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How to Prolong Plastic Biliary Stent Patency – Translational Research Into Patient, Underlying Disease and Treatment Related Factors

DOCTORAL DISSERTATION

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VILNIAUS UNIVERSITETAS

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Kaip prailginti plastikinio tulžies latakų stento funkcionavimą – paciento, ligos ir gydymo faktorių transliacinis tyrimas

DAKTARO DISERTACIJA

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ABBREVIATIONS

ACG	–	The American College of Gastroenterology
AE	–	alveolar echinococcosis
AGA	–	The American Gastroenterological Association
ASGE	–	The American Society for Gastrointestinal Endoscopy
ASV	–	Amplicon sequence variant
CBD	–	common bile duct
cSEMS	–	covered self-expandable metal stent
CT	–	computerized tomography
ERCP	–	endoscopic retrograde cholangiopancreatography
ESGE	–	The European Society of Gastrointestinal Endoscopy
EUS	–	endoscopic ultrasound
Faith PD	–	Faith's phylogenetic diversity
FDR	–	False Discovery rate
fcSEMS	–	fully covered self-expandable metal stent
HPB	–	hepatopancreatobiliary
IQR	–	interquartile range
LMM	–	linear mixed model
MRCP	–	magnetic resonance cholangiopancreatography
NA	–	not assessed
NSAID	–	nonsteroidal anti-inflammatory drug
PCoA	–	Principal Coordinates Analysis
PEP	–	post-ERCP pancreatitis
PERMANOVA	–	permutational multivariate analysis of variance
ROC	–	polylactide-octenidine-citrate
SE	–	standard error

SEMS	–	self-expandable metal stent
Spp.	–	species

CONTENT

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) and plastic biliary stent placement is an essential therapeutic modality for managing both benign and malignant biliary obstruction. However, the utility of plastic biliary stent is fundamentally constrained by the inevitable development of biofilm-mediated occlusion. While plastic stents are favoured for their ease of placement, removal, and cost effectiveness, their durability remains limited—typically maintaining patency for only 2 – 4 months, with reported medians ranging from ~55 days in malignant diseases to ~110 days in benign conditions (1,2). Plastic biliary stent occlusion has a significant negative impact on patient outcomes, including increased rates of hospitalization, delays or interruptions in chemotherapy, and a higher incidence of serious complications such as cholangitis and sepsis.

The pathophysiology of stent dysfunction is a complex interplay between microbial colonization, biofilm matrix structure, and the physical properties of the stent itself. It has been long known that obstruction of plastic stents most commonly results from bacterial biofilm formation, proteinaceous sludge accumulation, and tumor or tissue ingrowth. These processes are influenced by both stent-related and patient-specific factors (3–5). However, the inconsistent results of antimicrobial coated plastic stents efficacy in vivo and in vitro underpin the importance of other factors affecting biofilm formation and plastic biliary stent occlusion.

The biofilm formation is initiated by a rapid bacterial colonization of the stent surface, which occurs withing days of stent placement. This colonization is dominated by polymicrobial flora, with enterococci, *Enterobacteriaceae*, and *Candida* species being most prevalent. Biofilm formation is facilitated by the stents's exposure to bile and duodenal content, and is further promoted by prior antibiotic therapy and underlying biliary pathology (6–8).

Advances in sequencing technologies have transformed the study of the microbiome of plastic biliary stents, enabling comprehensive characterization of microbial communities and their role in stent occlusion. Early studies relied on culture-based methods, which underestimated microbial diversity and missed key anaerobic and fastidious organisms.

The mechanism of the biofilm formation on a plastic stent resulting in occlusion is well known, however, there remains a lack of comprehensive models that integrate procedure-related, stent-related, and patient variables to predict stent occlusion and complications.

The **aim** of this doctoral dissertation is to assess patient, underlying disease and treatment related factors affecting plastic biliary stent patency.

Tasks:

1. To identify the actual plastic biliary stent patency time and patient, underlying disease and procedure related factors affecting it.
2. To identify patient, procedural and management factors affecting the outcomes of ERCP associated perforations.
3. To assess the influence of patient, underlying disease and procedure related factors on biliary microbiome.

Statements to defend:

1. Male gender and cholangitis during the index ERCP are patient related factors affecting plastic biliary stent patency and patient outcomes.
2. Malignancy, especially intrabiliary maligancy, is an underlying disease factor affecting plastic biliary stent patency and patient outcomes.
3. Prescription of antibiotics, increasing number of stents being placed, early recognition of procedural complications and sequential stent exchange are treatment related factors affecting plastic biliary stent patency and patient outcomes.

LITERATURE REVIEW

Endoscopic retrograde cholangiopancreatography: history, development and current applications

Endoscopic retrograde cholangiopancreatography (ERCP) was first described in 1968 and rapidly evolved into a cornerstone for the diagnosis and management of pancreatobiliary diseases. Initially, ERCP was primarily a diagnostic tool, allowing direct opacification and radiographic visualization of the biliary and pancreatic ducts. However, with the advent of non-invasive imaging modalities such as endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP), the diagnostic role of ERCP has been largely supplanted, and its use is now almost exclusively therapeutic (9–13).

The development of ERCP paralleled advances in endoscopic technology, including side-viewing duodenoscopes and improved fluoroscopic imaging. Early therapeutic interventions, such as endoscopic sphincterotomy and stone extraction, were introduced in the 1970s, transforming ERCP into a minimally invasive alternative to surgery for choledocholithiasis and obstructive jaundice (14). Over the subsequent decades, the therapeutic scope of ERCP expanded to include stent placement for malignant and benign strictures, management of bile leaks, and treatment of pancreatic ductal pathologies (9,10,15).

Currently, the main indications for ERCP are therapeutic, including removal of common bile duct stones, relief of malignant or benign biliary obstruction, management of biliary leaks, and treatment of pancreatic ductal disruptions or strictures. In the context of pancreatic diseases, ERCP is utilized for interventions such as pancreatic duct stenting, stone extraction, and management of pancreatic fluid collections, particularly in chronic pancreatitis and post-surgical complications (9,10,15). The introduction of peroral cholangioscopy and pancreatoscopy has further refined ERCP, enabling direct visualization, targeted biopsies, and advanced interventions within the biliary and pancreatic ducts (15,16).

ERCP procedures are performed at a rate of approximately 83 to 105 per 100 000 persons per year in the United States and Canada, with majority now being therapeutic rather than diagnostic (17–19). The utilization of ERCP has increased over the past two decades, driven by its role in managing biliary and pancreatic diseases, espcecially in older populations and patients with comorbidities (18,19).

Biliary stent placement, which is most commonly performed during ERCP, accounts for approximately 29 – 35% of all ERCP procedures in population-based cohorts (20,21). Stenting is indicated for both benign and malignant biliary obstruction, and its use is widespread for conditions such as choledocholithiasis, cholangitis, and malignancy (21–23). For example, in a single-center study of elderly patients undergoing ERCP for choledocholithiasis, 29% required concurrent stent placement (21). In large tertiary centers, stent placement rates during ERCP are similar, ranging from 29% to 35% (20).

