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Pancreatoscopy-guided intraductal lithotripsy in patients with pancreatic stones

Litotrícia Intraductal Guiada por Pancreatoscopia em doentes com cálculos pancreáticos

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Resumo

Introdução: Até 90% dos doentes com pancreatite crónica apresentam cálculos no interior do ducto pancreático, embora apenas alguns desenvolvam sintomas. A abordagem atual destes doentes inclui terapia médica, cirúrgica, colangiopancreatografia retrógada endoscópica (CPRE) com realização de esfincterotomia pancreática, dilatação ductal e extração de cálculos e litotrícia extracorporal por ondas de choque (LEOC). Apesar da eficácia destas abordagens, um subgrupo de doentes continua refratário aos métodos de extração convencionais. Atualmente, a litotrícia intraductal guiada por pancreatoscopia per-oral (LIGP) emerge como uma alternativa, desafiando as diretrizes atuais da *European Society of Gastrointestinal Endoscopy.* O objetivo primário desta revisão sistemática é avaliar a eficácia e a segurança da LIGP em doentes com cálculos no ducto pancreático. O objetivo secundário é comparar os resultados das duas técnicas de LIGP e avaliar a qualidade de vida após o procedimento.

Métodos: Esta revisão sistemática (PROSPERO: CRD420261321254), em conformidade com as mais recentes diretrizes PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), sintetizou a evidência publicada entre 2016 e 2025 para avaliar a eficácia e segurança da LIGP. Os artigos foram retirados de três bases de dados: PubMed, Scopus e Web of Science. A eficácia do procedimento foi avaliada pelo sucesso técnico, que inclui limpeza do ducto pancreático, número de sessões e duração do procedimento; taxa de recorrência dos cálculos; e sucesso clínico, determinado pela resolução ou melhoria dos sintomas. Além disso, foi avaliada a qualidade de vida. A segurança do procedimento foi avaliada por alterações no curso clínico, internamentos de novo, hospitalização prolongada e complicações relacionadas com o procedimento. Dois revisores independentes realizaram a seleção dos estudos via Rayyan® e extração de dados, com a resolução de discrepâncias por um terceiro investigador. A qualidade metodológica foi avaliada através da ferramenta ROBINS-I.

Resultados: Foram incluídos 10 artigos na análise final. A eficácia técnica da LIGP foi elevada, com taxas de limpeza ductal entre 70,6% e 98,9%, demonstrando ser um preditor independente de sucesso (OR 6,98). A presença de estenoses e cálculos >10 mm foram identificados como fatores que reduzem as taxas de sucesso. Doentes submetidos a LIGP obtiveram uma limpeza ductal significativamente superior à CPRE convencional (98,9% vs. 87,6%, p < 0,001). O número médio de sessões de litotrícia variou entre 1,00 e 1,92, e o tempo de procedimento variou entre 48,0 e 101,6 min. Comparativamente à LEOC, a LIGP apresentou taxas de limpeza ductal semelhantes, mas menor número de sessões e menor tempo de intervenção. Não se registaram diferenças significativas na eficácia entre a litotrícia electro-hidráulica e a laser. A taxa de recorrência de cálculos variou entre 0,0% e 38,2%, sendo comparável à das técnicas convencionais. O sucesso clínico foi geralmente superior a 80,0%, mantendo-se em 70,7% dos doentes aos 24 meses. Contudo, não houve melhoria estatisticamente significativa na qualidade de vida. A taxa de complicações variou entre 0,0% e 40,0%, sendo a pancreatite pós-CPRE a mais frequente, sem diferenças significativas na segurança face às técnicas padrão.

Conclusão: A LIGP demonstra ser uma alternativa eficaz e segura, com taxas de limpeza ductal que superam a CPRE convencional e um menor número de sessões comparativamente à LEOC. Contudo, a evidência atual é limitada pela natureza retrospetiva dos estudos, amostras reduzidas e heterogeneidade nas definições de sucesso. Além disso, a dissociação entre a limpeza ductal e a melhoria da qualidade de vida reforça a necessidade de uma abordagem multimodal e de ensaios clínicos randomizados que consolidem o seu papel definitivo no algoritmo terapêutico da pancreatite crónica. O elevado sucesso clínico, mantido mesmo em casos complexos de cálculos impactados ou de grandes dimensões, sugere que a LIGP tem potencial para transitar de uma estratégia de resgate para uma abordagem de primeira linha em centros especializados.

Abstract

Introduction: Up to 90% of patients with chronic pancreatitis have stones in the pancreatic duct, although only a few develop symptoms. The current management of these patients includes medical therapy, surgical therapy, endoscopic retrograde cholangiopancreatography (ERCP) with pancreatic sphincterotomy, ductal dilation, and stone extraction, and extracorporeal shock wave lithotripsy (ESWL). Despite the efficacy of these approaches, a subgroup of patients remains refractory to conventional extraction methods. Currently, per-oral pancreatoscopy-guided intraductal lithotripsy (POP-L) is emerging as an alternative, challenging current European Society of Gastrointestinal Endoscopy guidelines and suggesting the need to reevaluate its role in the therapeutic algorithm. The primary objective of this systematic review is to evaluate the efficacy and safety of POP-L in patients with symptomatic pancreatic duct stones. The secondary objectives are to compare the outcomes of the two forms of endoscopic lithotripsy and assess quality of life following the procedure.

Methods: This systematic review (PROSPERO: CRD420261321254), in accordance with the latest PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, synthesized the evidence published between 2016 and 2025 to assess the efficacy and safety of per-oral pancreatoscopy-guided intraductal lithotripsy. Articles were retrieved from three databases: PubMed, Scopus, and Web of Science. Efficacy outcomes were divided into technical success, which included stone clearance rate, number of sessions and procedure time; stone recurrence rate; and clinical success, determined by the resolution or improvement of symptoms. In addition, quality of life was assessed. Regarding safety outcomes, we evaluated changes in clinical course, rehospitalization, prolonged hospitalization, and procedure-related complications. Two independent reviewers selected the studies using Rayyan® and extracted the data, with discrepancies resolved by a third investigator. Methodological quality was assessed using the ROBINS-I tool.

Results: Ten articles were included in the final analysis. The technical efficacy of POP-L was high, with ductal clearance rates ranging from 70.6% to 98.9%, and it was found to be an independent predictor of success (OR 6.98). The presence of strictures and stones >10 mm was identified as factors that reduce success rates. Patients undergoing POP-L achieved a significantly higher success rate than those undergoing conventional ERCP (98.9% vs. 87.6%, $p < 0.001$). The mean number of sessions ranged from 1.00 to 1.92, and the procedure duration ranged from 48.0 to 101.6 minutes. Compared to ESWL, POP-L showed similar technical success rates but with greater operational efficiency, requiring significantly fewer sessions and shorter procedure times. No significant differences in efficacy were observed between electrohydraulic lithotripsy and laser lithotripsy.

Stone recurrence rates (0.0% to 38.2%) were comparable to those of conventional techniques. Clinical success generally exceeded 80.0%, remaining at 70.7% of patients at 24 months. However, there was no statistically significant improvement in quality of life. The complication rate ranged from 0% to 40%, with post-ERCP pancreatitis being the most frequent (mild to moderate), with no significant differences in safety compared to standard techniques.

Conclusion: POP-L has proven to be an effective and safe alternative, with technical success rates that exceed those of conventional ERCP and a lower number of sessions compared to ESWL. However, current evidence is limited by the retrospective nature of the studies, small sample sizes, and heterogeneity in the definitions of success. Furthermore, the disconnect between ductal clearance and improved quality of life underscores the need for a multimodal approach and randomized clinical trials to establish its definitive role in the treatment algorithm for chronic pancreatitis. The high clinical success rate, maintained even in complex cases involving impacted or large stones, suggests that POP-L has the potential to transition from a rescue strategy to a first-line approach in specialized centers.

Abbreviations list

CFTR - Cystic Fibrosis Transmembrane Conductance Regulator

CP - Chronic Pancreatitis

EHL - Electrohydraulic Lithotripsy

ERCP - Endoscopic Retrograde Cholangiopancreatography

ESGE - European Society of Gastrointestinal Endoscopy

ESWL - Extracorporeal Shock Wave Lithotripsy

IPS - Izbicki Pain Score

ITT - Intention-to-treat

LL - Laser Lithotripsy

MCS - Mental Component Summary

MeSH - Medical Subject Headings do Index Medicus

MPD - Main Pancreatic Duct

NRS - Numerical Rating Scale

PCS - Physical Component Summary

PEP - Post-ERCP Pancreatitis

POP-L - Pancreatoscopy-guided Intraductal Lithotripsy

ROBINS-I - Risk of Bias In Non-Randomized Studies- of Interventions

SF-12 - Short Form-12 Health Survey

TPAIT - Total Pancreatectomy with Autologous Islet Transplantation

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Introduction

Chronic Pancreatitis and Pancreatolithiasis

Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas characterized by irreversible destruction of the pancreatic parenchyma, culminating in endocrine and exocrine insufficiency. [1, 2, 3] Up to 90% of patients with CP experience the long-term complication of stone formation within the pancreatic duct. However, most of these stones are detected incidentally in asymptomatic patients. [1, 4]

Pancreatic stones consist of a central core on which layers of calcium carbonate are deposited. The central core is amorphous and consists of trace elements such as nickel, chromium, and iron. [5] The stones, together with the strictures, act as a physical barrier, obstructing the flow of pancreatic secretion, leading to increased intraductal and interstitial pressure. This increase in pressure is responsible for the clinical course characterized by abdominal pain, recurrent episodes of acute pancreatitis, and progression of fibrosis and tissue damage. [1, 5]

Pancreatic stones can be classified based on density (radio-opaque, radiolucent, or mixed), number (single, multiple), or location (head, body, or tail). [5] They can also be classified as true stones, when located inside the pancreatic duct, or as pseudoliths, when located in the pancreatic parenchyma. [3]

Epidemiology of Chronic Pancreatitis

The diagnosis of CP usually occurs between the ages of 35 and 55. [6] The incidence is estimated to be approximately 10 cases per 100 000 person-years, with an increasing incidence over the last 5 years and about twice as high in males. [7, 8] Ten-year mortality ranges from 13.7% to 34%, figures that exceed those reported for some of the most common oncologic diseases. [8]

Patients with CP have a higher risk of developing pancreatic cancer, especially earlier after diagnosis. [9] This risk is about seven times higher than the general population. However, despite the increased relative risk, the absolute risk remains low and does not generally justify the implementation of screening programs. [7] Patients with hereditary pancreatitis associated with mutations in the PRSS1 gene have a risk approximately 60 times higher than the general population. Therefore, monitoring of these patients in centers specializing in pancreatic pathology is recommended. However, there is no standardized and validated screening method. [7]

Most pancreatic stones are calcified and radiopaque, and their prevalence increases over time, reaching 50% and 100% at 5 and 14 years, respectively, after the onset of CP. Pancreatic stones are more prevalent in men, heavy alcohol consumers and smokers. [9]

Mechanisms involved in the formation of stones in the pancreatic duct

Pancreatic stone protein is a physiological constituent of pancreatic fluid and has been proposed as an endogenous inhibitor of calcium carbonate crystallization. [3] Several factors, including changes in gene expression, can lead to reduce this protein levels. This reduction leads to calcium carbonate supersaturation in pancreatic fluid, with subsequent deposition on a nucleation site and formation of pancreatic stones. Regardless of the etiology of CP, the structure and composition of the stones are similar, suggesting the existence of a common pathway in stone formation. [10]

In CP, dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) compromises bicarbonate and pancreatic fluid secretion, reducing pH and ductal volume and promoting the precipitation of digestive proteins, leading to the formation of deposits susceptible of calcification. Mutations in the CFTR gene aggravate this process by increasing the viscosity of secretions and inflammation. At the same time, high levels of lactoferrin contribute to the formation of insoluble protein deposits in the pancreatic ducts. Osteopontin is overexpressed in pancreatic cells, and its exclusive presence in ductal stones is associated with calcium salt deposition, suggesting an active role in pancreatic lithogenesis. Additionally, genetic variants of the calcium-sensing receptor (CaSR) impair ductal calcium homeostasis, promoting the formation of insoluble salts and pancreatic stones. [3]

In addition to molecular factors, alcohol consumption, pancreatic duct obstruction, and chronic inflammation contribute to the formation of pancreatic stones. Alcohol stimulates acinar secretion, which promotes the formation of calcium-rich protein clots. Ductal obstruction promotes stasis and precipitation, and recurrent inflammation induces the release of fatty acids that chelate calcium, resulting in insoluble salts deposited in the pancreatic ducts. [3]

Classification of Chronic Pancreatitis

CP is traditionally classified as calcified CP, obstructive CP, and autoimmune CP. Calcified CP is the most common form and is characterized by progressive evolution, often preceded by episodes of acute pancreatitis. Over time, intraductal stones formation is accompanied by structural changes of the pancreatic duct, such as dilation, stenosis, and deformation, as well as atrophy of the glandular parenchyma. Progressive destruction of pancreatic tissue can lead to exocrine insufficiency and endocrine insufficiency. Calcifications are a distinctive feature of this form and are rare in other variants of CP. [11]

Obstructive CP results from partial or complete obstruction of the pancreatic duct, usually secondary to ductal strictures. These strictures may arise as complications of surgical or endoscopic procedures, trauma, acute necrotizing pancreatitis, anastomotic changes, or obstructive tumors.

