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REVIEW ARTICLE

Efficacy of endoscopic interventions versus surgery for pain management in patients with chronic calcific pancreatitis: a systematic review and meta-analysis

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Abstract

Introduction Chronic calcific pancreatitis (CCP) is a debilitating inflammatory condition characterized by the accumulation of calcific deposits in the pancreatic tissue, leading to chronic abdominal pain and functional insufficiencies. This study aims to systematically review and meta-analyse comparative studies assessing the efficacy of endotherapy versus surgery in managing CCP-related pain.

Methods MEDLINE, EMBASE, and Cochrane library (CENTRAL and CDSR), from inception to October 2023, were searched. The inclusion criteria encompassed randomized controlled trials (RCTs) and non-randomized controlled trials (NRS), and cohort studies comparing endoscopic interventions to surgery for pain management in patients with CCP. Pain relief, procedural technical success, and procedural-related complications were the outcomes of interest. Two review authors (CN, KK) independently assessed study eligibility criteria and performed data extraction. Using a random-effects model, pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated. The level of certainty of the evidence was assessed using the GRADE approach.

Results Five studies were included. For the outcome of pain relief, a meta-analysis of five studies (3 RCTs and 2 cohort studies) demonstrated a significant therapeutic effect in favour of surgery with an OR of 2.36 (95% CI: 1.12 to 5.00, $I^2 = 41.70$), with moderate level of certainty of evidence. In the analysis of five studies (3 RCTs, 1 NRS and 2 cohort studies), procedural technical success was comparable between the two groups (OR of 3.02, 95% CI: 0.47 to 19.59, $I^2 = 79.27\%$) as were adverse events (OR 1.31, 95% CI: 0.47 to 3.70, $I^2 = 50.93\%$).

Conclusion In conclusion, this systematic review and meta-analysis suggest that surgery may be more effective in relieving pain in patients with CCP compared to endoscopic interventions. Disease stage may be important to determine the appropriateness of each procedure.

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Keywords Chronic pancreatitis · ERCP · Sphincterotomy · Pancreatic duct stenting · Pancreatic stone retrieval · Surgery · Pain management · Lithotripsy

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Chronic calcific pancreatitis (CCP) is a progressive inflammatory disorder of the pancreas. Accumulation of calcific deposits within the pancreatic tissue is a distinctive feature, particularly within the ductal system resulting in increased ductal pressures. The process of chronic inflammation, calcification, and parenchymal fibrosis can significantly impair the function of the pancreas, resulting in endocrine and exocrine insufficiencies. However ultimately, the symptom that casts the most pronounced shadow on a patient's daily life is chronic pain [1]. The origin of pain in CCP is multifactorial and complex. Persistent inflammation and consequential fibrosis with ductal obstruction by calculi result in increased intraductal pressure and ischaemia, pancreatic duct hypertension, pseudocysts, and autodigestion of the pancreas [1–3]. These pathophysiological phenomena are regarded as the primary mechanism of CCP-related pain.

Addressing CCP-related pain remains a therapeutic challenge for clinicians. Numerous endoscopic and surgical interventions have been explored to alleviate debilitating abdominal pain and improve patients' quality of life. While both modalities are based on the principle of decompressing the obstructed pancreatic duct system, their mechanisms, risks, benefits, and long-term outcomes differ vastly [4–6]. Endoscopic interventions including sphincterotomy, pancreatic duct stricture dilatation, pancreatic duct stenting, and pancreatic stone removal all aim to facilitate drainage and decrease pancreatic ductal pressure by reducing stone burden and restoring pancreatic duct flow [7]. The addition of extracorporeal lithotripsy (ESWL) to endotherapy might have further reduced the need for decompressive surgery by enabling the fragmentation and extraction of large stones. Ultimately, pancreatic endotherapy is a well-established and safe alternative to decompressive surgery for CCP-related pain. However, the effect of endotherapy markedly decreases over time. Thus, currently and in select cases, endotherapy serves as a bridge to more definitive surgical intervention [8]. Surgical approaches include side-to-side or lateral pancreatico-jejunostomy [9] or total pancreatectomy with autologous islet cell transplantation [10]. Although surgical resection may provide superior long-term pain relief, it carries a considerable risk of morbidity and mortality with a complication rate of 6–30% and mortality rate of 0–2% [10]. This study aims to systematically review and meta-analyse comparative studies to assess the efficacy of endotherapy versus surgery in managing pain associated with CCP.