ERCP is a technically demanding procedure with a recognized risk profile, including post-ERCP pancreatitis, infection, haemorrhage, and perforation. The risk of complications underscores the importance of careful patient selection and operator expertise (24,25). Training in ERCP is rigorous, requiring structured programs and competency assessment to ensure procedural safety and efficacy (25).

ERCP has transitioned from a diagnostic to a predominantly therapeutic modality, driven by technological advances and the availability of non-invasive imaging. Its current applications are focused on the endoscopic management of complex biliary and pancreatic diseases, with ongoing innovations in device technology and procedural techniques continuing to expand its therapeutic potential (9,10,15,16,26).

ERCP, its efficacy and complications, as well as stent patency has been the area of interest in medical research for years. This holds true to Lithuanian researchers as well. In 2003 dr. Gintautas Radžiūnas has defended a doctoral dissertation on the outcomes of ERCP. The author has found ERCP and biliary tract stenting to be an efficatious management modality for both benign and malignant biliary obstruction with favorable complication profile and identified particular indications for ERCP.

Benefits of ERCP versus surgical approaches: biliary strictures

ERCP and surgical management are the principal modalities for treating biliary obstruction, particularly in the context of choledocholithiasis and malignant and benign strictures. ERCP has evolved into the mainstay minimally invasive therapeutic approach for biliary decompression, stone extraction, and stent placement, offering rapid symptom relief and reduced perioperative morbidity compared to traditional surgery. Its role is especially prominent in cases of acute cholangitis, where urgent biliary drainage via ERCP within 24 hours is associated with improved outcomes and lower complication rates than surgical or percutaneous alternatives (9,27). For malignant obstruction, ERCP with stenting is preferred for palliation and preoperative decompression, with surgical bypass reserved for cases where endoscopic or percutaneous methods fail (28,29).

Benign biliary strictures

ERCP is the cornerstone of management for benign biliary strictures, offering both diagnostic and therapeutic capabilities. Benign biliary strictures most commonly arise from postoperative injury (e.g., post-cholecystectomy or liver transplantation), chronic pancreatitis, or inflammatory conditions. The primary goals of ERCP in this context are to relieve biliary obstruction, prevent cholangitis and secondary biliary cirrhosis, and restore ductal patency (30–32).

The American Society for Gastrointestinal Endoscopy (ASGE) and the American Gastroenterological Association (AGA) both recognize ERCP with stent placement as the preferred first-line therapy for benign biliary strictures, particularly those related to chronic pancreatitis and postoperative injury (30,33). The standard approach involves progressive dilation of the stricture and sequential placement of multiple plastic stents, exchanged every 3 months over a 6 – 12 month period, to achieve long-term stricture resolution. This technique is supported by robust data demostrating clinical success rates approaching 80 – 90% for non-hilar strictures, though it requires multiple procedures and is techanically demanding (31–34). Similar position is held by the European Society of Gastrointestinal Endoscopy (ESGE), regarding therapeutic ERCP as the gold standard for benign biliary stricture management, primarily through progressive gradual placement of multiple plastic stents (35).

Sequential placement of increasing number of plastic biliary stents achieves long-term stricture resolution rates of approximately 80 – 90% for postoperative strictures and 50 – 70% for strictures due to chronic pancreatitis. Surgical management, typically via bilioenteric anastomosis (e.g., Roux-en-Y hepaticojejunostomy), remains the gold standard for strictures refractory to endoscopic therapy, complex hilar strictures, or those associated with significant ductal injury (32,36). Meta-analyses suggest that surgery yields the highest long-term stricture resolution rates, but the difference compared to endoscopic approaches is not statistically significant, and surgery carries higher perioperative morbidity and longer post-procedural recovery (36,37). Laparoscopic techniques have reduced surgical morbidity compared to open repair, but both approaches are associated with risks of anastomotic stenosis and bile leak (36).

Malignant biliary strictures

ERCP is a key procedure for both diagnosis and management for malignant biliary strictures, which are most commonly caused by cholangiocarcinoma and pancreatic adenocarcinoma. The primary clinical objectives in these patients are to confirm or exclude malignancy and to restore biliary drainage, as obstruction can lead to jaundice, cholangitis, and impaired hepatic function (38–40).

Therapeutically, stent placement during ERCP is the preferred first-line intervention for palliation of malignant obstruction. The American College of Gastroenterology (ACG) emphasizes that ERCP-directed stenting is associated with lower morbidity compared to surgical bypass and is the standard of care for extrahepatic and distal malignant strictures (41). In selected cases, ERCP may also be used for preoperative biliary drainage, particularly when neoadjuvant therapy is planned or in patients with severe cholestasis (41,42).

Recent advances include ERCP-guided therapies (e.g., photodynamic therapy, radiofrequency ablation) and integration of endoscopic ultrasound for complex or inaccessible strictures, expanding the therapeutic possibilities (39,43). Therefore, ERCP remains central to the multidisciplinary management of malignant biliary strictures, providing both diagnostic clarity and effective palliation (38,41).

Hepatic echnicoccosis – rare and specific underlying indication for ERCP and stent placement

Hepatic echinococcosis is a parasitic infection of the liver caused primarily by the larval stages of *Echinococcus granulosus* (cystic echinococcosis) and, less commonly, *Echinococcus multilocularis* (alveolar echinococcosis). The disease is acquired when humans, acting as accidental intermediate hosts, ingest eggs from contaminated food, water, or soil, typically in regions where the parasite is endemic. After ingestion, the eggs hatch in the small intestine, releasing oncospheres that penetrate the intestinal wall and enter the portal venous system, which transports oncospheres to the liver – the most common site of involvement (44–47).

Within the liver, the mechanisms of parasitic infiltration differ by species. In cystic echinococcosis, the oncosphere develops into a unilocular, fluid-filled cyst with an inner germinal layer and an outer laminated acellular layer. The cyst expands slowly, often over years, and may form daughter cysts and protoscolices, leading to mass effect and potential complications such as rupture or biliary compression (44,45,48). In contrast, alveolar echinococcosis is characterized by infiltrative, tumor-like growth of interconnected vesicles, with exogenous budding and local tissue destruction, mimicking malignancy and often resulting in progressive hepatic failure if untreated (46–48). The chronic nature and slow progression of both forms are due to the parasite's ability to evade host immune responses and establish persistent infection within hepatic tissue (44,46,48).

Plastic biliary stents are frequently employed for the management of biliary obstruction secondary to hepatic echinococcosis, particularly in cases of alveolar echinococcosis (AE) where infiltrative parasitic lesions cause biliary strictures, cholestasis, and recurrent cholangitis. The patency of these stents is a critical determinant of clinical success and complication rates.

Plastic biliary stents in hepatic echinococcosis typically remain patent for approximately 2 – 3 months, after which the risk of stent occlusion and subsequent cholangitis increases substantially. This is consistent with general recommendations for plastic stent management in benign biliary diseases, where elective stent exchange or removal within 3 months is advised to minimize adverse events such as stent occlusion, stentolith formation, and infection (49). In the context of AE, stent occlusion rates may be higher due to the intense inflammatory and necrotic environment, as well as the presence of debris and parasitic material within the biliary tree (50–52).