Inflammation is usually limited to the region proximal to the obstruction, with functional preservation of the distal pancreas. Although often asymptomatic, ductal obstruction increases the risk of recurrent episodes of acute pancreatitis and may, in advanced stages, progress to calcified CP. [11]

Autoimmune CP is characterized by immune-mediated pancreatic inflammation with a good response to corticosteroid therapy and is subdivided into types 1 and 2. Type 1 is characterized by multiorgan involvement, elevated serum IgG4 levels, and a high recurrence rate. It manifests mainly as obstructive jaundice, with abdominal pain being less prominent. Histologically, periductal lymphoplasmacytic infiltration, storiform fibrosis, and an abundance of IgG4-positive plasma cells are observed. Type 2, also known as idiopathic ductal CP, is not associated with IgG4 or systemic involvement. Its main histological feature is neutrophil infiltration in the ductal epithelium, leading to obliteration of the pancreatic ducts. [11]

Risk Factors for Chronic Pancreatitis

CP is a multifactorial disease resulting from the interaction between environmental, genetic, metabolic, and anatomical risk factors, with a single isolated factor rarely being sufficient to cause the condition. The M-ANNHEIM and TIGAR-O classification systems reflect this complexity by organizing risk factors into categories that often coexist and act synergistically. [7, 12]

Alcohol consumption, like smoking, is a dose-dependent risk factor, being present in more than half of patients. [7, 11] Smoking, in addition to being an independent risk factor, has a synergistic effect with alcohol in aggravating pancreatic inflammation and tissue ischemia. [7, 11, 12]

Genetic factors play a central role in predisposition to CP, particularly when combined with environmental factors. Mutations in the PRSS1 gene are associated with hereditary pancreatitis, characterized by early onset, high penetrance, rapid disease progression, and an increased risk of pancreatic adenocarcinoma. Other genetic variants, particularly in the SPINK1, CFTR, CTRC, and CASR genes, do not necessarily act as direct causes, but function as disease modifiers, facilitating the transition from acute to chronic pancreatitis. [7, 11, 12]

Other risk factors include autoimmune diseases such as inflammatory bowel disease, systemic lupus erythematosus, and celiac disease, [12] and other conditions such as hypercalcemia, malnutrition, and parasitic infections of the bile ducts or pancreas. [3]

Structural changes such as inflammatory stenosis, benign or malignant neoplasms, pancreatic trauma, and sequelae of severe acute pancreatitis are recognized risk factors, as they may impair pancreatic fluid flow. [11, 12] Pancreas *divisum*, rarely causes pancreatitis on its own, but may act as a cofactor in the presence of genetic mutations, such as those in the CFTR gene. [7, 11, 12]

M-ANNHEIM classification

The M-ANNHEIM classification [13] provides a comprehensive framework for CP, integrating etiological factors, clinical staging, and disease severity. It encompasses multiple risk domains, including alcohol and nicotine exposure, nutritional and hereditary factors, pancreatic duct abnormalities, immune-mediated mechanisms, and rare or metabolic causes. Clinical staging ranges from an asymptomatic phase (stage 0) to four symptomatic stages (I–IV), while severity is graded according to pain burden, treatment requirements, and the presence of exocrine or endocrine insufficiency, ranging from minor (A, ≤5 points) to severe disease (E, >20 points). The classification further incorporates morphological assessment based on the Cambridge criteria and accounts for major complications such as fistulas and pancreatic malignancy. [13, 14]

Clinical Presentation

CP is often preceded by a subclinical phase that progressively culminates in the loss of the exocrine and endocrine functions of the pancreas, with abdominal pain and unintentional weight loss as the most common symptoms. [7, 11]

Abdominal pain is the main clinical manifestation of CP and varies greatly in intensity, frequency, and pattern, and may be continuous or intermittent. It is typically located in the epigastric region, radiating to the back. [7, 11] Pain is often exacerbated by meals, contributing to reduced food intake and weight loss. [11]

Exocrine pancreatic insufficiency results from the destruction of acinar cells or obstruction of pancreatic flow and is associated with prolonged disease duration and smoking. [7] It manifests itself through symptoms of malabsorption such as chronic diarrhea, steatorrhea, abdominal distension, fatigue, weight loss, deficiencies in macronutrients such as fat, carbohydrates, and protein, and micronutrients, namely fat-soluble vitamins A, D, E, and K, magnesium, and zinc. [7, 11] In the long term, complications such as osteoporosis and low-impact fractures may occur. [7]

Endocrine insufficiency results from global impairment of pancreatic islet cells, causing hormonal deficiency of insulin, glucagon, and pancreatic polypeptide, which leads to the development of pancreatogenic diabetes, characterized by an increased risk of metabolic complications. Its incidence increases with disease progression and is associated with pancreatic calcifications, smoking, and surgical interventions. [7]

Overall, CP has a significant impact on patients' quality of life and social functioning, resulting from a combination of chronic pain, nutritional changes, and metabolic complications. [7, 11]

Diagnosis

The diagnosis of CP is based on a combination of the patient's medical history, including chronic abdominal pain, recurrent episodes of acute pancreatitis, excessive alcohol consumption and/or prolonged smoking, steatorrhea, unintentional weight loss, and recent-onset diabetes; and clinical presentation, laboratory assessment of pancreatic function, and imaging findings. [6, 7]

In contrast to acute pancreatitis, pancreatic enzyme levels in CP may be normal or midly elevated, particularly in advanced stages when the pancreatic parenchyma is progressively replaced by fibrotic tissue. In 5-10% cases, biliary obstruction occurs, and elevations in bilirubin, alkaline phosphatase, and liver transaminases may be observed. [6]

Direct pancreatic function tests assess enzyme secretion via catheterization of the pancreatic duct. Owing to their invasiveness, technical complexity, and cost, they are rarely used in clinical routine practice. However, their high negative predictive value makes them useful for ruling out CP in patients with strong clinical suspicion and normal imaging findings. Fecal elastase is an indirect test of pancreatic exocrine function, with high sensitivity but low specificity. [6]

In advanced stages, CP is usually diagnosed with imaging, which demonstrates pancreatic calcifications, parenchymal atrophy and ductal dilation or irregularity. [6, 12] Given their similar sensitivity and specificity, the selection of imaging modalities should be guided by invasiveness, cost, availability and reproducibility. Thus, it usually starts with computed tomography, followed by magnetic resonance cholangiopancreatography, and endoscopic ultrasound when the findings are inconclusive. [6, 7] Endoscopic retrograde cholangiopancreatography, despite its high diagnostic capability, is not recommended as a routine diagnostic method due to the significant risk of complications. [6, 7]

Treatment of pancreatic lithiasis

Several studies show that removing stones from the pancreatic duct has a significant impact on symptom relief in most patients with CP. [15] The current approach to these patients encompasses a range of options, including medical therapy (conservative therapy), surgical therapy, endoscopic retrograde cholangiopancreatography (ERCP) with pancreatic sphincterotomy, ductal dilation and stone extraction, extracorporeal shock wave lithotripsy (ESWL), and more recently, intraductal lithotripsy guided by per-oral pancreatoscopy (POP-L). [16, 17] Treatment strategy in CP is primarily determined by lithiasis burden and the anatomical location of the stones. [15]

Conservative medical treatment

Conservative medical treatment, based on oral replacement of pancreatic enzymes, analgesics, and adoption of a low-fat diet, is the main approach in the treatment of CP. Although these measures do not reduce the total number of stones, they act by suppressing cholecystokinin-mediated exocrine stimulation and decreasing intraductal pressure, thereby promoting pain relief.[3]

Currently, there is no pharmacological agent with proven safety and efficacy for the dissolution of pancreatic stones. Trimetadione, an anticonvulsant, has shown some potential in this regard, but its clinical application is restricted by its side effects, namely hematotoxicity, hepatorenal dysfunction, and neuropsychological complications associated with long-term treatment, [3] necessary to cause the dissolution of the stones. [5]

Pharmacological pain management in CP follows the recommendations of the World Health Organization, using the analgesic ladder. [7, 8] Adjuvant analgesics such as tricyclic antidepressants, gabapentinoids, selective serotonin reuptake inhibitors, and esketamine may have some benefit in the management of chronic pain, with pregabalin being the most investigated in the context of CP and showing promising results in relieving pain associated with the disease. [7] These drugs, together with cognitive behavioral therapy, can be considered in patients with insufficient response to conventional analgesia. [16] Opioids should be reserved for patients with refractory pain, as prolonged use is associated with dependence and opioid-induced hyperalgesia. [8]

Lifestyle changes are equally important. Patients should be encouraged to adopt a low-fat diet [3] and abstain from alcohol and tobacco use. [8]

Surgical Treatment

Before the advent of advanced endoscopic techniques, surgery was the gold standard treatment for the sequelae of CP, and it remains the definitive approach for pancreatolithiasis today. [3, 5] Surgical treatment is associated with longer-lasting pain control and provides higher rates of pain relief than endoscopic treatment (75-86% vs. 32-61%, respectively). [3]

Surgical treatment is indicated when there is extensive pancreatic lithiasis burden, multiple stones, complex ductal strictures, an inflammatory mass in the pancreatic head, tail-dominant disease, suspected malignancy, [3] or failure of endoscopic treatment. [5]

Surgical strategies include pancreatic drainage and resection of the affected segments. Drainage procedures, such as lateral pancreaticojejunostomy (Partington procedure), are indicated for stones in the main pancreatic duct with ductal dilation, preserving endocrine and exocrine function. For more complex cases or suspected malignancy, pancreatic resections such as the Whipple procedure, pancreatic head resection with preservation of the duodenum (DPPHR), limited resection combined with longitudinal jejunostomy of the pancreatic duct (Frey's recession), or total pancreatectomy with autologous islet transplantation (TPAIT) allow complete removal of stones, with variable results in functional preservation and postoperative quality of life. The Frey procedure stands out for balancing analgesic efficacy, fewer complications, and functional preservation, while TPAIT is indicated in refractory CP, providing pain relief and preservation of endocrine and exocrine functions, albeit with greater complexity and surgical risk. Overall success depends on surgical experience and individualized assessment of risks and benefits. [3]

Endoscopic Treatment

Endoscopic strategies are less invasive than conventional surgery and have a higher probability of success in patients with a small stone burden and stones located in the main pancreatic duct alone. [4]

Endoscopic treatment of pancreatolithiasis is based on ERCP combined with sphincterotomy, using techniques for extraction, stone fragmentation, and placement of pancreatic stents. [3, 5] According to the guidelines of the European Society of Gastrointestinal Endoscopy (ESGE), ERCP combined with endoscopic sphincterotomy is recommended as first-line treatment in patients with symptomatic obstructive CP involving the main pancreatic duct in the head or body of the pancreas. [3]

ERCP is most effective for radiolucent stones smaller than 5 mm in diameter located in the head or proximal body of the main pancreatic duct. However, the smaller size and greater tortuosity of the pancreatic duct, compared to the common bile duct, constitute significant technical limitations, hindering the progression of endoscopic instruments and the complete removal of stones. [5] The combination of sphincterotomy, balloon dilation, and extraction techniques or mechanical lithotripsy has proven to be effective and safe in removing impacted stones, allowing the drainage of stones, sludge, and debris into the duodenal lumen, with low invasiveness and good short-term clinical results. [3]