Methods

This study was a systematic review and meta-analysis of comparative studies (randomized controlled trials, non-randomized control trials, cohort studies) evaluating the efficacy and safety of endoscopic interventions versus surgery in the management of pain in patients with chronic calcific pancreatitis. This study is registered on PROSPERO (CRD42023476153). This study conforms to the PRISMA guideline for systematic reviews and meta-analyses.

Search strategy

A comprehensive literature search was conducted to identify relevant studies. The following electronic databases were searched from inception to April 25 2024: MEDLINE, Embase, and Cochrane (CENTRAL and CDSR) via Ovid. The search strategy was developed by a health information specialist (YY) with extensive experience in developing search strings for systematic reviews using a combination of medical subject headings (MeSH) terms and keywords related to chronic pancreatitis, pain, endoscopy, and surgery. For the complete search string, refer to Supplemental Data, Search Strategy. Four investigators (CN, KK, KP, TH) screened all the titles and abstracts and full text of potentially relevant studies. Two reviewers (CN, KK) then used a standardized data extraction form to extract study design, population characteristics, intervention data, outcomes, and adverse events. Inclusion criteria consisted of randomized controlled trials, non-randomized controlled trials, and cohort studies comparing endoscopic interventions including sphincterotomy, pancreatic duct stricture dilatation, pancreatic duct stenting, pancreatic duct stone removal, to surgery for pain management in patients with chronic calcific pancreatitis. Studies that reported pain relief as the primary or secondary outcome measured in the Izbicki Pain Score, reduction in doses of analgesics, McGill Pain Questionnaire, SF-36 questionnaire, and other relevant pain indicators were also included. Studies lacking sufficient data on pain outcomes were excluded (Table 1, 2, 3).

Outcomes assessed

The primary outcome of this study was pain relief evaluated after a follow-up period post-intervention. Pain relief definitions varied between studies but included reductions in Izbicki pain scores of greater or equal than 10 at follow-up compared to index and clinical responses to measure pain relief, with pain relief defined as complete absence of pain or attacks in patient surveys at follow-up. Precise definitions used in primary studies as well as follow-up periods are found in Table 4. Secondary outcomes included comparative measures of procedural technical success, which were defined as the successful resolution of pancreatic duct obstructions, the removal of calculi, and the restoration of normal pancreatic function; and the occurrence of adverse events such as pancreatitis, pseudocysts, infected collections, pancreatic fistulas, other procedural-related

Table 1 General characteristics of studies

Study	Location	Study design	Centres involved	Article type	Patients (surgery; endotherapy)	Endotherapy interventions	Surgical interventions	Outcomes measured
Dite et al., 2003 [15]	The Czech Republic	Non-randomized control trial	1	Full Text	140 (76; 64)	Pancreatic Sphincterotomy, dilation of Strictures, Stenting, Stone extraction, Mechanical lithotripsy	Resection for localized disease, Drainage for diffuse disease with ductal dilation	Clinical response (complete, partial, none), Necessity for further interventions (endoscopic, surgical), Other invasive measures
Cahen et al., 2007 [5]	The Netherlands	Randomized control trial	1	Full Text	39 (20; 19)	Stone extraction, Lithotripsy, Stenting	Pancreatico-jejunostomy, Whipple procedure, Frey procedure	Izbicki pain score, Pain relief (complete, partial, none), Conversion to surgery, technical success, Adverse Events, Death, Hospital Stay, Exocrine and Endocrine Function Tests
Cahen et al., 2011 [6]	The Netherlands	Randomized control trial	1	Full Text	33 (15; 16)	Stone extraction, Lithotripsy, Stenting	Pancreatojejunostomy, Whipple procedure, Frey procedure	Izbicki pain score, Pain relief (complete, partial, none), Conversion to surgery, technical success, Adverse Events, Death, Hospital Stay, Exocrine and Endocrine Function Tests
Hong et al., 2011 [16]	China	Cohort study	3	Full Text	62 (35;27)	ERCP (no specific details on which interventional method was done)	Pancreato-lithotomy, Duodenum preserving pancreatic head resection (DPPHR), Limited pancreatic head excision (Frey procedure)	Izbicki pain score, Success of stone removal, Number of procedures, Hospital stay, Adverse events, Readmission, Recurrence of pancreatic stones, Death
Jiang et al., 2018 [17]	China	Cohort study	1	Full Text	86 (46;40)	Pancreatic electroshock wave lithotripsy	Pancreatojejunostomy	Pain relief, Morbidity, Hospital stay, Changes in pancreatic function, medical expense