Serial procedures of ERCP with balloon dilation and repeated stent placement is the mainstay of endoscopic management for AE-related biliary strictures. Studies have demonstrated that repeated interventions, including the use of multiple plastic stents, can prolong bile duct patency and delay the need for surgical biliary bypass procedures. In a multicenter European survey, insertion of multiple plastic stents was associated with longer intervals between stent exchanges and improved long-term ductal patency, with 73% of patients achieving sustained patency and 95% of patients experiencing symptom resolution (52). The use of larger diameter stents (≥8,5Fr) and single stent implantation were identified as risk factors for post-ERCP cholangitis, suggesting that multiple smaller stents may be preferable in this setting (50).

Complications associated with plastic stent placement in AE include stent occlussion, cholangitis (reported in up to 10% of cases), and, less commonly, pancreatitis. Intensive lavage of the bile ducts during ERCP may reduce the risk of cholangitis by clearing debris and infectious material (50,52). The risk of stent occlusion is further increased in patients with hilar bile duct stenosis, a common finding in advanced AE, and in those with a history of cholangitis at the time of index ERCP (50). In cases where plastic stents fail to maintain patency or recurrent occlusion occurs, temporary placement of fully covered self-expandable metal stents (fcSEMS) may be considered, although this is not standard practice and should be reserved for refractory cases (51).

Long-term management of biliary complications in hepatic echinococcosis requires a multidisciplinary approach, combining endoscopic interventions with continuous antiparasitic therapy (e.g., albendazole or mebendazole) to control disease progression and reduce the risk of further biliary involvement (53). Surgical options, such as bilio-digestive anastomosis, are generally reserved for patients in whom endoscopic management fails or is not feasible due to extensive biliary destruction (51,53).

Plastic biliary stents in hepatic echnicoccosis provide effective short-term relief of biliary obstruction, with a typical patency of 2 – 3 months. Regular stent exchange, use of multiple stents, and adjunctive balloon dilation are key strategies to optimize outcomes and minimize complications. Vigilant follow-up and timely interventions are essential to prevent stent-related adverse events and maintain long-term biliary patency in this complex patient population (50–52).

Complications of ERCP

ERCP is associated with a range of complications, the most frequent and clinically significant being post-ERCP pancreatitis (PEP), bleeding, cholangitis, cholecystitis, perforation, and procedure-related mortality. The overall incidence of adverse events remains substantial, with recent meta-analyses reporting rates of pancreatitis at 4,6% overall and up to 6,5% in first-time patients, bleeding at 1,5%, cholangitis at 2,5%, cholecystitis at 0,8%, perforation at 0,5% and death at 0,2% (54). These rates have remained relatively stable over the past two decades despite advances in technique and prophylaxis.

Post-ERCP pancreatitis is the most common serious adverse event, with risk factors including younger age, female sex, prior pancreatitis, sphincter of Oddi dysfunction, difficult cannulation, and pancreatic duct instrumentation (55,56). The ESGE recommends routine rectal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) immediately before or after ERCP for all patients to reduce the risk of PEP, and prophylactic pancreatic stent placement in high-risk cases (57).

Bleeding typically follows sphincterotomy and occurs in 1 – 2% of cases. Risk factors include coagulopathy, anticoagulant use, and difficulty of the procedure. Management involves endoscopic therapy (diluted adrenaline injection, thermal coagulation, mechanical clips), with escalation to angiographic embolization or surgery in treatment-refractory cases (58).

Cholangitis and cholecystitis result from incomplete biliary drainage or bacterial contamination. Cholangitis occurs in 2 – 3% of cases and is managed with broad-spectrum antibiotics and urgent biliary decompression. Cholecystitis is less common (0,8%) and may require cholecystectomy or percutaneous drainage (54,58).

Perforation is a rare (0,5 – 0,9%) but serious complication, often related to sphincterotomy or guidewire injury. Early recognition is a critical factor in patient outcomes and in most cases can be managed conservatively with endoscopic closure, diversion of bile flow, and drainage. However, surgery may be required for large or uncontained leaks (58,59).

Sedation-related events (hypoxia, aspiration) and cardiovascular complications are less common but can occur, especially in older or comorbid patients (58,59). Procedure related mortality is low (0,2 – 0,3%), with most deaths occuring in patients with underlying malignancy or severe comorbidity (54,59,60).

ERCP-associated perforations

ERCP-associated perforations are rare but potentially life threatening complications. The Stapfer classification is the most widely used system for categorizing these perforations, as it correlates the mechanism and anatomical location of injury with clinical outcomes and guides management strategies (61). The classification divides ERCP-associated perforations into four types:

Type I (lateral or medial duodenal wall perforation):

These are large perforations of the duodenal wall, typically caused by the endoscope itself. They often result in free intraperitoneal leakage and present with severe symptoms. Type I injuries almost always require prompt surgical intervention, such as primary repair or duodenal exclusion, due to the high risk of peritonitis and sepsis. Conservative management is rarely successful, and delayed surgery is associated with increased morbidity and mortality (61–64). Early recognition during procedure is critical for optimal patient outcomes (65).

Type II (periampullary perforation):

Type II perforations are the most common and occur at the medial wall of the duodenum, usually as a result of sphincterotomy or precut papillotomy. They typically result in retroperitoneal air and fluid leakage with varying clinical severity. Most patients can be managed non-operatively with bowel rest, intravenous fluids, antibiotics, and close observation. Increasingly primary endoscopic closure, such as placement of fcSEMS or endoscopic clips, is performed to close the defect and divert biliary content with encouraging results (61,62,66,67). Surgery is generally reserved for cases with clinical deterioration or failure of conservative/endoscopic management.

Type III (bile duct or pancreatic duct perforation):

Type III perforations are small perforations in biliary or pancreatic ducts caused by guidewire or instrument trauma during cannulation, manipulation, stone extraction, or stenting. These injuries are generally minor and can be managed conservatively with antiobiotics and close monitoring. Endoscopic stenting may be considered in cases of persistent leakage or obstruction, whereas surgical interventions are rarely required (61,63,68).

Type IV (retroperitoneal air only)

Perforations of type IV include cases with only retroperitoneal air, usually due to excessive insufflation or minor sphincter manipulation, without a straightforward transmural defect. These injuries are considered clinically insignificant and are managed conservatively. Patients generally recover without major morbidity with observation and supportive care (61,66,69).

The management of ERCP-associated perforations is guided by the Stapfer type, clinical presentation, and timing of diagnosis. Early recognition, preferabily intraprocedural, is paramount for favorable outcomes and reduces morbidity (64,65,67). Conservative management is appropriate for most type II, III, and IV perforations, while type I injuries generally require surgery. Endoscopic closure techniques (clips, stents) are increasingly used for type II perforations, with evidence supporting their efficacy and safety (61,70,71). Multidisciplinary approach is essentianl for optimal management and patient outcomes (66).

