HGD/Ca and LGD in IPMNs with ≥ 95% specificity albeit low sensitivity [6, 32]. Using a DNA/RNA-based next-generation sequencing panel of 74 genes, advanced neoplasia can be diagnosed with 100% specificity and 82% sensitivity [42]. Confocal laser endomicroscopy also has the ability to differentiate HGD/Ca from LGD with 100% specificity and 88% sensitivity by quantifying the epithelial width and darkness of papillary structures (HGD/Ca demonstrates large papillary structures with thick and dark epithelium) [43]. Although these tests may

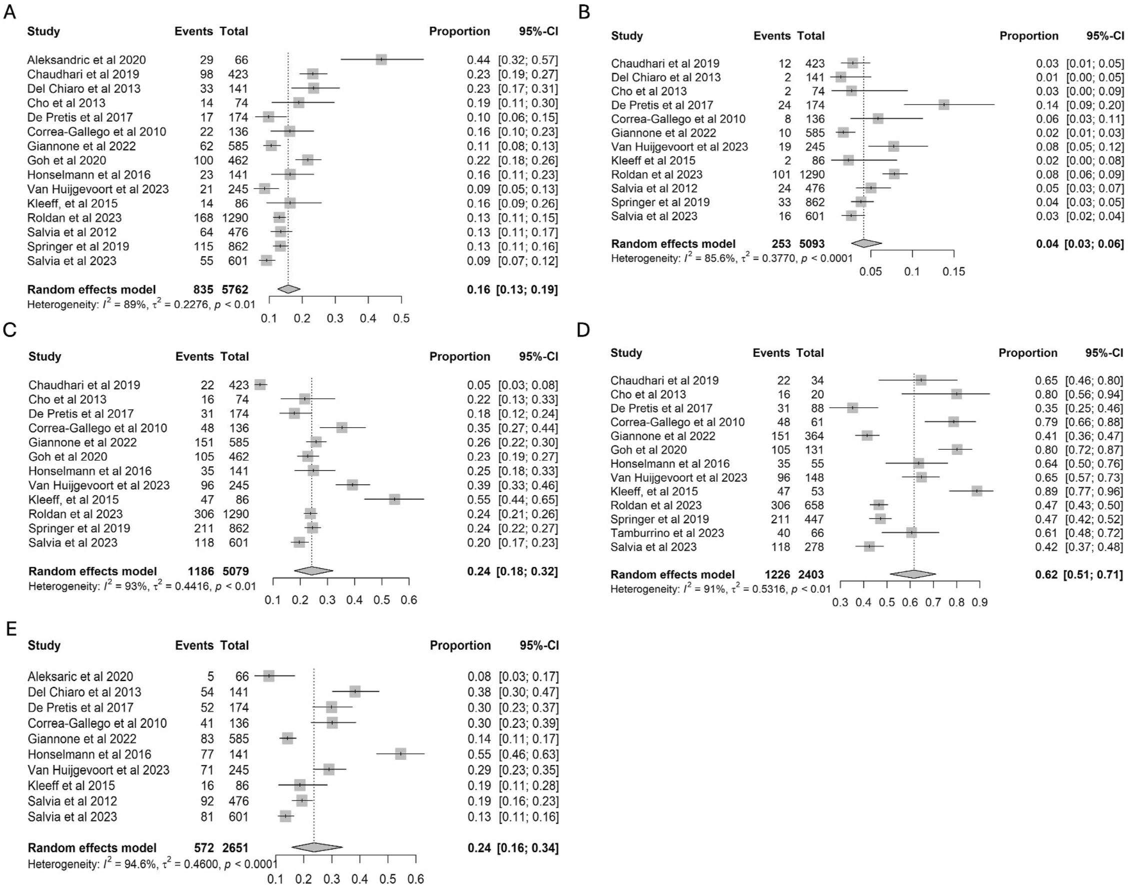

FIGURE 2 | Forest plot reporting prevalence of pre-operative misclassification of resected PCLs. (A) Prevalence of SCA among resected PCLs. (B) Prevalence of other benign cysts among resected PCLs. (C) Prevalence of IPMNs with LGD among resected PCLs. (D) Prevalence of IPMNs with LGD among resected IPMNs. (E) Misclassification rate of resected PCLs.

reduce surgeries for IPMN with LGD, they share problems with equity and accessibility even within academic institutions.