Table 2 Certainty assessments of outcomes; GRADE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopy	Surgery	Relative (95% CI)	Absolute (95% CI)		
Pain Relief												
4	randomised trials and observational studies	serious	not serious	not serious	Serious [a]	none	45/139 (32.4%)	77/157 (49.0%)	OR 2.360 (1.115 to 4.996)	204 more per 1,000 (from 27 to 337 more)	⨁⨁⨁◯ Moderate	Critical
Technical Success												
5	randomised trials and observational studies	serious	Serious [b]	not serious	Serious [a]	publication bias strongly suspected [c]	136/168 (81.0%)	177/192 (92.2%)	OR 3.022 (0.466 to 19.587)	51 more per 1,000 (from 76 fewer to 74 more)	⨁◯◯◯ Very low	Important
Adverse Events												
5	randomised trials and observational studies	serious	Serious [b]	not serious	Serious [a]	none	21/168 (12.5%)	30/192 (15.6%)	OR 1.312 (0.465 to 3.698)	39 more per 1,000 (from 77 fewer to 250 more)	⨁⨁◯◯ Low	Important

CI confidence interval, *OR* odds ratio; explanations: a. wide confidence interval, b. high i^2 value. c. low egger's p value

Table 3 Technical success definitions

Study	Technical success
Dite et al., 2003 [15]	Technically successful endoscopic treatment was defined as complete stone extraction or successful drainage of strictures and repeated stenting
Cahen et al., 2007 [5]	Technical success included sphincterotomy, stent placement, and stone extraction. Treatment was considered to have failed in patients whose treatment was converted from endoscopic drainage to surgery and in those who died because of treatment
Cahen et al., 2011 [6]	Technical success included sphincterotomy, stent placement, and stone extraction. Treatment was considered to have failed in patients whose treatment was converted from endoscopic drainage to surgery and in those who died because of treatment
Hong et al., 2011 [16]	Treatment was considered successful if pancreatic duct stone removal was achieved
Jiang et al., 2018 [17]	Technically successful endoscopic treatment was defined as complete stone extraction and stent placement

Table 4 Pain relief definitions

Study	Pain relief
Dite et al., 2003 [15]	Pain relief was classified as complete (absence of pain or attacks), partial (a reduction in pain of at least three points on the Melzack score), or none (similar pain/attacks, or even increased pain) Follow-up was conducted after 5 years
Cahen et al., 2007 [5]	Pain relief at the end of follow-up was classified as complete (Izbicki pain score, ≤ 10) or partial (Izbicki pain score, > 10 after a decrease of $> 50\%$) Follow-up was conducted after 2 years
Cahen et al., 2011 [6]	Pain relief at the end of follow-up was classified as complete (Izbicki pain score, ≤ 10) or partial (Izbicki pain score, > 10 after a decrease of $> 50\%$) Follow-up was conducted after 7 years
Jiang et al., 2018 [17]	Pain relief defined as complete absence of pain or attacks in patient surveys at follow-up Mean follow-up time was 65 ± 13.6 months

complications and death was collected. All types of adverse events recorded in each study are described in Table 5.

Statistical analysis

The statistical analysis was performed using random-effects models. Forest plots were generated for each outcome of interest. For the primary and secondary outcomes, the odds ratio (OR) with 95% confidence intervals (CI) was calculated. To examine the heterogeneity between study results, the I^2 statistic was employed. $I2 >= 50\%$ was considered substantial heterogeneity. The potential for publication bias was assessed by visual inspection of the generated funnel plots and use of the Egger's test [11]. Risk of bias was assessed by Cochrane ROB 2.0 for RCTs [12], NOS scale [13] for non-randomized studies and cohort studies. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was utilized to systematically rate the certainty of evidence across various study designs, taking into consideration factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias [14]. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using STATA 17.

Results

Studies

An initial 951 studies were identified from our literature search (Supplementary Data). Of these, 946 were excluded from the study due to a lack of fulfilment of inclusion criteria. The five [5, 6, 15–17] included studies yielded a total of 360 patients between endotherapy (168) and surgery (192) groups. Of these studies, 2 were randomized control trials, 1 was a non-randomized control trial, and 2 were retrospective cohort studies (Table 1). The risk of bias across all studies is outlined in Table 2.