Mechanical lithotripsy with a basket involves fragmenting stones using a retrieval basket, allowing the removal of stones that would otherwise be difficult to extract. However, this method is limited by its ineffectiveness in ducts with a diameter < 6 mm, and by the risk of device entrapment, wire fracture, and ductal injury. [3] Extraction balloons represent an alternative with a lower complication rate, given the lower risk of entrapment, but they may be less effective in large or calcified stones. In addition, if the stones are dense and spiculated, the balloons are susceptible to rupture. [3, 5]

In the presence of pancreatic duct stenosis, particularly of inflammatory or fibrotic origin, the sequential placement of stents of increasing caliber over 6-12 months is recommended to achieve gradual ductal and facilitate stone extraction. However, complications such as stent migration and occlusion may occur, leading to abdominal pain, pancreatitis, or infections. [3]

Endoscopic techniques are limited by the need for advanced technical expertise, restricted applicability to certain stone locations and morphologies, and the persistence of residual stones that may require further intervention. [3]

Acute pancreatitis is the most frequent complication of ERCP. [18] Despite standardized protocols aimed at risk reduction, such as routine rectal administration of 100mg of diclofenac or indomethacin immediately before ERCP, the global incidence of PEP (Post-ERCP Pancreatitis) stands at 3.5%, with a corresponding mortality rate of 0.11%. [18, 19] Most authors investigate PEP with the consensus definition and classification proposed by *Cotton et al.* in 1991. [20] PEP is diagnosed when a patient develops new or worsening abdominal pain accompanied by amylase or lipase levels at least three times above the normal limit, measured 24 hours after the procedure, and requires either an unplanned hospital admission or an extension of the current hospitalization. [18] According to Cotton criteria (1991) [21] PEP is stratified as: mild (2-3 days of hospitalization), moderate (4-10 days) and severe (>10 days or complications such as pseudocysts, hemorrhagic pancreatitis, or the need for invasive interventions); [22] The Atlanta Classification [23] classifies as mild (no complications), moderate (complications or transient organ failure resolved in <48h), and severe (organ failure persisting for > 48h). [23]

Extracorporeal shock wave lithotripsy (ESWL)

ESWL, developed in the 1980s, uses externally generated focused shock waves to break up intraductal stones. [3] Sessions are usually repeated on consecutive days until adequate fragmentation of the stones is achieved. [5] In certain situations, such as in the presence of stones larger than 10 mm, several repeated sessions are necessary to achieve satisfactory results. [3]

Effective fragmentation after ESWL is defined by the reduction of stones to fragments ≤ 2–3 mm or by radiographic changes indicative of fragmentation, such as decreased density, increased stone surface area, and stone heterogeneity. Pancreatic duct clearance is classified as complete, partial, or unsatisfactory when stone removal exceeds 90%, is between 50–90%, or is less than 50%, respectively. [9] After adequate fragmentation, ERCP is usually performed to remove the fragments and clean the pancreatic duct, with stenting indicated in cases where drainage is incomplete or there is associated ductal stenosis. [5]

The 2018 European Society of Gastrointestinal Endoscopy guidelines recommend ESWL followed by ERCP as the first-line approach in the treatment of symptomatic, uncomplicated radiopaque stones in the main pancreatic duct larger than 5 mm in diameter, located in the head and body of the pancreas. [3, 5]

Recent studies show complete removal rates in about half of patients, and long-term follow-up suggests that combining it with endoscopic drainage provides sustained pain relief, avoiding surgery in about two-thirds of cases. However, some studies question the universal benefit of combining ESWL and ERCP, as comparative studies have indicated a higher incidence of pancreatic pain and increased costs with combined therapy when compared to ESWL alone. [3]

Complications of ESWL described include skin bruising, bleeding, infection, papillary impaction, Steinstrasse formation (accumulated fragmented stones within the duct), and post-procedural pancreatitis. [3]

Pancreatoscopy-guided intraductal lithotripsy (POP-L)

Pancreatoscopy-guided intraductal lithotripsy allows direct endoscopic access to the main pancreatic duct. [3] Thus, lithotripsy can be performed under direct visualization by pancreatoscopy, a technique that evolved from an initial diagnostic method, introduced in 1976, to a therapeutic approach starting in 1999. Its use has become more widespread with the development of the SpyGlass™ system and the SpyGlass™ DS version, which offers better visualization (wider viewing angle) and a larger working channel, at 1.3 mm. [5]

Depending on the energy source used to fragment the stones, there are two options for POP-L: electrohydraulic lithotripsy (EHL) and laser lithotripsy (LL). Both techniques fragment the initial stone into smaller fragments that can be removed later using balloon and basket retrieval devices. [1]

The EHL technique uses a charge generator and a bipolar probe to create a spark that produces a vapor plasma, which causes cavitation in the stones. The vapor plasma transforms into a cavitation bubble that oscillates around the tip of the probe, and the rebound of this bubble generates additional shock waves. These high-frequency hydraulic waves lead to the fragmentation of the stone by the absorption of the shock waves reflected by the vapor and the subsequent waves generated by the rebound of the cavitation bubble. [1, 5] The LL technique uses laser light at a specific wavelength to induce fragmentation. [1] The most common type of laser is the Nd:YAG dual-pulse laser, which combines green light (532 nm) and infrared light (1064 nm), producing plasma on the surface of the stone and shock waves that promote its fragmentation. The holmium laser, with a wavelength of 2100 nm, acts through a photothermal mechanism, directly transmitting energy to the stone to fragment it. [5]

The guidelines of the ESGE recommends POP-L as an alternative when ESWL combined with ERCP is contraindicated or ineffective in clearing the pancreatic duct. [3]

A meta-analysis showed an overall technical success rate of 76.8% for POP-L, associated with a complication rate of 14.9%. The most frequently reported complications were abdominal pain, acute post-procedural pancreatitis, hemorrhage, and ductal perforation. [3]

Rationale of the thesis

As mentioned above, POP-L is generally considered a second-line strategy due to the technical complexity of the procedure and the need for specialized equipment. [4] Thus, these techniques remain reserved for situations in which ERCP and ESWL fail. [4, 10]

Although there are some studies on this topic, the evidence base for the use of pancreatoscopy-guided lithotripsy remains somewhat unclear, with varying rates of stone fragmentation and ductal clearance reported in the literature. Furthermore, there is a notable lack of studies comparing the efficacy and safety of the two types of POP-L (EHL vs. LL), which makes it difficult to choose the ideal approach in clinical practice. The technical complexity of the procedure and the need for specialized equipment are also factors contributing to the scarcity of data. [4]

However, despite these limitations, this technique is a promising therapeutic modality for the treatment of pancreatic duct stones, demonstrating high success rates and a relatively low incidence of adverse events. Thus, as a minimally invasive approach, it may assume a role as a first-line treatment in the future. [24] In this context, there is a clear need for a critical and systematic synthesis of the available evidence, which would allow the efficacy and safety of pancreatoscopy-guided lithotripsy in patients with pancreatic duct stones to be assessed.

Objectives

The primary objective of this systematic review is to evaluate the efficacy and safety of POP-L in patients with symptomatic pancreatic duct stones. The secondary objectives are to compare the outcomes of the two forms of endoscopic lithotripsy, EHL and LL, and assess quality of life following the procedure.

Systematic Review - Pancreatoscopy-guided intraductal lithotripsy in patients with pancreatic stones

Methods

This systematic review was written in accordance with the most recent PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [25] and is registered in the PROSPERO database under the following code: CRD420261321254.

Eligibility criteria

Inclusion criteria of this systematic review included randomized controlled trials (RCTs), cohort studies, and case series, both retrospective and prospective, published between 2016 and 2025, written in English, addressing POP-L and at least one of the predefined outcomes.

Exclusion criteria included studies published in languages other than English and in other types of scientific literature (reviews, meta-analyses, single case reports, letters to the editor, book chapters, and guidelines). Studies involving pediatric or animal populations, those evaluating alternative diagnostic or therapeutic approaches, and those not addressing the predefined outcomes were also excluded.

Sources of Information

The search was conducted in three electronic databases: PubMed (Medline), Scopus (Elsevier), and Web of Science (Clarivate Analytics) on October 2nd, 2025.

Search Strategy

In the three databases, the search was performed according to the following query: (“pancreatitis”[Mesh] OR “pancreatitis” OR “pancreatic stones” OR “pancreatic diseases[Mesh]” OR “pancreatic diseases” OR “pancreatolithiasis” OR “pancreatic lithiasis” or “pancreatic duct stones”) AND (“Lithotripsy”[Mesh] OR “lithotrips*” OR "intraductal lithotripsy“ OR ”Intracorporal lithotripsy“ OR ”laser lithotripsy“ OR ”electrohydraulic lithotripsy" OR EHL OR "laser fragmentation“ OR ”stone fragmentation“) AND (”Per-oral pancreatoscopy“ OR “pancreatoscopy” OR ”SpyGlass" OR Single operator pancreatoscopy OR “Cholangiopancreatography, Endoscopic Retrograde”[Mesh] OR "endoscopic retrograde cholangiopancreatography" OR ERCP).

On all search platforms, results were filtered to show only articles in English published between 2016 and 2025, according to the eligibility criteria mentioned above.

Selection process

The results of the above-mentioned searches were exported to Rayyan®, a systematic literature review application, where duplicates were first detected and excluded. Subsequently, the articles were pre-selected by two separate researchers, Bruna Moreira and Dr. João Pedro Paulo

(MD), based on their title and abstract. Finally, the remaining articles underwent full-text screening to determine their eligibility based on the inclusion criteria. Disagreements between the researchers were resolved by a third investigator, Dr. Paulo Salgueiro (MD, PhD).

Data collection process

Data from the included studies were extracted and entered into an Excel® spreadsheet by one researcher and subsequently reviewed and verified by a second investigator. Any discrepancies between reviewers were resolved through discussion until consensus was reached. We collected the following data from each included study: author and year of publication, study design, study period, follow-up time, overall number of patients, baseline characteristics of all included patients (age – mean and median; sex – male/female), etiology of pancreatitis, location of pancreatic stones, size of the stone (mean and median), previous treatments, type of lithotripsy procedure used, presence of stenoses and evaluated outcomes.

Data items (outcomes)

Efficacy outcomes were divided into technical success, which included stone clearance rate, number of sessions and procedure time; long-term technical success defined by stone recurrence rate; and clinical success, determined by the resolution or improvement of symptoms (e.g., reduction in opioid use, pain scores, or length of hospital stay). In addition, quality of life was assessed. Regarding safety outcomes, we evaluated changes in clinical course, rehospitalization, prolonged hospitalization, and procedure-related complications, such as post-ERCP pancreatitis, abdominal pain, fever, bleeding, contrast extravasation, and perforation.

Study risk of bias assessment

The methodological quality of the selected studies was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [26], which is specifically designed to evaluate non-randomized study designs. The ROBINS-I instrument examines seven principal domains: bias due to confounding, bias in participant selection, bias in intervention classification, bias resulting from deviations from intended interventions, bias related to missing data, bias in outcome measurement, and bias in the selection of reported results. Based on the evaluation of these domains, each study received an overall risk-of-bias judgment categorized as Low, Moderate, Serious, Critical, or No Information when insufficient data were available for assessment.

To enhance reliability, the evaluation was initially conducted by one investigator and subsequently reviewed by a second researcher.

Effect measures and synthesis methods

Data from each study were initially described individually, in a table format (Table I, II and III). Subsequently, in instances where multiple studies examined the same outcome, a descriptive comparative analysis was conducted. Differences with a p-value < 0.05 were considered statistically significant. No meta-analysis was conducted due to the heterogeneity of outcome measurements.

Results

A total of 771 records were initially identified across PubMed (n=215), Scopus (n=337) and Web of Science (n=219). Of these, 533 remained after duplicate removal. Initially screening based on title and abstract led to the exclusion of 511 articles and the remaining 22 were sought for retrieval. Eight of these articles lacked full-text availability, so a full-text analysis was conducted on the remaining 14. Following the full-text review, four additional studies were excluded: one was a duplicate not previously identified, one was a study protocol without results, one was published in a non-peer-reviewed journal with a small sample size, and one did not focus specifically on the technique under investigation. Consequently, 10 articles were included in the final analysis.

The flowchart illustrating the process of study selection (Figure 1) is provided in appendix.

Study characteristics and risk of bias

Tables I to III in the appendix delineate the characteristics of the included studies. Figure 2 presents the results of risk of bias evaluation.

Results of individual studies

The outcomes evaluated in each study are presented in Table III and specified in Tables IV and V.