ERCP-associated cholangitis

ERCP-associated cholangitis is a significant iatrogenic complication defined by infection and inflammation of the biliary tree following ERCP. The incidence of post-ERCP cholangitis in general population is approximately 2,5% (95% CI 1,9 – 3,3%), as demonstrated in a large systematic review and meta-analysis of over 120 000 ERCP procedures (54). This risk is significantly higher in certain subgroups, such as patients with hepatic alveolar echinococcosis, where rates of post-ERCP cholangitis may approach 9,8% (50).

Development of ERCP-associated cholangitis relies on bacterial contamination of the biliary tract, often facilitated by incomplete biliary drainage, intervention, or stent placement during ERCP. Biliary obstruction, whether due to stones, strictures, or malignancy, further predisposes to infection (50,72). Enterobacteriaceae (notably *Escherichia coli* and *Klebsiella spp.*), *Enterococcus spp.*, are the most commonly isolated microorganisms from bile cultures in post-ERCP cholangitis, whereas anaerobes are less frequently encountered pathogens. Importantly, prior biliary sphincterotomy increases the risk of colonization with vancomycin-resistant *Enterococcus* (VRE) and multidrug-resistant organisms (73).

Risk factors for post-ERCP cholangitis include perihilar biliary strictures, endoscopic retrograde biliary drainage, large diameter stents (≥8,5 Fr), and a single stent placement (50). Technical factors such as incomplete drainage, multiple cannulation attempts, and pre-existing biliary infection increase the risk of ERCP-associated cholangitis even further (24,74).

Prompt initiation of broad-spectrum intravenous antibiotics targeting both gram-negative and gram-positive organisms, with adjustment to local resistance patterns and culture results is essential in the management of post-ERCP cholangitis. Empiric antibiotic regimens often include a third-generation cephalosporin or piperacillin – tazobactam, while carbapenems should be considered in high-risk or resistant cases (72,73). Infection source control is crucial in management of post-ERCP cholangitis and ERCP is the preferred modality for decompression, with percutaneous or surgical options reserved for cases where ERCP is not feasable (72,74). The timing of intervention is critical, as delays in biliary drainage are associated with increased morbidity and mortality (75).

With early recognition and appropriate management the outcomes of ERCP-associated cholangitis are generally favorable, but severe cases can progress to sepsis and multi-organ failure. Mortality rates have declined with advances in diagnostic and therapeutic modalities but remain significant in cases of severe cholangitis (72).

ERCP carries a significant risk of complications, with post-ERCP pancreatitis being the most frequent and severe. Risk stratification and procedural expertise are paramount to reduce the rate of adverse events and early recognition and evidence-based management of complications are essential to optimize patient outcomes (76).

Biliary stents

Biliary stents are the cornerstone in the management of obstructive biliary diseases, inlcuding both benign and malignant aetiologies. The two principal categories – plastic and metal stents – differ significantly in their material properties, clinical indications, patency, complication profiles, and cost-effectiveness. ERCP remains the primary modality for stent placement, with the choice of stent type tailored to the underlying pathology, anticipated duration of stenting, and patient-specific factors (42,43).

Plastic biliary stents, typically composed of polyethylene or polyurethane, are widely used for short-term drainage in benign strictures, post-surgical leaks, and as a temporizing measure in malignant obstruction. Their advantages include ease of placement and removal, lower upfront costs, and suitability for situations requiring frequent stent exchange. However, plastic stents are limited by relatively short patency (approximately 3 months), with a higher risk of occlusion, cholangitis, and need for re-intervention if retained beyond recommended intervals. Current practice emphasizes removal or exchange within 3 months to mitigate these risks (49).

Metal stents, particularly self-expandable metal stents (SEMS), have become the preferred option for malignant biliary obstruction due to their superior patency and lower rates of recurrent biliary obstruction and cholangitis compared to plastic stents (79–81). Covered SEMS (cSEMS) have further expanded indications to include select benign strictures, offering sustained radial force, longer patency, and removability, while minimizing tissue ingrowth and hyperplasia (78). In preoperative and neoadjuvant settings for pancreatic and periampullary cancers, metal stents are associated with fewer delays in therapy, lower intervention rates, and comparable postoperative outcomes to plastic stents (79–81).

Despite these advantages, metal stents are associated with higher upfront costs, potential for stent migration, and, in some cases, increased risk of procedure-related pancreatitis (81). The choice between plastic and metal stents must therefore balance clinical efficacy, complication risk, cost, and patient-specific factors.

Plastic versus metal stents: benign biliary strictures

The evidence comparing plastic biliary stents and metal biliary stents (specifically cSEMS/fcSEMS) for benign biliary strictures demonstrates that both modalities are similarly effective in achieving stricture resolution, with comparable safety profiles and recurrence rates. Multiple randomized controlled trials and meta-analyses have addressed this question across different aetiologies including post-liver transplant anastomotic strictures and chronic pancreatitis.

Meta-analyses and multicenter randomized trials consistely show that stricture resolution rates are similar between multiple plastic stents and cSEMS. For example, Kamal et al. found no significant difference in stricture resolution rates (risk ratio 1,02; 95% CI 0,96 – 1,10) between groups (82). Cote et al. demonstrated noninferiority of cSEMS compared to multiple plastic stents, with resolution rates of 92,6% for cSEMS and 85,4% for multiple plastic stents (77). Ramchandani et al. reported 24 month resolution rates of 77,1% for multiple plastic stents and 75,8% for fcSEMS in chronic pancreatitis associated bening biliary strictures (83).

Recurrence rates after stent removal are also comparable. Kamal et al. found no significant difference (risk ratio 1,68; 95% CI 0,72 – 3,88) (82). Other meta-analyses confirm similar recurrence rates between multiple plastic stents and cSEMS (84,85).

The overall adverse event rates do not differ significantly between the two stent types. Kamal et al. reported a risk ratio of 1,17 (95% CI 0,73 – 1,87) for adverse events (82). Ramchandani et al. found most common complications to be cholangitis, stent migration and pancreatitis, with serious adverse event rates of 19,0% for multiple biliary stents and 23,8% for fcSMES, with no significant difference between treatment modalities (83).

Stent migration is more frequent with cSEMS/fcSEMS than with multiple plastic stents (82,77,83,85). This is a recognized limitation, particularly in post-surgical anastomotic strictures, and there are ongoing technological developments to address this issue (77,86).

A consistent finding is that metal stents require fewer ERCP procedures to achieve stricture resolution (84,85). Kamal et al. and Cote et al. both found that significantly fewer ERCP procedures are needed to achieve stricture resolution in the cSEMS group (mean difference -1,99 and -1,10, respectively) (77,82). Ramchandani et al. reported a mean of 2,6 ERCP procedures for fcSEMS versus 3,9 for multiple plastic stents over two years (83).