Primary outcome

Pain relief

The meta-analysis of four studies included a total of 296 patients comparing pain relief in endotherapy (139) and surgery (157). Surgery was associated with 2.4 times greater pain relief in comparison to endotherapy (OR of

Table 5 Adverse events

Study	Adverse events
Dite et al., 2003 [15]	Endoscopy: adverse events recorded in endoscopy included bleeding, post-ERCP acute pancreatitis, and pancreatic abscess. No mortality was present Surgery: adverse events recorded in surgery acute pancreatitis, fistulas, ileus and anastomotic leakage. No mortality was present
Cahen et al., 2007 [5]	Endoscopy: adverse events recorded in endoscopy included stent-related complications, pancreatitis, cholecystitis, and a skin wound from shock-wave lithotripsy. One patient died from a duodenal ulcer following shock-wave lithotripsy. The overall mortality rate for endoscopy was 5% Surgery: adverse events recorded in surgery included leakage of anastomosis, bleeding from operative site, pneumonia, and wound infection. No mortality was present
Cahen et al., 2011 [6]	Endoscopy: adverse events recorded in endoscopy included stent-related complications, pancreatitis, cholecystitis, and a skin wound from shock-wave lithotripsy. No mortality related to pancreatitis was present Surgery: adverse events recorded in surgery included leakage of anastomosis, bleeding from operative site, pneumonia, and wound infection. No mortality related to pancreatitis was present
Hong et al., 2011 [16]	Endoscopy: adverse events recorded in endoscopy included post-ERCP pancreatitis and perforation at the sphincterotomy site. No mortality was present Surgery: adverse events recorded in surgery included pancreatic leakage, bile leakage, wound infection, and dehiscence requiring secondary closure. No mortality was present
Jiang et al., 2018 [17]	Endoscopy: adverse events recorded in endoscopy included stent-related complications, post-ERCP pancreatitis, and bleeding. No mortality was present Surgery: adverse events recorded in surgery included gastrointestinal bleeding requiring arterial embolization, anastomosis leakage, pneumonia, pancreatic abscess, intraperitoneal haemorrhage, and wound infection. No mortality was present

2.36 [95% CI: 1.12 – 4.99, $I^2 = 41.70\%$, (p = 0.02]) (Table 2 and Fig. 1). There was no publication bias through visual inspection of the funnel plot and an Egger's regression test (p = 0.60) (Supplemental Data, Fig. 2). For Pain Relief, the GRADE assessment indicates a moderate level of certainty, with an absolute risk reduction of 204 more per 1,000 patients (95% CI from 27 to 337 more).

Secondary outcomes

Technical success Five studies including 360 patients were meta-analysed to evaluate technical success (Table 3). There were no significant differences between surgery and endotherapy (OR was 3.02 [95% CI: 0.47 – 19.59, $I^2 = 79.27\%$, p = 0.25]) (Table 2 and Fig. 1) No publication bias was noted through inspection of the funnel plot and with an Egger's regression test (p = 0.18) (Supplemental Data, Fig. 2). Regarding Technical Success, the GRADE assessment shows very low certainty, with an absolute risk increase of 51 more per 1,000 patients (95% CI from 76 fewer to 74 more).

Adverse events Five studies including 360 patients were meta-analysed to evaluate adverse events. There were no significant differences between endotherapy and surgery (OR 1.31 [95% CI: 0.47—3.71, $I^2 = 50.93\%$, $p = 0.65$]). (Table 2 and Fig. 1). No evidence of publication bias was observed both via visual inspection of a funnel plot and the Egger's regression test ($p = 0.63$) (Supplemental Data, Fig. 2). For Adverse Events, the GRADE assessment suggests low certainty, with an absolute risk increase of 39 more per 1,000 patients (95% CI from 77 fewer to 250 more).

Discussion

This systematic review and meta-analysis included five studies totalling 360 patients and compared the efficacy and safety between pancreatic endotherapy and surgery for CCP-related pain management. Surgery was associated with a significant improvement in pain relief compared to endotherapy. In contrast, technical success and adverse events were equivalent between the two interventions.

Endoscopic interventions offer pain relief that is comparable to surgery in the early to medium term [18]. However, numerous studies have now reported the marked decrease in sustained pain relief over time in patients who undergo endotherapy alone [5, 7, 11]. The relatively recent introduction of ESWL into the endotherapy armoury has resulted in longer term reduction in pain; however, the reported rate of success remains mediocre (50–80%) [5, 7, 11, 14]. Comparatively, surgery has been reported to provide long-term pain relief in 70–85% of patients [13]. This study confirms similar findings, with surgical intervention providing more than double (OR 2.36) the odds of substantial and long-lasting pain relief when compared with pancreatic endotherapy. Given the debilitating impact on patient's quality of life, this is a relevant finding.