Technical success

The efficacy of POP-L for the management of MPD (Main Pancreatic Duct) stones has been consistently demonstrated throughout several studies, characterized by high technical success rates even in complex clinical scenarios. The single-center retrospective study conducted by *Bekkali et al.* [27] evaluated the use of direct pancreatoscopy combined with EHL in 6 patients with painful CP over a mean follow-up time of 2.7 years. All patients had failed previous endoscopic attempts at stone removal, including pancreatic sphincterotomy and stent placement. In this study, *Bekkali et al.* [27] reported stone fragmentation and pancreatic duct decompression in 83% of cases, with a mean procedure time of 48 ± 15 minutes. Notably, 4 of 6 patients required only a single session, while the remaining two required two procedures. Similarly, the single-center retrospective study conducted by *Ogura et al.* [28] evaluated 21 patients with symptomatic stones in the MPD. In this study, technical success, defined as direct visualization of the stone via digital single-operator cholangiopancreatoscope followed by effective fragmentation by EHL, was achieved in 85.7% of patients, with a corresponding complete stone clearance rate of 85.7%. This required an average of 1.31 (range 1-3) EHL sessions.

Comparative analyses have highlighted the superiority of POP-L over standard techniques. The single-center retrospective study by *Han et al*. [29] evaluated the efficacy and safety of ERCP, with and without POP-L, for the removal of pancreatic duct stones in 223 patients with CP. With a median follow-up of 5.1 years, the sample was divided between the POP-L group (94 patients) and the conventional ERCP group (129 patients). Within POP-L group, EHL was utilized in 101 procedures and LL in 24, with EHL typically used as the first-line approach. Patients with prior endotherapy or ESWL were included and POP-L was typically performed in cases with stones refractory to standard ERCP. *Han et al.* [29] defined technical success as partial (50.0% to 90.0%) or complete (≥ 90.0%) clearance of the MPD. In this study, technical success rate was significantly superior in the POP-L group compared to standard ERCP (98.9% vs. 87.6%, $p < 0.001$), despite the POP-L group presenting with more complex cases, including larger stones (8.9 mm vs. 6.1 mm, $p = 0.001$), a higher frequency (33.8% vs. 21.1%, $p = 0.002$) of multiple stones (≥ 5 stones), a higher rate of impacted stones (48.8% vs. 10.3%, $p < 0.001$), and more stones located in the body/tail (10.7% vs. 2.4%, $p = 0.03$). Multivariate analysis in this study identified POP-L as the main independent predictor of technical success, increasing the probability of stone removal by almost seven times compared to the conventional technique (adjusted OR 6.98; 95% CI 2.64 -18.46). Interestingly, a greater number of stones was also associated with an increase in technical success (adjusted OR 4.39; 95% CI 2.58 - 7.48), possibly reflecting the presence of smaller stones that were easier to extract. However, although the single stones tended to be larger than multiple stones, this difference was not statistically significant: mean diameter of 8.5 mm vs. 7 mm ($p = 0.07$). Conversely, the presence of impacted stones drastically reduced the chances of successful removal, showing a significant inverse association (adjusted OR 0.09; 95% CI 0.04 -0.17). In this study, the POP-L group required a higher mean number of ERCPs sessions per patient than the conventional group (3.1 vs. 1.9, $p = 0.02$). Regarding specific lithotripsy modalities within POP-L group, no significant difference in technical success between EHL and LL was observed: 99.0% vs. 100%, $p = 0.62$. However, EHL demonstrated a significantly higher complete clearance rate (23.8% vs. 4.2%, $p = 0.03$) in fewer sessions (1.39 vs. 1.92, $p = 0.04$).

The multicenter retrospective cohort study conducted by *Gerges et al*. (2019) [30] evaluated the efficacy and safety of POP-L using the SpyGlass DS system in 20 patients with symptomatic and refractory CP over a follow-up of 3-6 months. The study included a high-complexity cohort in which 95% of patients had previously failed endoscopic treatment, ESWL, and surgery and 40.0% had pancreatic duct stenosis. LL was used in 21 procedures, while EHL was performed in 2 successful procedures. Technical success was defined as the ability to target the stone with the SpyGlass DS and successful pancreatic duct decompression by complete removal of the stone or significant duct decompression, making stent placement possible. The overall technical success rate was 95.0%, with pancreatoscopy enabling stone access in 100% of the procedures and ductal clearance or decompression in 95.0% of cases. Technical success was independent of stone number, location, or the presence of stenosis. Later, in a multicenter prospective cohort trial, *Gerges et al*. (2023) [31] evaluated the efficacy and safety of single-operator digital pancreatoscopy in 40 patients with CP, over a 6-month follow-up time. Of the 53 procedures, EHL was used in 49 and LL in 1. The technical success rate was defined as complete stone clearance within 3 sessions of POP-L. Complete stone clearance was achieved in 90.0% of patients on intention-to-treat analysis (ITT), after a mean of 1.36 (± 0.64) interventions, significantly exceeding the predefined performance goal of 74.0% ($p = 0.01$). A total of 72.5% of cases were cleared in the first session. In the per-protocol analysis, the technical success rate was 92.1%.

When compared to ESWL, POP-L shows comparable clearance rates but superior efficiency. The multicenter retrospective cohort study conducted by *Iwata et al*. [32], with a median follow-up period of 310 days, included 66 patients, of whom 47 underwent ESWL. In the POP-L group, among the 19 patients, pancreatic stones were inaccessible in 2 patients due to bending or narrowing of the pancreatic duct. Within this group, EHL was prioritized as the first-line modality, with LL reserved for cases where EHL was unavailable: 13 EHL and 4 LL. In this study, no significant difference in complete stone clearance was found between POP-L (78.9%) and ESWL (70.2%), $p = 0.55$. This finding was supported by multivariate analysis that confirmed that the choice between POP-L and ESWL did not independently influence the success rate of stone clearance (OR 1.43; 95% CI 0.402 - 5.958, $p = 0.582$). However, POP-L demonstrated a significant advantage regarding the number of sessions required for successful treatment, with a median of only 1 session (range 1-4) compared to 5 sessions (range 2-28) in the ESWL group, $p < 0.01$. In this study, the total number of sessions corresponds to the sum of all procedures performed, including ERCP (for sphincterotomy, dilation or stone fragment removal) and lithotripsy sessions. In the POP-L group, the median total procedure time was 72 minutes (range 30-187 minutes). The single-center retrospective cohort study conducted by *Bick et al*. [33] corroborated these findings. The cohort included 258 patients, of whom 18 underwent EHL, and 240 underwent ESWL. POP-L group presented a more challenging clinical profile, with greater stone burden characterized by a higher number of large MPD stones (1.7 ± 1.0 vs. 1.3 ± 0.7, $p = 0.036$) and a significantly higher prevalence of cases with ≥ 3 large stones (22.2% vs. 4.6%, $p = 0.014$). Furthermore, these patients had higher rates of previous unsuccessful ERCP attempts (38.9% vs. 7.5%, $p \leq 0.0001$) and failed lithotripsy (38.9% vs. 2.9%, $p \leq 0.0001$). Despite this increased complexity, technical success (defined as stone fragmentation and clearance >90%) was comparable between the groups: 88.9% for POP-L vs. 86.7% for ESWL, $p = 1.00$. Notably, the POP-L group required significantly fewer total procedures (mean 1.6 ± 0.6 vs. 3.1 ± 1.5, $p < 0.001$) and a shorter cumulative intervention time (101.6 ± 68.2 min vs. 191.8 ± 111.6 min, $p = 0.001$). Furthermore, POP-L was strongly associated with higher treatment efficiency, defined as successful removal in two or fewer procedures, when compared to ESWL (OR 5.241; CI 1.348–20.369, $p = 0.017$). However, this efficiency was significantly attenuated by stone size, with stones >10 mm showing a marked decrease in clearance success (OR 0.484; CI 0.256–0.912, $p = 0.025$).

Finally, the single-center prospective consecutive case series conducted by *van der Wiel et al.* [34], with a 6 month follow-up time, evaluated the efficacy and safety of EHL, as first-line therapy in patients with CP. The sample included 34 patients, of whom 25 underwent EHL. This study highlighted the impact of anatomical challenges, reporting that deep cannulation failed in 14.7% of cases due to stenoses or obstructive stones in the head or neck of the pancreas. In this study, technical success was defined as complete (100%) or partial (50% - 99%) clearance of MPD stones, and overall technical success was achieved in 70.6% of patients. From a per-protocol perspective, among the 26 patients in whom pancreatoscopy was attempted after successful cannulation, the technical success rate of EHL was 92.3%. Within this group, complete clearance was achieved in 20 patients and partial clearance in 5. To achieve stone clearance, a median of 2 ERCPs (range, 1-3) and 1 EHL procedure (range, 1-2) was required.

Long-term technical success

The recurrence of pancreatic stones varies across clinical literature, influenced by the specific therapeutic techniques employed and the criteria used to define a relapse. In the study by *Han et al*. [29], stone recurrence was defined as the appearance of new symptomatic stones in the MPD following complete clearance. Their findings showed that stones recurred in 38.2% of patients who underwent ERCP with POP-L and 32.3% of those without POP-L after a median duration of 180 days, a difference that was not statistically significant ($p = 0.8$).

Similarly, *Iwata et al*. [32] defined recurrence based on imaging findings regardless of symptoms. They reported comparable rates between groups: 26.6% in the POP-L group (mean observation of 176 days) vs. 24.2% in the ESWL group (mean observation of 329 days), with similar cumulative recurrence curves ($p = 0.53$).

The single-center retrospective observational study conducted by *de Rijk et al.* [35], with a median follow-up time of 35 months, included 19 patients treated with EHL and compared them with a historical cohort (with a median follow-up time of 76.5 days) of 18 patients who underwent ESWL. In this study, *de Rijk et al*. [35] found a more distinct gap in outcomes, noting a symptomatic recurrence rate of 37.0% in the EHL group compared to 61.0% in the ESWL group. Despite this difference, the median time to recurrence was very similar between the two techniques (12.0 vs.

13.0 months, respectively). Regarding reintervention, 71.0% of patients in the EHL group required a second endoscopic procedure, which was successful in 80.0% of cases. In the ESWL group, all patients with symptomatic recurrence underwent endoscopic reintervention, though with a lower clinical success rate of 64.0%.

Finally, the study by *Ogura et al*. [28] stood out from the others, as no recurrence of stones in the main pancreatic duct was observed during their non-specified follow-up period.

Clinical Success

Clinical outcomes and pain control after treatment for pancreatic stones have been assessed using diverse metrics, ranging from reduction in analgesic use to standardized pain scales. In the study by *Bekkali et al*. [27], all successfully treated patients reported significant improvement, with 3 patients discontinuing analgesia entirely and two others markedly reducing their opioid intake. Similarly, *Ogura et al.* [28] reported complete resolution of abdominal pain in all patients who completed treatment.

Standardized scoring systems, such as the Izbicki Pain Score (IPS) and the Numerical Rating Scale (NRS), provide more objective assessment of these improvements. In the study of *Gerges et al*. (2023) [31] pain relief was categorized as complete (IPS ≤ 10) or partial (IPS >10 with a reduction >50% from baseline), with 82.4% of patients achieving overall relief, specifically 61.8% complete and 20.6% partial. This clinical success was mirrored by a significant reduction in mean IPS, which dropped from 55.3 ± 46.2 at baseline to 10.9 ± 18.3 at the 6-month follow-up ($p < 0.001$). Similarly, in another study, *Gerges et al*. (2019) [30] reported a 95.0% success rate (NRS reduction > 50%), with mean scores dropping significantly from 5.4 ± 1.6 to 2.8 ± 1.8 at a 3 to 6 month follow-up ($p < 0.01$). This clinical improvement was accompanied by a 95% reduction in analgesic use and 89% of patients reporting minimal to no daily impairment. Corroborating these findings, *van der Wiel et al.* [34] reported clinical success in 72.0% of patients, defined as a 50% IPS reduction or decreased opiate usage at the 6-month follow-up, with the mean IPS decreasing from 62.3 ± 23 to 27.5 ± 35 after 6 months ($p < 0.001$). Opioid consumption also fell from 52.0% to 16.0%. Of the patients with clinical success, 2 showed partial elimination of the stones and 14 complete removal.