Plastic stent placement typically involves serial increase in number and diameter of the stents and exchange every 3 months. This approach requires multiple stents to be placed in parallel and 3 – 4 ERCP procedures over 12 months (77). cSEMS/fcSEMS are usually left in place for 6 – 12 months, with removal at a single session, provided that the stent does not overlap the cystic duct in patients with an intact gallbladder (77,87). Longer indwelling time (up to 180 – 365 days) may improve outcomes, but optimal duration is still under investigation (87).

fcSEMS are more cost-effective than multiple plastic stents for benign biliary strictures, primarily due to reduced procedural burden and lower overall healthcare resource utilization, despite higher upfront device costs (77,83,88). The latest evidence demonstrates that fcSEMS require significantly fewer ERCP procedures and stent exchanges to achieve comparable rates of stricture resolution and recurrence, resulting in lower cumulative costs over the course of therapy (77,82,83).

Long-term outcomes, including quality of life, are improved with fcSEMS due to fewer interventions and shorter treatment duration, which reduces patient morbidity and time away from regular activities (83,87,88).

Plastic versus metal stents: malignant biliary strictures

For malignant biliary strictures, the evidence consistently demonstrates that SEMS are superior to plastic stents in terms of stent patency, clinical success, and reduction in reintervention rates, particularly for distal strictures. Large cohort studies and meta-analyses show that SEMS provide longer patency (mean difference 4 – 9 months), lower rates of stent occlusion (odds ratio 0,27 – 0,43), and fewer late complications such as cholangitis and sepsis when compared to plastic stents, without significant differences in 30-day mortality or overall survival in most settings (89–92). SEMS placement also requires fewer reinterventions (mean difference -0,83 interventions) and lower rates of stent occlusion from sludge (odds ratio 0,11) (90).

For distal malignant biliary strictures, SEMS placement is associated with higher clinical success (94,1% versus 87,4%) and lower unplanned reintervention rates (17,1% versus 27,4%) compared to plastic stents, as well as lower rates of cholangitis (89). Based on these advantages, ESGE recommends SEMS as the first-line endoscopic treatment for distal malignant biliary strictures (93).

In malignant hilar strictures, the evidence is more nuanced. SEMS offer longer stent patency and lower occlusion rates, but technical challenges and the inability to reposition uncovered SEMS may complicate reintervention if initial drainage is inadequate (41). For complex hilar strictures (Bismuth-Corlette II – IV), ESGE suggests initial placement of plastic stents to confirm adequate liver drainage before exchanging for SEMS (93). Some randomized trials and meta-analyses show similar clinical success and adverse event rates between suprapappilary plastic stents and SEMS, suggesting that plastic stents may be a viable alternative in select hilar cases (94,95).

In preoperative biliary drainage for pancreatic cancer, SEMS provide more durable drainage and lower reintervention rates, with similar perioperative outcomes compared to plastic stents (80,96). However, in short-term preoperative settings, outcomes between plastic stents and fcSEMS are similar, and cost-effectiveness may favor plastic stents (97).

The selection of biliary stent type is a nuanced decision informed by the underlying disease, expected duration of stenting, and risk-benefit considerations. Metal stents offer superior patency and reduced reintervention rate for malignant and select benign indications, while plastic stents remain valuable for short-term drainage and situations necessitating frequent exchange (49,78–81).

Plastic biliary stents

Plastic biliary stents are temporary instruments to assure bile duct patency in both benign and malignant biliary obstruction. Their physical properties are determined by the polymer used, stent geometry, surface characteristics, and manufacturing processes.

The most common polymers used in the manufacturing of plastic biliary stents are polyethylene and polyurethane, with some stents being made from ethylene-vinyl acetate copolymer. Polyethylene is the preferred material due to its superior biocompatibility, flexibility, and resistance to chemical degradation. On the other hand, ethylene-vinyl acetate has been associated with increased protein deposition and occlusion risk, making it less suitable for long term indwelling (98). Polyurethane offers greater flexibility but is less commonly used due to its tendency for biofilm formation.

Stent diameter typically ranges from 7Fr to 12Fr, with lengths from 5cm to 15cm, allowing customization to patient anatomy and stricture location (99,100). However, plastic stent diameter is limited by technical constraints: standard therapeutic duodenoscopes typically accommodate stents up to 10 – 12Fr in diameter and larger diameter stents cannot be passed through the working channel or safely through the biliary tract during percutaneous placement (101,102). In contrast, SEMS can be deployed in a compressed state and then expand to a larger diameter in situ, circumventing this limitation (102,103). Larger diameter plastic stents are associated with longer patency, but the maximal diameter is ultimately restricted by the delivery system and anatomy (101–103).

The geometry of the plastic stents encompass straight, double-pigtail, and more recently, spiral or twist designs, that aim to improve stent anchoring and reduce migration (104). The surface of plastic stents is generally smooth to minimize tissue trauma, as well as reduce bacterial adhesion and biofilm formation (105).

Mechanical properties such as flexibility and tensile strength are critical for deployment and resistance to deformation. Stents must withstand bending during catheter placement without permanent deformation or fracture. Recent advances in 3D printing and resin optimisation have focused on improving elasticity and mechanical resistance, but excessive bending can still exceed the yield stress of some polymers, risking damage during placement (106).

Plastic stents are radiopaque, typically due to the incorporation of barium sulfate or other radiopaque fillers, allowing visualization during fluoroscopic placement and follow-up (6). They are nondegradable, necessitating removal or exchange within 3 months to prevent occlusion and infection, as recommended by the current clinical practice (49). Surface modifications, such as antibacterial or antibiofilm coatings, are under investigation to improve patency and reduce the risk of infection, but are not yet standard in clinical practice (7,105).

Plastic biliary stents offer several advantages: they are cost-effective, widely available, and relatively easy to place and remove endoscopically, making them suitable for short-term biliary drainage in both benign and malignant conditions, as well as for preoperative decompression (8,101,102). Their lower upfront cost is particularly relevant in patients with limited life expectancy or when temporary drainage is required (107). In benign strictures, multiple plastic stents can be sequentially exchanged to achieve ductal remodelling (108).

However, plastic stents are limited by shorter patency, typically remaining functional for approximately 2 – 3 months before occlusion risk rises due to bacterial biofilm formation and sludge accumulation (49,101,102). This necessitates scheduled exchanges to prevent complications such as cholangitis, stent occlusion, and more rarely, proximal or distal migration (49). Compared to SEMS, plastic stents are associated with higher rates of stent dysfunction, more frequent reinterventions, and increased rate of late complications in malignant biliary obstruction (8,89,90,102). Larger diameter plastic stents (e.g., 12Fr) may reduce occlusion rates but do not match the patency of SEMS (101).

The physical properties of plastic biliary stents, such as polymer type, diameter, length, geometry, surface characteristics, mechanical strength, and radiopacity, directly influence their clinical performance, patency, and complication profile. Plastic biliary stents are advantageous for short-term, cost-sensitive, and easily reversible biliary drainage, but their use is constrained by limited patency and higher complication rates, necessitating careful patient selection and timely exchange (8,49,101,102,107,108).

Ongoing research aims to optimize these properties through advanced manufacturing techniques to address the limitations of current stent designs (6,7,100,106).