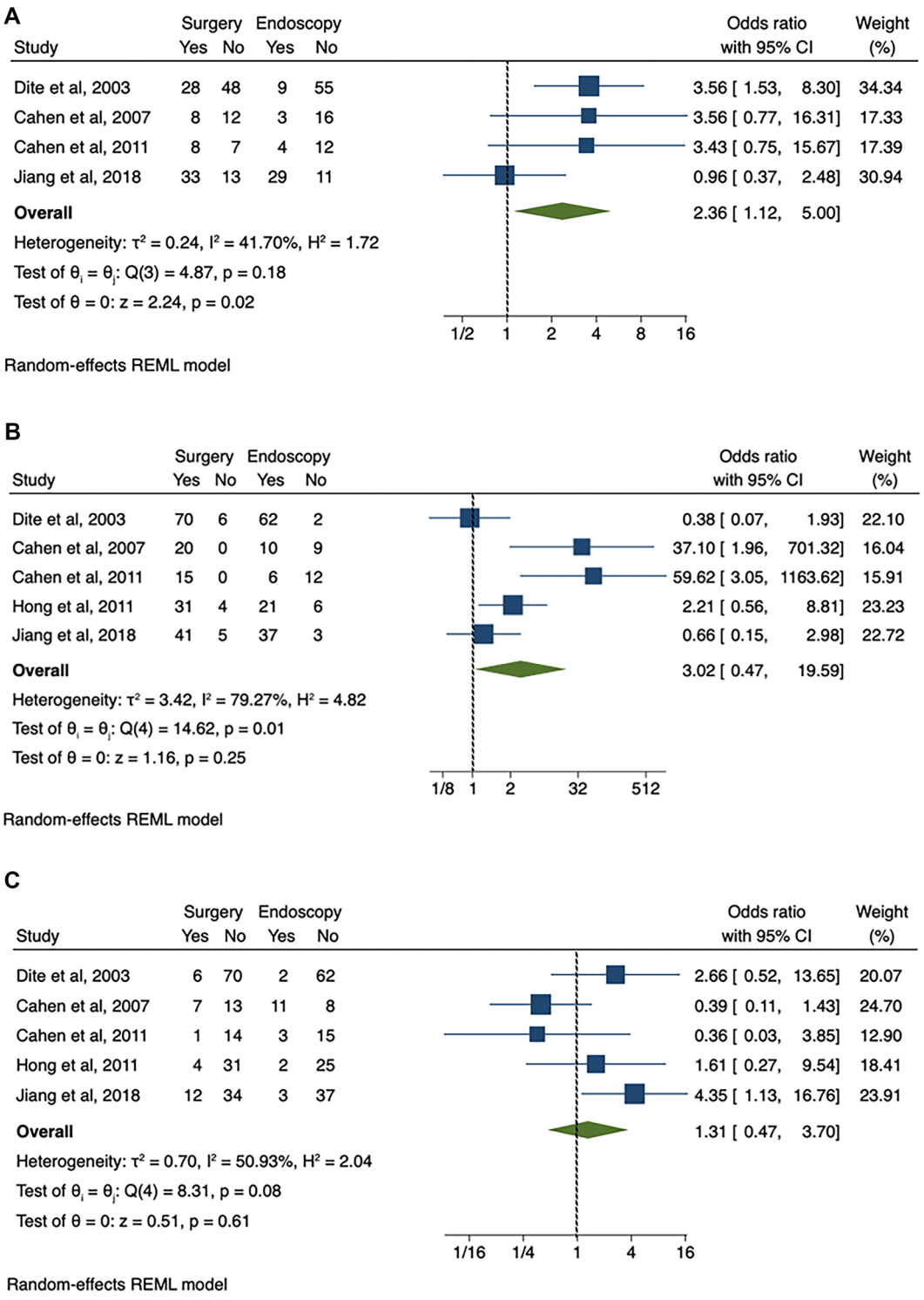

Fig. 1 Forest plots of included studies evaluating Pain Relief (**A**), Technical Success (**B**), Adverse Events (**C**)