The durability of these results remains a point of focus. The multicenter retrospective cohort study by *Conrad et al*. [36] aimed to evaluate the durability of clinical success, defined as a pain reduction > 50% on the NRS, over 24 months. In this study were included patients with CP who achieved initial complete duct clearance and clinical success after EHL for pancreatic duct stone removal. It was demonstrated that clinical success was sustained in 70.7% of patients from month 3 through month 24. In the study by *de Rijk et al*. [35] long-term clinical success, defined as a similar or lower Izbicki Pain Score or reduction in opiate usage as compared to 6-month follow up, was obtained in 58.0% of patients. However, *de Rijk et al*.[35] noted that, although the IPS showed a statistically significant long-term improvement (decreasing from 64.2 ± 22.4 at baseline to 35.8 ± 33.5 at a median of 35 months follow-up, p=0.001), there was a late increase in opioid use, rising from 16% at 6 months to 32% at the final follow-up.

Other clinical success metrics, such as hospital readmissions, emergency visits, and the need for surgery, were addressed by *Han et al*.[29], who reported comparable success rates between patients treated with POP-L (82.9%) and those without (84.5%). Interestingly, a multivariate analysis identified female sex as a negative predictor for clinical success (adjusted OR 0.19; 95% CI 0.05–0.7), indicating a higher risk of persistent symptoms or rehospitalization compared with males. The authors suggest this association warrants further investigation. In terms of comparative techniques, *Bick et al*.[33] found no statistically significant difference in symptomatic improvement between ESWL (82.7%) and POP-L (93.8%), p=0.483. This assessment was based on patient-reported outcomes collected through follow-up calls and clinical evaluations.

Quality of life

Despite clear improvements in pain scores, several studies, including *de Rijk et al*.[35], *van der Wiel et al*.[34], and *Conrad et a*l.[36], noted that these gains did not always translate into statistically significant improvements in overall quality of life, measured by Short Form-12 Health Survey (SF-12) scores.

In the study by *de Rijk et al*.[35], no statistically significant improvements in quality of life were observed compared to the results obtained at 6 months of follow-up. Specifically, the Physical Component Summary (PCS) remained stable, from 39.3 ± 9.7 at baseline to 39.9 ± 12.9 in the long-term follow-up, whereas the Mental Component Summary (MCS) improved from 41.1 ± 12.4 to 46.6 ± 11.6. Similarly, *van der Wiel et al*.[34] reported an increase in the physical component (from 40.1 ± 11.1 to 43.2 ± 10.3) and the mental component (from 43.4 ± 12.7 to 45.9 ± 12.3). However, these changes did not reach statistical significance (p = 0.080 and p = 0.164, respectively). Finally, in the study by *Conrad et al*.[36], there were also no significant differences: MCS of 50.36 ± 13.3 at baseline and 49.75 ± 11.1 at month 12, p = 0.15; PCS of 44.9 ± 9.8 at baseline and 44.9 ± 10.8 at month 12 (p = 0.1).

In the study by *Gerges et al*. (2019)[30], quality of life was assessed via a standardized questionnaire (in parts adjusted from UK SF-12 Score, at the 3 to 6 month follow-up. Notably 89% of patients reported no or only mild disability in their daily routines, and 47% rated their overall health status as "excellent" or "very good".

Safety

The safety outcomes of the procedures analyzed varied across the included studies, ranging from a complete absence of complications to higher rates of mild-to-moderate adverse events. Notably, *Bekkali et al*. [27] reported that the procedure was entirely safe, with no complications recorded. Similarly, *Ogura et al*. [28] demonstrated a favorable safety profile with no serious adverse events and only a single case of mild acute pancreatitis (5.8%).

In the study by *Gerges et al.* (2019) [30], adverse events were recorded in 30.0% of cases, with a PEP rate of 26.1%, four classified as mild and two as moderate. Additionally, there were 4.3% cases of post-sphincterotomy bleeding and 4.3% cases of pancreatic duct extravasation. Statistical analysis in this cohort identified that a prior history of PEP was a significant risk factor for recurrence ($p < 0.01$). In a later study, *Gerges et al*. (2023) [31] reported serious adverse events in 12.5% of patients during follow-up, including 5.0% cases of pain exacerbation, 2.5% cases of prosthesis displacement-related pancreatitis and post-sphincterotomy bleeding, and unrelated hospitalizations for conditions such as myocardial infarction and vertigo.

Comparative studies provided further insight into the safety of POP-L. *Han et al*. [29] reported an overall adverse event rate of 9.8%, with no statistically significant difference between ERCP with POP-L and without POP-L (6.3% vs. 11.3%, $p = 0.07$). Notably, the POP-L group exhibited a very low incidence of PEP (0.6%) and presented 3.1% cases of abdominal pain and 0.6 cases of bacteremia. Similarly, *Bick et al*. [33] found no significant differences in adverse events between POP-L (5.6%) and ESWL (6.3%), $p = 1.00$. All complications were mild or moderate, PEP was the most frequent complication in both groups, and the only one in the POP-L group (5.6%). In contrast, *Iwata et al.* [32] reported a higher complication rate for POP-L compared to the ESWL group (21.0% vs. 6.3%), although this difference did not reach statistical significance ($p = 0.09$). The nature of the adverse events also differed between the two modalities: while the POP-L group primarily experienced hyperamylasemia (15.8%) and laser-induced perforation (5.3%), the ESWL group was characterized by mild PEP (2.1%) and bleeding (4.3%). Despite one instance of laser-induced perforation requiring surgical intervention in the POP-L group, all patients across both cohorts eventually achieved full recovery.

In a long-term assessment, *de Rijk et al*. [35] noted that 47.3% of patients in the EHL group required readmission for CP exacerbations or inadequate pain relief, with a mean number of hospital admissions of 1.6 ± 2.5 and a mean length of hospital stay of 14.6 ± 12.7 days. Furthermore, new exocrine and endocrine pancreatic insufficiency developed in four and one patient, respectively. *Conrad et al.* [36] observed an overall adverse event rate of 26.0% over a 24-month follow-up, primarily driven by mild to moderate pancreatitis (22.0%).

Finally, *van der Wiel et al*.[34] reported adverse events in 40.0% of patients undergoing EHL, with PEP being the most common complication (28.0%), 24.0% classified as mild and 4.0% as moderate. Other adverse events included abdominal pain (8.0%) and cholangitis (4.0%). Despite their frequency, all complications were mild, resolved with conservative treatment or antibiotics, and required only short hospital stays of 2 to 5 days.

Results of synthesis

Technical success

Ductal Clearance Rate

Across the various studies, high rates of stone fragmentation and clearance were observed. *Bekkali et al.*[27] reported an 83.0% rate of stone fragmentation and duct decompression, while *Ogura et al.*[28] achieved a complete clearance rate of 85.7%. *Gerges et al.* (2019)[30] reported a success rate of 95.0% and, in a later prospective study[31], reported a 90.0% complete ductal clearance rate on the ITT analysis. Finally, *van der Wiel et al.*[34] reported an overall clearance rate of 70.6%, 20 of 25 patients achieved complete clearance (100%) and 5 achieved partial clearance (>50.0%). *Han et al.*[29] found that the POP-L group achieved a significantly higher success rate compared to standard ERCP (98.9% vs. 87.6%, $p < 0.001$), identifying POP-L as the main independent predictor of success (adjusted OR 6.98; 95% CI 2.64-18.46). In this study, a greater number of stones was associated with an increase in clearance rate (adjusted OR 4.39; 95% CI 2.58 -7.48), and the presence of impacted stones drastically reduced the chances of successful clearance (adjusted OR 0.09; 95% CI 0.04-0.17). No significant difference was observed between EHL and LL: 99.0% vs. 100%, $p = 0.62$.

Despite high success rates, several factors limit the generalizability and strength of these conclusions. *Han et al*.[29] noted inherent selection bias, as endoscopists typically reserved POP-L for the most challenging cases, while *Gerges et al*. (2019)[30] focused on restricted populations with complex conditions and a history of treatment failure, potentially compromising external validity. Finally, *van der Wiel et al.*[34] introduced bias by modifying therapeutic strategies based on cannulation difficulty, such as utilizing delayed EHL for difficult cases, which created heterogeneity that may influence both technical and clinical outcomes.

When compared to ESWL, POP-L showed no significant differences in stone clearance rates in the studies by *Iwata et al.*[32] (78.9% vs. 70.2%, $p = 0.55$) and *Bick et al.*[33] (88.9% vs. 86.7%, $p = 1.00$). Multivariate analysis confirmed that the choice between both techniques did not independently affect stone clearance (OR 1.43; 95% CI 0.402–5.958; $p = 0.582$).[32]

In the study by *Iwata et al.* [32], the absence of randomization and the reliance on institutional or physician discretion introduced significant selection bias, limiting direct comparisons between POP-L and ESWL. The study is also subject to bias, as it included asymptomatic patients contrary to clinical guidelines, thereby prioritizing stone clearance over symptomatic relief. Similarly, *Bick et al.*[33] faced a high risk of selection bias due to non-randomized treatment allocation. Baseline differences indicated that the POP-L group managed more complex cases, including larger stones and rescue therapy after failing ESWL. This group also consisted of a smaller sample, consequently, the study may be underpowered to detect rare adverse events, suggesting that success rates might fluctuate as the POP-L sample size increases.

Number of Sessions

Three studies by *Bekkali et al.* [27], *Ogura et al*. [28] and *Gerges et al*. (2023) [31] reported similar mean numbers of POP-L sessions (1.33, 1.31, and 1.36, respectively), while one study by *van der Wiel et al.* [34] reported a median of 1 EHL session (range 1-4). Compared to ESWL, POP-L was significantly more efficient, requiring fewer sessions in both *Iwata et al.* [32] (median 1 vs. 5, $p < 0.01$) and *Bick et al.* [33] (mean 1.6 ± 0.6 vs. 3.1 ± 1.5, $p < 0.001$). This efficiency was further quantified by *Bick et al*. [33], who associated POP-L with higher efficiency for stone removal in ≤ 2 procedures (OR 5.241; 95% CI 1.348-20.369), a benefit significantly attenuated by stone size >10 mm (OR 0.484; CI 0.256–0.912; $p = 0.025$).

According to *Iwata et al.* [32] the assessment of ESWL efficiency is complicated by international and institutional variations in treatment protocols, particularly regarding the number of shock waves administered per session.

Han et al. [29] reported that EHL achieved higher stone clearance in fewer sessions than LL (1.39 vs. 1.92, $p = 0.04$). However, POP-L required significantly more ERCP sessions than conventional ERCP (3.1 vs. 1.9, $p=0.02$).

Procedure Time

According to *Bick et al.* [33], the POP-L group had a significantly shorter cumulative intervention time (101.6 ± 68.2 min) compared to the ESWL group (191.8 ± 111.6 min), $p = 0.001$. *Bekkali et al.* [27] reported a mean procedure time of 48 ± 15 min, and *Iwata et al.* [32] reported a median total procedure time of 72 min (range 30-187 min) for the POP-L group.

Long-term technical success: stone recurrence

Stone recurrence rates show no significant difference between treatment modalities. *Han et al.* [29] reported a recurrence rate of 38.2% in the POP-L group and 32.3% in the non-POP-L group over a median of 180 days ($p = 0.8$). Similarly, *Iwata et al.* [32] found comparable recurrence rates between POP-L (26.6% at 176 days) and ESWL (24.2% at 329 days) with similar cumulative curves (p = 0.53). Conversely, *de Rijk et al.* [35] noted a lower symptomatic recurrence rate with EHL (37.0%) compared to ESWL (61.0%), despite similar median times to relapse (12.0 vs. 13.0 months). Reintervention success in this study was 80% for the EHL group (71.0% of whom required a second procedure) vs. 64.0% for the ESWL group. In this study, the small sample sizes of the EHL and ESWL groups prevented them from being statistically matched. *Ogura et al*. [28] observed no recurrence during their unspecified follow-up period.