Mechanism of plastic biliary stent occlusion

Plastic biliary stent occlusion is a multifactorial process driven by the interplay of microbial biofilm formation, duodenobiliary reflux, dietary fiber deposition, and stent design characteristics. The biofilm formation is initiated by a rapid bacterial colonization of the stent surface, which occurs within days of stent placement. This colonization is dominated by polymicrobial flora, with enterococci, *Enterobacteriaceae*, and *Candida* species being most prevalent. Biofilm formation is facilitated by the stents's exposure to bile and duodenal content, and is further promoted by prior antibiotic therapy and underlying biliary pathology (109–111).

The process of biofilm formation follows particular stepwise pattern and can be divided into distinct stages:

1. Initial conditional film formation: within minutes to hours of stent placement, the plastic surface is coated by host-derived proteins, glycoproteins, and bile components. The conditioning film alters the physicochemical properties of the stent, facilitating microbial attachment (112).
2. Microbial attachment: early colonizers, predominantly aerobic gram-positive bacteria (e.g., *Enterococcus spp*.), and *Candida spp.*, adhere to the conditioned surface via specific adhesins and non-specific interactions. Initial attachment is reversible, but becomes irreversible as microbial surface structures (fimbriae, pili) interact with the stent and conditioning film (112,113).
3. Microcolony formation and early biofilm development: attached microflora proliferate and begin to secrete extracellular polymeric substances, primarily polysaccharides and proteins, which anchor cells to the stent and to each other. This matrix provides structural integrity and protection from shear forces and host defences. Early

biofilm formation is often localized around stent side holes, where microturbulence and bile flow disturbances promote microbial aggregation (3).

4. Biofilm maturation: over days to weeks, the biofilm thickens and matures. The microbial community diversifies, with polymicrobial consortia predominating (113,114). Anaerobes (e.g., *Clostridium spp.*), gram-negative bacteria (e.g., Enterobacteriaceae, *Klebsiella spp.*), and fungi (*Candida spp.*) link to the biofilm, especially as indwelling time increases (109,113). The extracellular polymeric substances matrix becomes more complex, incorporating host and microbial proteins, DNA, and bile pigments. Channels form within the biofilm, allowing nutrient and waste exchange.
5. Sludge accumulation and stent occlusion: the mature biofilm traps bile pigments, cholesterol crystals, calcium bilirubinate, and cellular debris, forming sludge. This process is accelerated by longer stent indwelling times, smaller stent diameters, and the presence of side holes (3,113,114). Sludge accumulation leads to a progressive narrowing and eventual occlusion of the stent lumen.
6. Late stage community shifts and resistance: with the passing of time, the microbial spectrum shifts towards increased abundance of anaerobes and resistant microorganisms (e.g., vancomycin-resistant enterococci, ESBL-producing Enterobacteriaceae, azole-resistant *Candida spp.*), especially in patients with prior exposure to antibiotics (109,113). Biofilm architecture confers significant antimicrobial resistance and evasion of host immunity.
7. Clinical consequences: stent occlusion manifests as cholestasis and/or cholangitis in a subset of patients. Notably, biofilm formation does not always result in a symptomatic obstruction, but increases the risk of infection and necessitates stent exchange (3,113).

Key modulating factors that affect the rate of stent occlusion have been identified:

- Indewelling time: longer duration increases biofilm complexity and occlusion risk (3,113,114).
- Stent design: side holes and smaller diameters promote biofilm formation (3).
- Microbial diversity: host factors and hospital environment influence microbial composition, with *Bifidobacterium spp.* and Actinomycetota associated with sever occlusion (111,115).

- Antibiotic exposure: administration of antibiotics promotes selection of resistant organisms and increases fungal colonization (109).

Biofilm development is initiated at stent side holes and progresses to cover the entire inner surface within 30 – 60 days. The biofilm matrix consists of living and dead bacteria embedded in extracellular polymeric substances, which trap bile pigments, cholesterol crystals, and calcium bilirubinate, forming amorphous sludge (3,4). The presence of dietary fibers, introduced via duodenobiliary reflux, creates a scaffold that accelerates intraluminal debris accumulation and acts as a filter, further impeding bile flow (3,116). Plant material and food particles are frequently identified in occluded stents, underscoring the importance of reflux in the occlusion process (4,116).

The mechanism of plastic biliary stent occlusion is primary driven by a rapid microbial biofilm formation, intraluminal sludge and dietary fiber deposition, and duodenobiliary reflux. Stent design and patient-specific factors modulate the rate and severity of occlusion, whereas timely stent exchange, typically within 3 months, remains the cornerstone of occlusion prevention (3,4,49,109,111).

The importance of plastic biliary stent occlusion

Plastic biliary stent occlusion has a significant negative impact on patient outcomes, including increased rates of hospitalization, delays or interruptions in chemotherapy, and a higher incidence of serious complications such as cholangitis and sepsis. The median patency of plastic stents in patients undergoing chemotherapy for pancreatic cancer is often less than two months, with premature stent occlusion occuring in up to 35 – 55% of cases, frequently necessitating urgent reintervention and hospitalization (117,118). Hospitalization rates for stent-related complications are substantial, with 44,6% of patients requiring admission for stent dysfunction, and a median hospital stay of three days per event (118,119).

Stent occlusion is a leading cause of chemotherapy interruption. In Lamarca et al. study patients experiencing stent-related events such as occlusion or cholangitis had chemotherapy delay in 24%, discontinuation in 17%, and death in 22% of cases (120). Cholangitis and interruptions of neoadjuvant chemotherapy due to stent failure are independently associated with reduced overall survival and progression free survival. For example, median overall survival was reduced drom 36 to 26 months and median progression free survival from 17 to 8 months in patients with cholangitis or chemotherapy interruption (121).

Other complications of plastic stent occlusion include recurrent biliary obstruction, abnormal liver function, jaundice, stent migration, stentolith formation, and rarely, perforation (49). Infectious complications are common, with up to 75% of stent-related events being infections in advanced cancer cohorts (120). These events often require urgent endoscopic or surgical intervention and can compromise the ability to deliver optimal oncologic or palliative care.

Plastic biliary stent occlusion is strongly associated with increased rates of hospitalization, delays or discontinuation of chemotherapy, infectious complications, and worsened survival in patients with biliary obstruction, especially those with malignancy (117–122). Timely stent exchange and individualized risk assessment are critical to mitigate these risks.

Patient-related factors affecting plastic biliary stent patency

Plastic biliary stent patency is influenced by several patient-related factors, with evidence supporting a major role of prior infection and antibiotic exposure in premature stent occlusion.

A prior episode of cholangitis at the time of index ERCP is a risk factor for early stent occlusion and recurrent cholangitis. Quantitative analysis confirms that stents retrieved from patients with cholangitis have significantly higher protein content in biofilms, indicating more robust microbial colonization and biofilm formation, correlating with increased occlusion rates and reduced patency (114). For post-transplant strictures, urgent re-stenting due to cholangitis predicted failure of plastic stent therapy, but the underlying aetiology of the biliary stricture (post-transplant versus other benign causes) did not independently affect patency or recurrence rates (123).