There are multiple factors that likely contribute to surgery's higher success rate. Firstly, surgical approaches, such as pancreatico-jejunostomy and total pancreatectomy with autologous islet cell transplantation, offer a direct correction of anatomical abnormalities [19]. Chronic pancreatitis is a progressive inflammatory condition with irreversible structural changes, hence there is no complete cure for patients with CCP. Endoscopic interventions are designed to decompress increased ductal pressures without addressing the root cause [18]. Furthermore, surgical procedures allow for a

more thorough clearance of pancreatic duct obstructions and removal of calculi [20]. Pancreatic endotherapy, while effective in some cases, may face limitations in achieving complete ductal clearance, especially in the presence of extensive calcifications [21]. While both groups contain slight variability in the interventions that were performed, the larger heterogeneity observed in endoscopic interventions in particular (including sphincterotomy, pancreatic duct dilatation, pancreatic duct stenting, and pancreatic stone removal including ESWL) may contribute to variations in measured outcomes [20]. Jiang et al. reported in a small cohort of 86 patients that ESWL with ERCP effectively reduced pain in 80% of patients with a median follow-up time of 4 years. Thus, it is relevant to consider that our analysis may indeed be underestimating the therapeutic effect of endotherapy. Furthermore, differences in patient selection and procedural expertise can also impact the effectiveness of these endoscopic interventions, potentially leading to less consistent pain relief [22]. With regard to technical success, surgery showed a much higher success rate (OR 3.02); however, the difference was not statistically significant. This reiterates the heterogeneity of many factors that can influence results which include the endoscopic and surgical techniques, confounding by indication and the varying skill levels of the practitioners [23].

Pain relief is an important factor when considering a patient's quality of life and one of the most challenging symptoms to treat in this population of patients. The risk–benefit equation of either surgery or endoscopic interventions needs to be carefully evaluated. This study confirms that given the available data, surgery appears to be associated with a higher rate of pain relief with equivalent technical success and adverse event rates. [23]. Findings indicate that, when appropriately indicated, surgery can be as safe of an option for CCP pain management as endotherapy. Furthermore, findings indicate no significant difference in adverse events between endotherapy and surgery, which might seem counterintuitive given the complexity of surgical procedures for chronic pancreatitis. This result could be influenced by variations in the reporting of adverse events, particularly in observational studies and the selection of patients for these procedures given that some studies were non-randomized. It is also possible that some studies may have underreported complications or used different criteria for classifying adverse events. Chronic pancreatitis surgeries are complex and carry a significant risk of complications and should be performed in tertiary care centres by experienced surgeons. In real-life clinical practice, the decision between endoscopic and surgical interventions often hinges on individual patient factors and specific anatomical issues. Endoscopic interventions are typically preferred for patients with localized ductal obstructions or smaller calcific deposits, where non-invasive methods can potentially provide sufficient relief and avoid the risks associated with surgery. For patients with more complex anatomical problems, such as extensive ductal obstruction or significant calcification, surgical options may be more appropriate, also depending on disease stage and ductal dilatation. Surgical procedures like pancreatico-jejunostomy or total pancreatectomy with islet cell transplantation offer a more direct approach to addressing anatomical abnormalities and can be beneficial in patients with advanced or diffuse calcific pancreatitis. Additionally, the choice of intervention may be influenced by patient factors such as overall health, comorbidities, and previous treatment history. Therefore, a personalized approach is crucial in optimizing treatment outcomes for patients with chronic calcific pancreatitis.

This study has several limitations. The presence of moderate heterogeneity in our results indicates potential variability in study designs, patient populations, and intervention techniques. Additionally, the variations in endoscopic techniques (including lack of ESWL) and the paucity of standardized reporting across studies likely further contribute to the observed heterogeneity. Furthermore, the limited number of studies meeting the inclusion criteria underscores the need for more extensive research in this field.

In conclusion, this systematic review and meta-analysis indicate that surgery provides more effective and sustained pain relief when compared with pancreatic endotherapy in patients with CPP. Future research should focus on comparing newer endoscopic interventions including the adjuvant ESWL for patients with CPP and determine what alternatives are more efficacious depending on disease stage.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00464-024-11328-2.

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Declarations

Disclosures AF—Consultant: Boston Scientific; JDM—Speaker: Boston Scientific, Pendopharm, Vantage, Medtronic. Medical Advisory Board: Pendopharm, Boston Scientific, Janssen, Pentax, Fuji; CWT—Speaker for Medtronic and Boston Scientific, Consultant for Boston Scientific; GRM—Consultant for Olympus. Speaker: Pentax, Fuji and Medtronic; All the authors have no conflicts of interest or financial ties to disclose.

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