Our study has some limitations. There was a high degree of heterogeneity between the studies. This is expected in proportional meta-analyses reporting prevalence estimates due to differences in the time and location where the included studies were conducted [14]. To mitigate this, extensive pre-planned subgroup analysis, meta-regressions, and sensitivity analyses were conducted. Most studies were conducted at large referral centers, possibly leading to selection bias and making our findings not generalizable to non-expert centers, where the complexity of PCLs or multidisciplinary expertise may differ. Additionally, only two studies from Asia (n = 885) were included, and none from Africa, Australia, or South America. This may impact the generalizability of our results, which may not fully reflect global practices. Although we measured the proportion of EUS utilization across studies, studies did not report data on final needle aspiration/biopsy, molecular analysis, or confocal laser endomicroscopy. Studies also did not systematically report on the indication for surgical resection, making it difficult to assess the appropriateness of these procedures. For example, resecting a large symptomatic SCA or IPMN with LGD would be appropriate. Similarly, resection of an IPMN with LGD might be justified in a young patient without comorbidities if several worrisome and/or high risk features are present, with the goal of decreasing progression to HGD/Ca. Other individual covariates such as age, comorbidities, and morphologic features were only present as aggregates, but individual level meta-analysis with these variables was not possible.

Our study has several implications. Understanding the rates of surgical resections for IPMNs with LGD and benign cysts can guide shared decision-making conversations regarding the risk of resecting cystic lesions that histologically do not warrant surgery. Our estimates justify a wider implementation of advanced diagnostic tools for PCLs in clinical practice as a measure to reduce unnecessary surgical resections. Our results can inform the development of quality benchmarks for surgical resections of PCLs. Finally, our findings highlight the need for novel biomarkers to better stratify PCLs preoperatively.

In conclusion, benign cysts and IPMNs with LGD account for ~44% of all surgically resected PCLs. Preoperative classification of PCL is a challenging endeavor, with one in every four patients being misclassified pre-operatively. Although there have been improvements in the pre-operative diagnosis of PCLs over the past few decades, surgical overtreatment remains a pervasive problem in the management of PCLs. Further discovery and

TABLE 2 | Subgroup analyses and meta-regressions for primary outcomes based on pre-operative EUS use, years of enrollment, and location.

	Subgroup analyses					Meta-regression[a]
	Number of studies (K)	Number of patients (*n*)	Pooled prevalence (% (95% CI))	I^2 (%)	*p*-value	*p*-value
Prevalence of SCAs among resected PCLs	15	5762	16 (13–19)	89		
Prevalence by Pre-operative EUS					< 0.001	0.01
< 50% of study population	5	1643	19 (16–23)	78		
≥ 50% of study population	6	2810	12 (10–14)	60		
Prevalence by Continent					< 0.001	0.20
North America	4	1794	13 (12–15)	39		
Europe	8	2409	15 (11–22)	91		
Asia	2	885	22 (20–25)	0		
Prevalence of IPMNs with LGD among resected PCLs	12	5079	24 (18–32)	93		
Prevalence by Pre-operative EUS					0.19	0.11
< 50% of study population	3	1026	15 (6–31)	96		
≥ 50% of study population	6	2810	26 (18–35)	90		
Prevalence by Continent					0.12	0.27
North America	4	1794	24 (19–31)	77		
Europe	5	1660	31 (22–43)	94		
Asia	2	885	11 (4–29)	98		
Prevalence of IPMNs with LGD among resected IPMNs	13	2403	62 (51–71)	91		
Prevalence by Pre-operative EUS					0.16	0.43
< 50% of study population	3	1026	72 (71–80)	71		
≥ 50% of study population	6	2810	57 (38–74)	88		
Prevalence by Continent					0.19	0.39
North America	4	1794	60 (39–78)	91		
Europe	6	1726	61 (46–74)	92		
Asia	2	885	75 (64–85)	72		
Misclassification rate	10	2651	24 (16–34)	95		
Prevalence by Time of Enrollment					0.01	< 0.01
Prior to 2000	3	229	42 (6–90)	77		
2000–2010	10	1531	33 (26–41)	84		
2011–2021	6	1596	23 (18–29)	66		
Prevalence by Pre-operative EUS					0.03	0.10
< 50% of study population	3	758	36 (10–75)	97		
≥ 50% of study population	4	1446	18 (10–30)	89		
Prevalence by Continent					0.17	0.48
North America	2	310	30 (8–67)	—		
Europe	8	2341	22 (13–35)	96		