Polymicrobial colonization, especially with Enterococci, *Enterobacteriaceae*, and *Candida spp.*, is common and potent driver of biofilm formation on stent surfaces. Prior antibiotic exposure increases the risk of fungal colonization, which further reduces stent patency (109,110,114). Early attachment of anaerobic bacteria may play a role in stent blockage even in patients receiving antibiotic prophylaxis, suggesting that targeting only gram-negative bacteria is insufficient (124).

Female gender appears to be a protective factor against early stent occlusion. A retrospective cohort study found that female patients had a significantly lower risk of early stent occlusion compared to males (adjusted odds ratio 0,54; 95% CI 0,32 – 0,90), though the mechanism is unclear and may be related to differences in bile composition or immune response (1). There is currently no evidence supporting age as an independent predictor of stent patency, though data in the elderly are limited and adjunctive therapies may influence outcomes (1,125). Age does not significantly affect protein content in biofilms, but older patients may have higher polysaccharide concentrations in the biofilm composition (114).

Broad-spectrum antibiotics and prolonged courses of antibiotics are associated with increased colonization of plastic biliary stents by resistant organisms and fungi, particularly *Candida* species. In a prospective cohort study, patients who received prolonged antibiotic therapy prior to stent placement had a significantly higher rate of *Candida* colonization (63% versus 46,7%, p=0,023), and a notable prevalence of vancomycin-resistant enterococci and ESBL-producing *Enterobacteriaceae* was observed, indicating that broad-spectrum agents promote selection of resistant strains and fungi (109). In vitro, specific antibiotics have differential effects on bacterial adherence: ciprofloxacin and ceftazidime (broad-spectrum antibiotics) markedly reduced *E.coli* attachment, while ampicillin (narrow-spectrum antibiotic) reduced *Enterococcus* adherence but not *E.coli*. Prolonged exposure to ciprofloxacin sustained the reduction in *E.coli* adherence, suggesting that both the spectrum and duration of antibiotic exposure can shape the initial microbial biofilm composition (124). However, clinical studies and meta-analyses do not demonstrate a reliable effect of prior antibiotic exposure, regardless of type and duration, on subsequent stent patency or infection rates. Randomized trials and systematic reviews show no significant benefit of prophylactic or therapeutic administration of antibiotics in prolonging stent patency or reducing infectious complications, and do not support routine antibiotic use for this purpose (126).

Disease-related factors affecting plastic biliary stent patency

Disease-related factors affecting the patency time of plastic biliary stents include the underlying aetiology of biliary obstruction, the presence of malignancy, and the location of the stricture.

Underlying malignant biliary obstruction is associated with reduced patency of plastic biliary stents. Multiple studies demonstrate that plastic stents occlude more rapidly in the setting of malignancy, with median patency durations limited to 2 months, and a higher risk of early occlusion and cholangitis compared to bening indications (1,117). In a prospective cohort study of 343 patients undergoing 561 ERCP procedures, malignant strictures were associated with a higher rate of stent occlusion and cholangitis compared to benign strictures, with hilar location further increasing risk of early occlusion (1). The mechanism of the premature stent occlusion is multifactorial, and includes time-dependent increase in tumor burden, local inflammation, immunosuppression, and a propensity for biofilm and sludge formation. In patients with pancreatic cancer undergoing neoadjuvant chemotherapy, more than half required repeat ERCP for stent exchange due to occlusion or cholangitis, with a median time to exchange of 82,5 days (117). Benign strictures, especially post-surgical or inflammatory, tend to have longer patency, but repeated interventions are often required to assure clinical resolution (110,127).

Multiple studies have evaluated the effect of stricture location on plastic biliary stent patency. Hilar strictures are consistently associated with an increased risk of early stent occlusion and reduced patency compared to distal (extrahepatic) strictures. In the aformentioned study of 343 patients, multivariate analysis showed that hilar location increased the odds of early occlusion (adjusted odds ratio 3,41; 95% CI 1,68 – 6,90), regardless of aetiology (1). Long-term outcome studies of sequential plastic stent therapy for benign strictures show lower success rates in stricture resolution for hilar strictures (25%) compared to distal strictures (81%), though differences may not always reach statistical significance due to small sample sizes (128). In contrast, patients with nonhilar extrahepatic strictures have low rates of premature stent occlusion even when stent exchange intervals are prolonged beyond 6 months (127). Meta-analyses confirm that the placement of a single plastic stent results in inferior long-term patency compared to multiple stents, and that stricture location (especially hilar) is a key determinant of the outcome (37).

Procedure-related factors affecting plastic biliary stent patency

The most important procedure-related factors, such as the number and size of stents placed, placement technique, stent design and indwelling time have been shown to significantly contribute to plastic biliary stent patency time.

Number and size of placed plastic biliary stents have an important effect on stent patency time. Evidence consistently demonstrates that larger diameter biliary stents (≥8,5Fr versus 7Fr) are associated with longer stent patency and lower rates of premature occlusion in both benign and malignant biliary strictures (129,130). In a large retrospective study, median stent patency was significantly shorter for 7Fr stents compared to larger stents (28 days versus 34 days, p=0,001), and the rate of premature exchange was higher with smaller diameter stents (31,3% versus 22,4%, p=0,03) (129). Similarly, a cohort study in malignant distal biliary obstruction found that large-diameter stents had a significantly higher patency rate until surgery (89,5% versus 41,7%, p=0,0006) and were independently associated with improved patency (130). Regarding stent number, placement of multiple plastic stents increases patency and reduces premature occlusion in benign strictures (127,129). A tertiary center study showed that the placement of multiple stents was associated with longer occlusion-free survival and a low rate of premature symptomatic occlusion, even when left in place for more than 6 months (127). However, in the case of malignant strictures, the benefit of multiple stents is less clear, and increasing the number of stents may not further improve patency and could increase the risk of complications (129). Larger diameter stents and multiple stent placement in benign strictures are preferred for maximizing plastic stent patency, while in malignant diseases, the benefit of multiple stents must be weighted against increased risk of complications.

Placement technique for plastic biliary stents affects stent patency through several mechanisms. Placement across the papilla (transpapillary) is standard, as it facilitates endoscopic access for future stent exchanges and reinterventions. However, this technique allows for duodenobiliary reflux, which introduces intestinal contents and bacteria into the stent lumen, accelerating biofilm formation and debris accumulation, thereby shortening stent patency. Studies have shown that biofilm formation begins around side holes and the distal end of the stent, particularly within 30 days, and progresses to full occlusion by 90 days, with reflux playing a key role in this process (3). Inside-type stents, placed above the papilla, may reduce duodenobiliary reflux and biofilm formation, potentially prolonging patency, but are technically more challenging to place and remove. Comparative data suggest that across-the-papilla placement is associated with similar patency to inside-type stents, but the latter may be preferable in select cases with high risk of reflux-related occlusion (131). Transpapillary placement increases risk of early occlusion due to duodenobiliary reflux, while inside-type placement may reduce this risk but is less commonly used due to technical limitations and negligible added stent patency benefit in unselected cases (3,131).