Clinical Success

Clinical improvement was consistently observed across studies. Pain relief was observed in 100% of patients in the studies by *Bekkali et al.* [27] and *Ogura et al.* [28], and in 82.4% in the study by *Gerges et al*. (2023) [31] (61.8% complete and 20.6% partial), with the mean IPS dropping from 55.3 ± 46.2 to 10.9 ± 18.3 after 6 months ($p < 0.001$). The same group reported in another study [30] a 95.0% success rate as mean scores fell from 5.4 ± 1.6 to 2.8 ± 1.8 at a 3-6 month follow-up ($p < 0.01$), alongside a 95.0% reduction in analgesic use. *van der Wiel et al*. [34] reported clinical success in 72.0% of patients, with mean IPS decreasing from 62.3 ± 23 to 27.5 ± 35 after 6 months ($p < 0.001$) and opioid consumption falling from 52.0% to 16.0%. *Han et al.* [29] found comparable clinical success between POP-L (82.9%) and the conventional group (84.5%), identifying female sex as a negative predictor (OR 0.19; 95% CI 0.05–0.7). In this study, ductal strictures served as a confounding factor, since their treatment may have caused clinical improvement independent of stone removal. Finally, *Bick et al.* [33] found no significant difference in symptomatic improvement between ESWL (82.7%) and POP-L (93.8%), p = 0.483.

In the study by *Conrad et al.* [36], long-term success was sustained in 70.7% of patients from 3-24 months. *de Rijk et al*. [35] reported a significant long-term improvement in IPS (64.2 ± 22.4 to 35.8 ± 33.5, p = 0.001), although opioid dependence doubled from 16.0% at 6 months to 32.0% at final follow-up. This study may be subject to selection bias due to cohort imbalance, as mandatory opioid use was required only for the ESWL group, suggesting potentially milder disease in the EHL group.

Quality of Life

Despite pain reduction, overall quality of life improvements remained statistically nonsignificant across studies. *de Rijk et al*. [35] reported the PCS of 39.3 ± 9.7 at baseline to 39.9 ± 12.9 in the long term, and the MCS, from 41.1 ± 12.4 to 46.6 ± 11.6 in the long term. *van der Wiel et al.*[34] observed an increase in the PCS from 40.1 ± 11.1 to 43.2 ± 10.3, p = 0.080; and the MCS from 43.4 ± 12.7 to 45.9 ± 12.3, p = 0.164. Similarly, *Conrad et al*. [36] found no significant changes at 12 months for MCS (50.36 ± 13.3 vs. 49.75 ± 11.1; p = 0.15) or PCS (44.9 ± 9.8 vs. 44.9 ± 10.8; p = 0.1).

In the study by *Gerges et al*. (2019) [30], 89% of patients reported no or only mild disability in their daily routines, and 47% rated their overall health status as "excellent" or "very good", at the 3- to 6-month follow-up.

Safety

Safety profiles showed variability. *Bekkali et al.* [27] and *Ogura et al.* [28] reported favorable safety profiles, with complication rates of 0.0% and 5.8% (only one case of PEP), respectively. Similarly, *Han et al.* [29] reported no significant difference between ERCP with or without POP-L (6.3% vs. 11.3%, $p = 0.07$), with 0.6% cases of PEP and 3.1% cases of abdominal pain in the POP-L group. Higher morbidity was noted by *Gerges et al.* (2023) [31] who reported serious adverse events in 12.5% of patients, with 2.5% cases of PEP and 5.0% of abdominal pain. In their earlier study, *Gerges et al*. (2019) [30] showed a 30.0% rate of adverse events (26.1% PEP), identifying prior PEP as a significant risk factor for recurrence ($p < 0.01$). [30] The highest complication rates were reported by *van der Wiel et al*. [34] with an overall event rate of 40.0% and 28.0% of PEP. No difference between POP-L and ESWL was found in the studies by *Iwata et al.* [32] (21.0% vs. 6.3%, $p = 0.09$) *and Bick et al.* [33] (5.6% vs. 6.3%, $p = 1.00$). In the study by *Iwata et al*. [32], the most common adverse event in the POP-L group was hyperamylasemia (15.8%) and there were no cases of PEP. In contrast, the study by *Bick et al.* reported PEP (5.6%) as the only adverse event in the POP-L group.

In a long-term assessment, *de Rijk et al*. [35] noted that 47.3% of patients undergoing EHL required hospital readmission, with a mean number of hospital admissions of 1.6 ± 2.5 and a mean length of hospital stay of 14.6 ± 12.7 days. New exocrine and endocrine pancreatic insufficiency developed in four and one patients, respectively. *Conrad et al.* [36] observed an overall adverse event rate of 26.0% over a 24-month follow-up, with 22.0% cases of PEP.

It should be emphasized that the retrospective nature of 8 of the 10 studies included in this systematic review, and the lack of routine hospital admission following POP-L, increases the risk of underreporting adverse events.

Discussion

For decades, the therapeutic mainstay for symptomatic pancreatic stones has relied on ERCP with sphincterotomy, pancreatic stenting for underlying strictures, and ESWL. Despite the efficacy of these standard approaches, a small but clinically relevant subset of patients remains refractory to conventional extraction methods, necessitating more advanced therapeutic interventions.

Although the current ESGE guidelines [9] do not recommend POP-L as a first-line treatment, the findings of this systematic review suggest that this position may warrant reconsideration. This perspective is supported by previous reviews and meta-analyses, specifically those by *McCarty et al.* [4], *Huang et al.* [24]*,* and *Saghir et al.* [1], whose technical success rates (85.77%, 81.0%, and 76.4%, respectively) are in close alignment with the high efficacy observed in the present review.

Technical Success

Clerance rates across the included studies ranged between 70.6% [34] and 98.9% [29], highlighting both the effectiveness and reproducibility of the technique, supporting its transition to a more central role in future clinical recommendations. The variability may stem from the specific type of pancreatoscopy performed, the operator's clinical experience, and the criteria used to define clearance.

According to *Han et al.* [29], POP-L is the main independent predictor of technical success, increasing the likelihood of stone clearance nearly sevenfold compared to conventional techniques. Notably, POP-L maintained high success rates even in more complex clinical scenarios, including patients with larger, multiple, or impacted stones. [29, 33]

However, interpretation of these results requires caution due to heterogeneity in the definition of technical success. While some studies defined success as complete stone removal [28, 30, 31, 32], others defined it using broader definitions that included partial removal. [29, 33, 34] The definition of complete clearance also varied, as some studies defined total clearance as >90% [29], while others defined it as 100% clearance. This lack of standardization not only hinders direct comparison between modalities but may also overestimate the therapeutic benefit, given that residual fragments predispose to clinical recurrence. Future studies should adopt uniform definitions to improve comparability and clinical applicability.

ESWL vs. POP-L

ESWL remains the standard first-line approach, with reported success rates between 59.0% and 80.0%, following an average of 3 sessions. [30] However, the present analysis suggests that POP-L offers superior procedural efficiency. As demonstrated by *Iwata et al.* [32] and *Bick et al.* [33] this modality requires significantly fewer sessions and shorter cumulative procedure times compared to ESWL. Fewer procedures improve patient comfort and the cost-effectiveness of CP treatment. [31] This efficiency likely reflects the ability of POP-L to combine fragmentation and extraction under direct visualization, allowing for more precise and targeted treatment. Moreover, POP-L enables the management of radiolucent stones and ductal strictures within the same session. [32, 33] Furthermore, POP-L avoids serious complications associated with ESWL, such as splenic or hepatic trauma or cardiac arrhythmias. [33]

Despite these advantages, it is important to note that most comparative studies were non-randomized, with potential selection bias influencing treatment allocation. Therefore, while POP-L appears more efficient, definitive conclusions regarding superiority over ESWL require randomized controlled trials.

Anatomical Challenges

Ductal anatomy remains a key determinant of procedural success. Factors such as stone impaction, ductal angulations, and severe strictures pose physical obstacles to both pancreatoscope navigation and post-ESWL clearance. [28, 32, 33] This finding has also been reported in other studies, notably those by *Brewer Gutierrez et al*. [16] and *Attwell et al.* [37] However, stenoses are not always absolute contraindications to POP-L and can be treated during the same intervention. [30]

Additionally, stone size >10 mm negatively impacts success, whereas the presence of multiple stones appears to favor the technique, likely due to their smaller individual size. [29] Another limitation is the presence of calculi in the ampulla. These are not suitable for POP-L due to the inability to stabilize the device and maintain the direct visual contact required during the transition to the ductal outlet. [33]

Comparing Lithotripsy Modalities: EHL vs. LL

Both EHL and LL demonstrated high efficacy, with no clear evidence of superiority of one modality over the other. The choice between techniques appears to be determined by institutional availability and the team's experience. [1] However, *Han et al.* [29] reported that EHL achieved a significantly higher complete clearance rate (23.8% vs. 4.2%, p = 0.03) in fewer sessions (1.39 vs. 1.92, p = 0.04). This difference is likely due to LL being reserved for complex cases that had already failed EHL treatment. This clinical preference is echoed by *Iwata et al.* [32], who prioritized EHL as the first-line modality. In the study by *Gerges et al.* (2023) [31], due to the small cohort, no definitive conclusion could be drawn whether LL or EHL is more effective.

Current literature suggests a trend toward greater technical efficacy with LL compared to EHL, although not statistically significant, with comparable safety profiles and fragmentation rates.[1, 4,] *Saghir et al.* [1] also suggest that LL may offer a theoretical advantage in cases of extremely dense lesions and emphasize that the effectiveness of these modalities is heavily contingent upon institutional volume and operator expertise, underscoring the decisive role of the learning curve in achieving optimal outcomes. However, based on the data from this systematic review, it is not possible to compare the safety of the two POP-L techniques.

Overall, current evidence does not support a definitive preference for either modality, emphasizing the importance of individualized decision-making and institutional expertise.

Stone Recurrence: Technical Failure vs. Disease Progression

The long-term management of pancreatic stones is significantly challenged by recurrence, with rates in this synthesis ranging from 0.0% [28] to 38.2% [29]. According to *Han et al*. [29] and *Iwata et al.* [32], the recurrence rates for POP-L are comparable to those of conventional ERCP or ESWL, respectively, with no statistically significant differences.

Although incomplete duct removal could theoretically lead to early symptomatic recurrence, the evidence in this synthesis may point to true disease progression, rather than technical failure. This is supported by the fact that although POP-L minimizes retained fragments through direct visual confirmation, its recurrence rates are similar to those of ESWL, reinforcing the notion that lithogenesis is inherent to CP. The prolonged interval until symptom recurrence suggests the formation of new stones. Thus, since POP-L treats only the mechanical obstruction and not the underlying pathophysiology, the pancreas remains a lithogenic environment that requires continuous long-term monitoring.

Clinical Success

The clinical impact of POP-L is reflected in the significant reduction of pain scores (IPS and NRS) and analgesic requirements, with success rates often exceeding 80.0% in our review. These findings align with those reported by *Saghir et al.* [1] (76.8%) and *Huang et al.* [24] (90.0%). Importantly, sustained benefit was observed in long-term follow-up, with clinical success maintained in approximately 70.7% of patients up to 24 months. [36]

Research like those by *Gerges et al*. (2023) [31] and *Conrad et al.* [36] emphasize that complete duct clearance is a key determinant of clinical success. When achieved, symptomatic relief from the endoscopic intervention may become comparable to that from surgery. Therefore, the observed superiority of surgery in earlier trials, such as the ESCAPE study [38], may be partly explained by the limited ability of earlier endoscopic techniques to achieve complete stone clearance.

However, a critical nuance of this synthesis is the dissociation between technical efficacy and quality of life. Studies show that, although stone removal and pain relief are achieved, there is no statistically significant improvement in physical and mental health scores. This indicates that pain is not the only factor affecting the patient's life, which is influenced by a complex array of psychosocial stressors, occupational limitations, and metabolic deficiencies. [34, 35, 36] Thus, despite its technical excellence in mechanical decompression, POP-L should be integrated into a multimodal therapeutic approach.

Safety Profile

The safety of intraductal procedures remains a key concern, with the rates of adverse events in this review ranging from 0.0% [27] to 40.0% [34]. This variability likely reflects differences in study design, reporting practices, and follow-up intensity. For instance, *van der Wiel et al*. [34] observed a 40.0% adverse events rate (including PEP affecting 28.0% of patients), which is considerably higher than the 14.09% pooled rate (8.73% PEP) reported by *McCarty et al.* [4] However, this higher frequency likely reflects a more comprehensive and realistic safety profile captured through a prospective methodology and active follow-up. Despite these higher reported rates, most complications were mild or moderate and were successfully managed with conservative care.