Abbreviations: EUS = endoscopic ultrasound, IPMN = intrapapillary mucinous neoplasm, LGD = low-grade dysplasia, PCLs = pancreatic cystic lesions, SCAs = serous cystadenomas.

[a]For meta-regression, EUS proportion treated as a continuous variable and average year of enrollment for each study subgroup treated as a continuous variable.

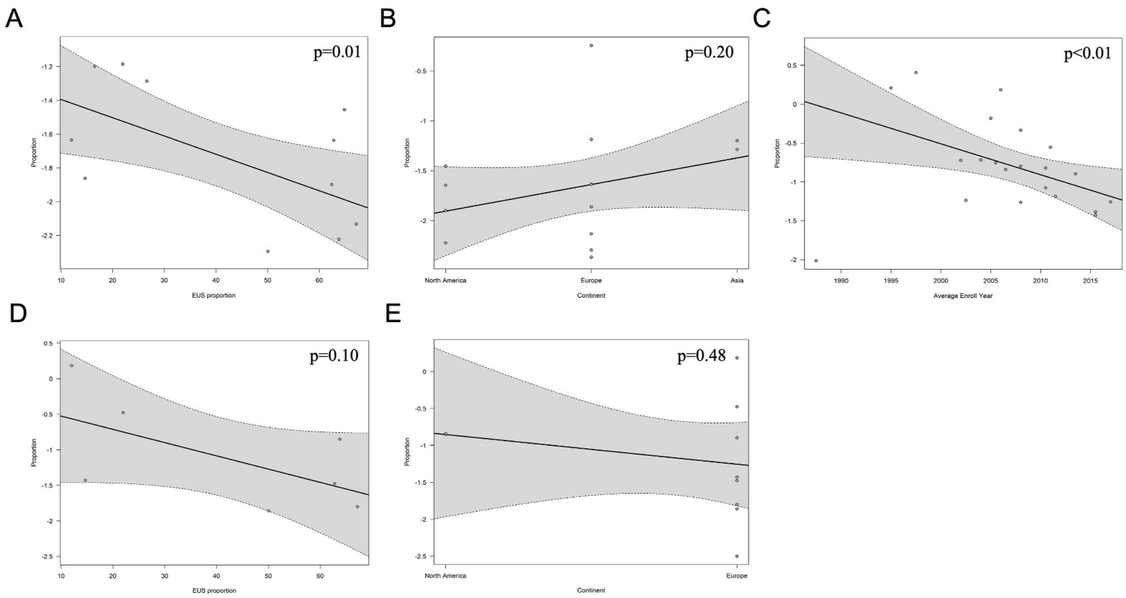

FIGURE 3 | Meta-regression bubble plots reporting (A) SCA based on percentage of preoperative EUS, (B) SCA based on continent, (C) misclassification rate based on average year of patient enrollment (D) misclassification rate based on percentage of preoperative EUS, and (E) misclassification rate based on continent.

implementation of novel diagnostic tools are needed to more accurately guide surgical decisions of PCLs.

Author Contributions

Study concept and design: S.T., J.D.M., A.F., G.C. Statistical analysis: U.J.L. Drafting of the manuscript: S.T., P.D., J.D.M. Generation of data: S.T., P.D., E.Q., F.H. Data interpretation and final approval of the manuscript: all authors

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Conflicts of Interest

Jorge D. Machicado is funded by an ACG Junior Faculty Career Development Award and Robert A. Winn Diversity in Clinical Trials Career Development Award, and served on the advisory board of Amgen LCM. The other authors have no competing interests to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
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