In this review, PEP was the most common complication, as reported by *Huang et al*. [24], *McCarty et al.* [4] and *Saghir et al*. [1], reaching up to 28.0% [34] in some series. *Gerges et al. (2019)* [30] identified a prior history of PEP as a significant risk factor for recurrence. This suggests that careful patient selection and prophylactic measures (such as rectal indomethacin or pancreatic duct stenting) remain essential, particularly in those with a predisposed inflammatory profile. [30] *Han et al.* [29] and *Gerges et al*. (2023) [31] attribute lower rates of serious adverse events to systematic PEP prophylaxis and growing institutional expertise. Additionally, *Han et al*. [29] propose that the "burnout" effect of parenchymal atrophy in CP may attenuate the inflammatory response, potentially decoupling abdominal pain from pancreatic enzyme elevation.

According to *Han et al.* [29], adding POP-L to ERCP does not significantly increase complications, with a remarkably low PEP incidence of 0.6%. *Bick et al.* [33] and Iwata *et al*. [32] confirm the safety of POP-L, as they found no significant differences in complications compared with ESWL (5.6% vs. 6.3%). Although *Iwata et al.* [32] observed a higher absolute rate for POP-L, the difference was not statistically significant.

Moreover, the evolution of pancreatoscopy technology provides superior intraductal visibility, which may reduce procedural complications such as perforation, hemorrhage, and ductal trauma

Study limitations

This systematic review has significant limitations. Primarily due to its reliance on small-scale observational and retrospective studies (only two prospective studies), combined with the absence of randomized clinical trials, introducing a considerable risk of selection bias (no randomization) and unmeasured confounding factors (observational studies), despite the use of multivariate regressions in some studies. The analysis faces significant heterogeneity due to variations in stone characteristics, different locations and prior treatments, as well as the difficulty in comparison caused by the lack of standardization in the definition of technical and clinical success. The generalizability of the findings is limited, as the data come primarily from tertiary referral centers and depend on high technical expertise and specific protocols, which may not reflect the reality of less experienced centers or endoscopists. Furthermore, the absence of long-term follow-up prevents definitive conclusions regarding the efficacy of interventions in a chronic disease such as CP, since temporary improvements in pain and quality of life can be misleading.

Finally, there is a scarcity of comparative data between the use of POP-L as first or second-line treatment. Large-scale prospective studies are still needed to confirm the superiority of POP-L over ESWL and to evaluate the comparative efficacy and safety between EHL and LL.

Conclusion

Pancreatoscopy-guided intraductal lithotripsy is an effective and safe therapeutic option for the management of pancreatic duct stones in patients with CP.

The analyzed evidence indicates that POP-L achieves high technical success rates, maintaining its efficacy even in highly complex clinical scenarios involving large, multiple, or impacted stones. Notably, POP-L demonstrated superior technical success compared to conventional ERCP techniques. Additionally, it outperformed ESWL by significantly reducing both the number of sessions and cumulative intervention time, ultimately translating into greater cost-effectiveness. Furthermore, stone recurrence rates for POP-L remain comparable to conventional methods.

The clinical impact is supported by substantial pain relief, and significant reductions in IPS and NRS. However, a clear dissociation exists between technical success and overall quality of life, suggesting that pain in CP is a multifactorial challenge that requires POP-L to be integrated into a broader, multimodal therapeutic approach.

Regarding safety, the procedure maintains a favorable profile. Although adverse event rates varied, complications were predominantly mild to moderate, with PEP being the most common in most of the studies.

Since no definitive clinical superiority has been established between EHL and LL, the choice currently relies more on institutional availability and operator expertise than on distinct efficacy profiles.

In conclusion, these findings suggest that POP-L can meet the necessary criteria to transition from a second-line rescue strategy to first-line treatment in specialized centers. Nevertheless, the lack of standardized success definitions and the scarcity of randomized controlled trials highlight the need for large-scale prospective studies to confirm these advantages and refine clinical protocols.

Appendix

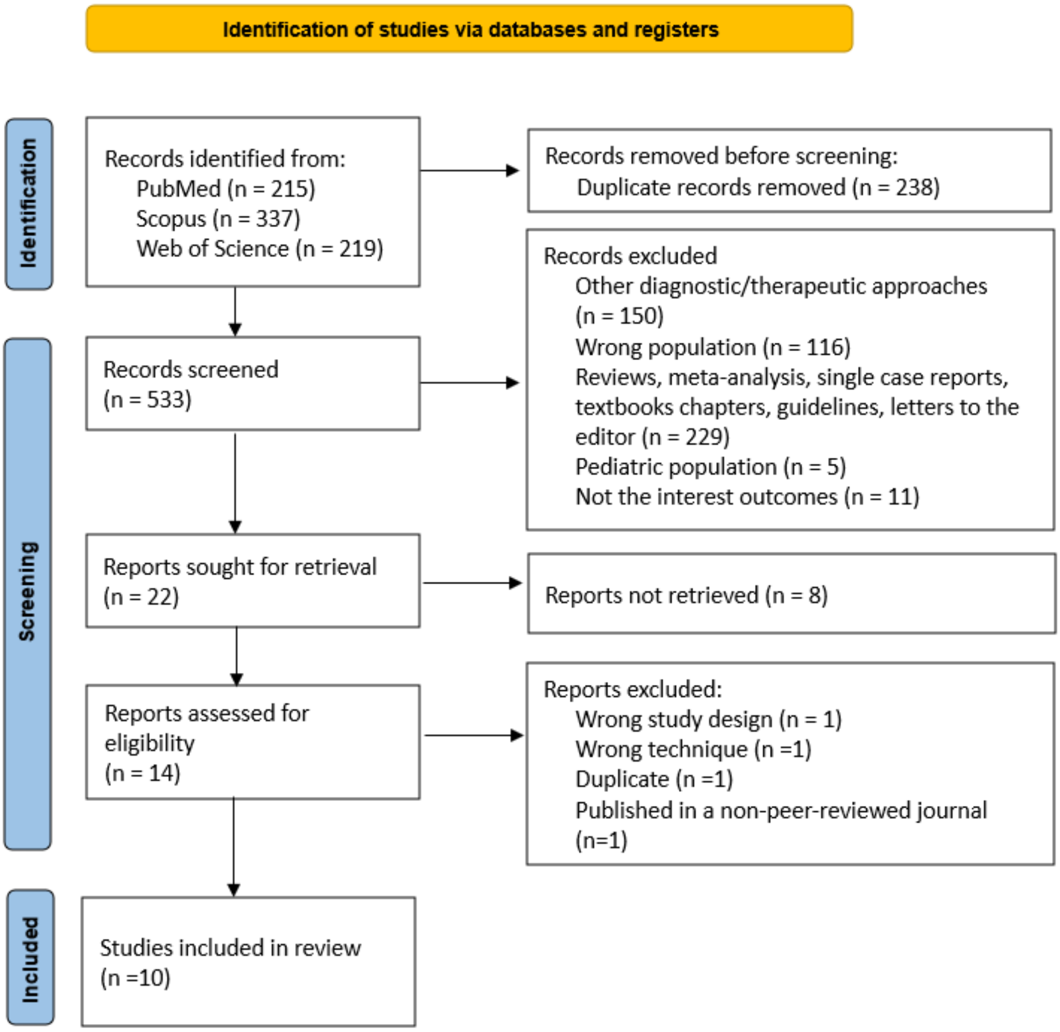

Figure 1 Flowchart of the study selection

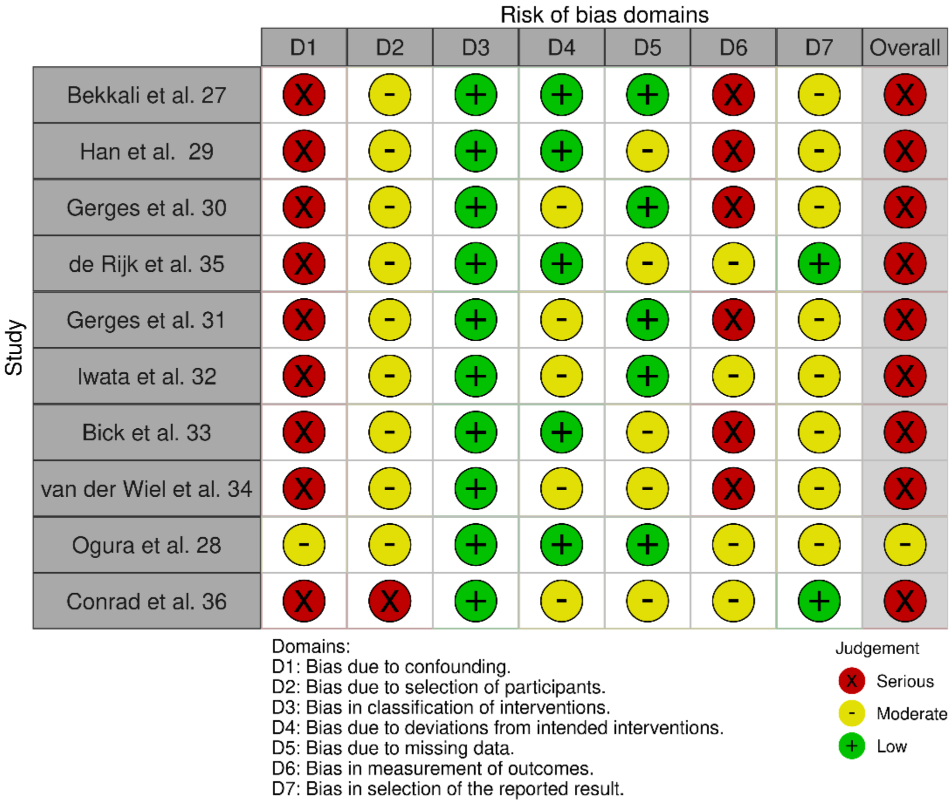

Figure 2 Risk of bias using ROBINS-I tool

Table I Included studies' design and baseline characteristics regarding all participants

Title	Author, publication year	Study design, study period	Follow-up time	Number of participants				Baseline characteristics (regarding all participants)		
				Total	ESWL	EHL	LL	Age (years)	Sex (%)	
									Female	Male
Pancreatoscopy-Directed Electrohydraulic Lithotripsy for Pancreatic Ductal Stones in Painful Chronic Pancreatitis Using SpyGlass [27]	*Bekkali et al.,* 2017	Single center retrospective Observational Study, February 2013 to April 2016	2.7 years	6	0	6	0	45.0 ± 7 [4]	50.0	50.0
A Comparison of Endoscopic Retrograde Pancreatography With or Without Pancreatoscopy for Removal of Pancreatic Duct Stones [29]	*Han et al.,* 2019	Single Center retrospective cohort study, January 2000 to June 2017.	5.1 years	223	0	94 [6]		51.2 ± 16.8 [3]	48.0	52.0
SpyGlass DS-guided lithotripsy for pancreatic duct stones in symptomatic treatment-refractory chronic calcifying pancreatitis [30]	*Gerges et al.,* 2019	Multicenter retrospective cohort study, 2015-2017	3-6 months	20	0	2 [1]	18	62.4 ± 14.8 [3]	45.0	55.0
Long-term outcomes of pancreatoscopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones [35]	*de Rijk et al.,* 2023	Single center retrospective cohort study, December 2017 to July 2020 (EHL) and February 2012 to May2017 (EAWL)	35.0 (EHL) and 76.5 (ESWL) months	37	18	19	0	EHL: 60.8 ± 10.5 [3] ESWL: 55.2 ± 9.5 [3]	40.5	59.5
Digital single-operator pancreatoscopy for the treatment of symptomatic pancreatic duct stones: a prospective multicenter cohort trial [31]	*Gerges et al.,* 2023	Multicenter prospective cohort trial, February 2019 and June 2021	6 months	40	0	[5]		56.7 ± 15.5 [3]	45.0	55.0
Peroral Pancreatoscopy-Guided Lithotripsy Compared with Extracorporeal Shock Wave Lithotripsy in the Management of Pancreatic Duct Stones in Chronic Pancreatitis: A Multicenter Retrospective Cohort Study [32]	*Iwata et al.,* 2024	Multicenter retrospective cohort study, 2006-2022	310 days	66	47	13[2]	4	64.0 (22-86) [4]	34,1	65,9
A comparative study between single-operator pancreatoscopy with intraductal lithotripsy and extracorporeal shock wave lithotripsy for the management of large main pancreatic duct stones [33]	*Bick et al.,* 2022	Single center retrospective cohort study, September 2013 to September 2019.	NS	258	240	18	0	58.0 ± 12.6[3]	45.0	55.0
Pancreatoscopy-guided electro hydraulic lithotripsy for the treatment of obstructive pancreatic duct stones: a prospective consecutive case series [34]	*van der Wiel et al.,* 2022	Single-center prospective consecutive case series, December 2017 and July 2020	6 months	34	0	25	0	56.7 ± 13.5 [3]	38.0	62.0
Electrohydraulic Lithotripsy for Pancreatic Duct Stones Under Digital Single-Operator Pancreatoscopy (with Video) [28]	*Ogura et al.,* 2019	Single center retrospective study, October 2016 and August 2017	NS	21	0	21	0	55.0 (17-78) [4]	28.6	71.4
Long-Term Efficacy and Safety of Digital-Single-Operator Video-Pancreatoscopy Guided Lithotripsy for Pancreatic Duct Stones [36]	*Conrad et al.,* 2025	Multicenter retrospective cohort study, 2015-2022.	24 months	58	0	58	0	59.2 ± 12.8 [3]	37.9	62.1

EHL: Electrohydraulic Lithotripsy; ESWL: Extracorporeal Shock Wave Lithotripsy; LL: Laser Lithotripsy; NS: not specified
[1] : 23 procedures were performed on 20 patients, 2 of which were successful EHL procedures; [2]: Of 19 patients, in 2 patients it was impossible to reach the pancreatic stone with the pancreatoscopy tool; [3]: Expressed as mean ± SD; [4]: Expressed as median (range); [5]: EHL was used in 49 of 53 DSOP procedures and LL in 1/53; [6]: EHL was used in 101 procedures and LL in 24.

Table II Included studies' design and baseline characteristics regarding all participants

Study	POP-L Technique	Stone Size, mm (mean ± SD)	Stone Location (%)	PD stenosis [2]	Previous treatment	Chronic pancreatitis etiology
Bekkali et al. [27]	EHL	10.6 ± 3.9	83.3% head, 16.7% head/tail	NR	Medical, endoscopic techniques such as stent placement	33.3% Alcohol, 33.3% SPINK1-mutation, 16.7% Idiopathic, 16.7% Biliary
Han et al. [29]	EHL/LL	8.9 ± 5.3	89.4% head, 6.4% body, 2.7% tail	Nearly in all cases	Endotherapy and ESWL	55.2% Alcohol, 19.3% Idiopathic, 7.2% Hereditary, 7.2% Gallstone, 6.7% Pancreas divisum, 1.4% Autoimmune, 2.2% other
Gerges et al. [30]	EHL/LL	9.3 ± 2.5	40% head, 50%, genu, 10% corpus/tail	8/20	ERCP, ESWL and pancreatic surgery	Chronic Calcifying Pancreatitis (not specified)
de Rijk et al. [35]	EHL	8.0 ± 2.6	89.5% head, 10,5% neck	13/19	Medical	62.2% Alcoholic, 24.3% Idiopathic, 5.4% Hypercalcemia, 2.7% Pancreas divisum and alcohol, 2.7% Medication-induced, 2.7% genetic
Gerges et al. [31]	EHL/LL	9.8 ± 3.5	60% head, 12.5% genu, 35% corpus	19/40	Medical	35.0% Alcohol, 57.5% Idiopathic, 2.5% Metabolic, 2.5% Abnormal anatomy, 2.5% Hereditary
Iwata et al. [32]	EHL/LL	10 (5-21) [1]	78.9% head, 21,0% body/tail	11/19	NR	87.8% Alcohol, 10.6% Idiopathic, 1.5 Autoimmune
Bick et al. [33]	EHL	10.3 (7.4) [1]	94.4% head, 11.1% neck, 33.3 % body, 5.6 % tail	7/18	Endoscopic techniques such as stent placement, ESWL and prior failed POP-L	55.6% Alcohol, 72,2% Tobaco, 11.1% Hereditary, 5,6% Obstructive, 22.2% Idiopathic
van der Wiel et al. [34]	EHL	8.6 ± 3.3	92% head, 8% neck	14/25	Medical	59.0% Alcohol, 30.0% Idiopathic, 6.0% Hypercalcemia, 6.0% Pancreas divisum and alcohol
Ogura et al. [28]	EHL	12.0 (8-18) [1]	28.6% head, 52.4% body, 4.8% tail, 9.5% head/body, 4.8 body/tail	4/21	NR	81,0% Alcohol, 19,0% Idiopathic
Conrad et al. [36]	EHL	NR	69% head, 20.7% genu, 10.3% corpus	NR	Surgery, ESWL or ERCP	43,1% Alcohol, 8,6% Idiopathic, 1.7% Auto-immune, 13,85% Other, 32,8% Unknown

EHL: Electrohydraulic Lithotripsy; ERCP: Endoscopic Retrograde Cholangiopancreatography; ESWL: Extracorporeal Shock Wave Lithotripsy; LL: Laser Lithotripsy; NR: not reported; POP-L: Pancreatoscopy-guided Intraductal Lithotripsy; SD: Standard Deviation

[1]: Expressed as median (range); [2]: number of cases/total of patients

Table III Outcomes accessed

Study	Outcomes Accessed	Study	Outcomes Accessed
Bekkali et al. [27]	Technical success (stone fragmentation and removal) Ductal decompression (reduction in MPD size on imaging) Clinical success (pain relief and reduction in opioid use) Procedure time Adverse events	***Iwata et al.*** [32]	Technical success (complete clearance) Number of sessions (corresponds to the sum of all procedures performed, including ERCP for sphincterotomy, dilation, or stone fragment removal and lithotripsy sessions) Procedure time Cumulative stone recurrence rate Factors influencing stone clearance Adverse events
Han et al. [29]	Technical success (complete or partial clearance of MDP, >90% and >50% respectively) Clinical success (absence of emergency room visits, hospitalizations for CP exacerbations, and pancreatic surgery during follow-up) Stone recurrence (new, pancreatography-proven symptomatic pancreatic stones, following complete stone clearance) Adverse events	***Bick et al.*** [33]	Technical success (complete or >90% clearance rate) Clinical success (patient-reported pain improvement) Efficiency (use of ≤ 2 procedures for clearance) Aggregate procedure duration Adverse events
Gerges et al. [30]	Technical success (Ability to reach the target stone with SpyGlass DS and achieve either complete PD stone clearance or significant duct clearance making stent placement possible) Clinical success (>50% post-interventional reduction on NRS pain score) QoL (standardized questionnaire adjusted from UKSF-12 score) Adverse events	***van der Wiel et al.*** [34]	Technical success (complete or partial clearance of MPD, 100% and 50-99% stone clearance, respectively) Clinical success (≥ 50% reduction in IPS or reduced opiate usage at the 6-month follow-up) Total number of ERCPs performed QoL (SF-12 score) Adverse events
de Rijk et al. [35]	Long-term treatment success (no symptomatic stone recurrence confirmed by imaging) Long-term clinical success (IPS and reduced opioid usage) QoL (SF-12, pancreatic function, pain control and hospital readmission)	***Ogura et al.*** [28]	Technical success (fragmentation) Complete ductal clearance (100%) Clinical success (pain relief, no scale) Stone recurrence Adverse events
Gerges et al. [31]	Technical success (complete ductal clearance in ≤ 3 sessions with DSOP) Clinical success (IPS at 3 and 6 months after the last intervention) PD diameter before treatment and 6 months after the final intervention Visualization of the stone with DSOP Successful drainage after complete/incomplete fragmentation Successful PD stent placement if needed Number of interventions Adverse events	***Conrad et al.*** [36]	Long-term clinical success (pain reduction > 50% on the NRS scale at 24 months) QoL (SF-12 score) Adverse events

DSOP: Digital single-operator pancreatoscopy; ERCP: Endoscopic Retrograde Cholangiopancreatography; IPS: Izbicki Pain Score; MPD: Main Pancreatic Duct; NRS: Numerical Rating Scale; QoL: Quality of Life; SF-12: Short Form-12 Health Survey

Table IV Details of outcomes accessed

				Adverse events (%)				
Study	**Clearance**	**Number of lithotripsy sessions (mean)**	**Clinical Success**	**Overall AEs**	**PEP**	**Abdominal Pain**	**Post-sphincterotomy bleeding**	**Others**
Bekkali et al. [27]	83.0%	1.33	100.0%	0.0	0.0	0.0	0.0	0.0
Han et al. [29]	98.9%	LL:1.92 [7] EHL: 1.39 [7]	82.9%	6.3	0.6 [3]	3.1	NR	Bacteremia: 0.6
Gerges et al. [30]	95.0%	NE	95.0%	30.0	26.1 [2] Mild-moderate	NR	4.3	PD contrast extravasation: 4.3.
de Rijk et al. [35]	NE	NE	58.0%	NE	NE	NE	NE	New exocrine pancreatic Insufficiency: 21.1 New endocrine pancreatic insufficiency: 10.5
Gerges et al. [31]	90.0%	1.36	82.4%	12.5	2.5 [4]	5.0	2.5	NR
Iwata et al. [32]	78.9%	1.00 (1-4) [1]	NR	21.0	NR	NR	NR	Hyperamylasemia: 15.8 PD perforation: 5.3
Bick et al. [33]	88.9%	1.60	93.8%	5.6	5.6 [2] Mild	NR	NR	NR
van der Wiel et al. [34]	70.6%	1.00 (1-2) [1]	72.0%	40.0	28.0 [2] Mild-moderate	8.0	NR	Cholangitis: 4.0
Ogura et al. [28]	85.7%	1.31	100.0%	5.8	5.8 [5] Mild	NR	NR	NR
Conrad et al. [36]	NE	NE	70,7%	26.0	22.0 [6] Mild- moderate	NR	NR	Fever: 4.9

EHL: Electrohydraulic Lithotripsy; LL: Laser Lithotripsy; NE: Not evaluated; NR: Not Reported; PD: Pancreatic Duct; PEP: Post-ERCP Pancreatitis

[1]: Expressed as median (range); [2]: Cotton criteria [21]; [3]: Adverse events and their severity were defined in accordance with the ERCP-associated adverse events outlined by the American Society for Gastrointestinal Endoscopy (ASGE) [20]; [4]: Severity not assessed; [5]: ASGE criteria [39]; [6]: Severity scale not specified; [7]: Data obtained from the per-procedure analysis

Table V Efficacy and Safety: POP-L vs. ESWL

		Iwata et al. [32] **(EHL and LL)**		***Bick et al.*** [33] **(EHL)**	
		POP-L (n=19)	**ESWL (n=47)**	**POP-L (n=18)**	**ESWL (n=240)**
Stone Clearance Rate		78.9%	70.2%	88.9%	86.7%
Total Number of Sessions		1.00 (1–4)[1]	5.00 (2–28)[1]	1.6 ± 0,6 [3]	3.1 ± 1.5 [3]
Procedure time (min)		72.0 [2]	NR	101.6 [4]	191.8 [4]
Size of stones (mm)		10.0 [2]	10.0 [2]	10.3 [4]	10.0 [4]
Pancreatic Duct stenosis		57.8%	36.1%	38.9%	55.4%
Pancreatic duct diameter (mm)		Upstream MPD stone: 8.5 [2] Downstream MPD stone: 3.15 [2]	Upstream MPD stone: 7.0 [2] Downstream MPD stone: 3.0 [2]	8.2 [4]	7.2 [4]
Stones location		78.9% head, 21,0% body/tail	76.6% head, 23,4 % body/tail	94.4% head, 11.1% neck, 33.3 % body, 5.6 % tail	81.7% head, 11.7% neck, 13.3 % body, 3.3 % tail
Pancreatic Stone Recurrence		26.6%	24.2%	NR	NR
Time of follow-up		176 days [2]	329 days [2]	NR	NR
Clinical success (pain relief)		NE	NE	93.8%	82.7%
Complications	**Overall**	21%	6.3%	5.6%	6.7 %
	Hyperamylasemia	15.8%	0		
	Pancreatitis	0	2.1%	5.6%	4.6%
	MPD perforation	5.3%	0	0	
	Bleeding	0	4.3%	0	0,4%
	Ascending cholangitis	NR	NR	0	0,4%
	Symptomatic intrabdominal hematoma	NR	NR	0	0,4%
	Ventricular arrhythmia	NR	NR	0	0,4%

EHL: Electrohydraulic Lithotripsy; ESWL: Extracorporeal Shock Wave Lithotripsy; LL: Laser Lithotripsy; NE: Not evaluated; NR: Not reported; POP-L: Pancreatoscopy-guided Intraductal Lithotripsy
[1]: Expressed as median (range); [2]: Expressed as median; [3]: Expressed as mean ± SD; [4]: Expressed as mean

Other information

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