Longer indwelling time is associated with reduced plastic biliary stent patency and increased risk of stent occlusion and related complications. Multiple large retrospective and prospective studies consistently show that plastic biliary stents typically remain patent for approximately 2 – 3 months, after which the risk of occlusion rises substantially due to biofilm formation and debris accumulation (3,49,118). The occlusion process generally initiates around 80 days and progresses to full occlusion by a median of 90 days (3). ESGE advises stent exchange within 3 – 6 months since prolonged indwelling time beyond 6 months is associated with significantly higher rates of recurrent jaundice, urgent ERCP, and stent reinsertion (132,133).

Models to predict plastic biliary stent occlusion

Models used to predict plastic biliary stent occlusion are primarily based on clinical risk factors and scoring systems derived from retrospective and prospective cohort studies. The most robust evidence supports models that incorporate patient-specific and procedural variables, such as indication for stenting (malignant versus benign), history of cholangitis, number of stents placed, stricture location, and biochemical markers (e.g., bilirubin level). A multicenter study developed a simple score model for patients with malignant biliary strictures, identifying plastic stent type, tight stricture requiring dilation, and high initial bilirubin as independent predictors of occlusion. This model stratified patients into high- and low-risk groups for stent patency duration (134). Additionally, hilar stricture location was shown to significantly increase the risk of early occlusion, supporting early elective exchange in these cases (1).

Microbiological and biofilm studies have further elucidated the pathogenesis, identifying polymicrobial colonization (notably Enterobacteriaceae, Enterococci, and *Candida spp*.), biofilm formation, and duodenobiliary reflux as contributors to occlusion, but these findings have not yet been integrated into widely used predictive models (109–111,114).

Current predictive models for plastic biliary stent occlusion rely on clinical and procedural risk factors, with scoring systems available for malignant strictures. No universally accepted or guideline-endorsed model exists, but risk stratification based on these factors is supported by the literature (1,134).

Biliary and stent microbiome

The microbiome of bile and plastic biliary stents is characterized by complex, polymicrobial communities, with significant clinical implications for stent occlusion and infection. Bile in desease-free individuals contains low-biomass, diverse microbiota, but biliary obstruction and drainage alter this composition, increasing antibiotic resistance and reducing diversity (135). Placement of plastic biliary stents leads to rapid and dense colonization, predominantly by *Enterococcus spp.*, Enterobacteriaceae (including *Escherichia coli* and *Klebsiella spp.*), *Streptococcus spp.*, and *Candida spp.*, and frequent polymicrobial biofilms (109,113,114,136,137).

Recent evidence contradicts the previous notion of biliary sterility, revealing low-biomass microbiota along the gut-biliary axis with metabolic and immunologic effects (138). In benign and malignant biliary diseases, distinct microbial consortia drive pathogenesis, with Pseudomonadota and

Bacillota providing enzymes that promote bile supersaturation and stone formation. Enterococcus expansion is linked to taurolithocholic acid in primary sclerosing cholangitis and other autoimmune conditions. In cholangiocarcinoma, colibactin-positive *Escherichia coli* and intratumoral *Gammaproteobacteria* contribute to DNA damage and chemoresistance (138).

Biofilm formation on stents is a major driver of stent occlusion, with the spectrum of colonizing organisms shifting over time: early colonization favors aerobic gram-positive bacteria and *Candida spp.*, while longer indwelling times (>60 days) ir marked by increased gram-negative and anaerobic species, including *Clostridium* and *Bifidobacterium* (111,113,115). The composition of microbiome is patient-dependent and influenced by stent placement, with stenting itself reshaping the biliary microbiome more than antibiotic exposure (139).

Culture-based studies consistently show that polymicrobial colonization predominates in occluded stents, with over 90% of stents harboring multiple organisms (109,114,136,140). The most frequently isolated taxa are *Enterococcus spp.* (up to 79%), Enterobacteriaceae (including *Escherichia coli* and *Klebsiella spp.*), *Streptococcus spp.*, anaerobes (*Clostridium*, *Bacteroides*), *Staphylococcus spp.*, and *Candida spp.* (109,113,114,136). Fungal colonization, especially with *Candida spp.*, is more common in patients with prior antibiotic exposure (109).

Molecular analyses using 16S rRNA sequencing and next-generation sequencing have expanded the understanding of stent microbiome, revealing a broader diversity including *Actinobacteria*, *Synergistetes*, *Bifidobacterium spp.*, *Veillonella*, *Fusobacterium*, and other obligate anaerobes to be present (111,115,138). Notably, *Bifidobacterium animalis* abundance has been shown to correlate with stent occlusion severity, independent of indwelling time (111). The microbial composition is patient-dependent and varies by hospital, stent location, and clinical factors such as underlying malignancy, cholangitis, and number of stents placed (115,138).

Antimicrobial resistance is a significant concern in stent-associated infections. Vancomycin-resistant enterococci, ESBL-producing Enterobacteriaceae with co-resistance to ciprofloxacin, and azole-resistant *Candida* are frequently detected (109). Empirical antimicrobial treatment of stent-associated cholangitis should be guided towards enterococci, Enterobacteriaceae, streptococci, anaerobes, and *Candida*, with accurate microbiological analysis of extracted stents recommended for pathogen identification (109,136).

The spacial and temporal dynamics of stent biofilms are complex, with bacterial diversity and community composition varying by patient, hospital, and stent location (115). Co-colonization patterns, such as *Veillonella sp.*, *Streptococcus anginosus*, and *Fusobacterium nucleatum*, suggest important attachment and survival strategies. The diversity of obligate anaerobes is greater than previously detected by culture-based methods (115). Standardized protocols and spatial, multiomic prospective studies are required to enable risk stratification and microbiota-informed therapeutics (138).

Innovations in stent design to prolong plastic biliary stent patency

Current evidence-based strategies to prevent or disrupt biofilm formation on plastic biliary stents focus on three main domains: antimicrobial coatings, stent design modifications, and the role of prophylactic antibiotics. Recent clinical trial data and meta-analyses have begun to clarify the effectiveness and safety of these approaches in reducing biofilm-related complications.

Antimicrobial coatings represent the most advanced and promising strategy. Polyactide-based coatings incorporating agents such as octenidine, triclosan, gentamicin, and ofloxacin have demonstrated sustained drug release and broad-spectrum antimicrobial activity against key biliary pathogens, including Enterobacteriaceae, *Enterococcus spp.*, and *Candida spp.* In particular, polylactide-octenidine-citrate coatings show the highest log reduction in pathogen counts, favorable inhibition zone profiles, and high biocompatibility (141). Multifunctional coatings, which combine anti-adhesive, bactericidal, and biofilm-disruptive properties, are under development and have shown efficacy in preclinical models (7,105). Trilayered stent films, with directional release of anti-tumor and antimicrobial agents, further enhance anti-biofilm activity and may be particularly useful in patients with cholangiocarcinoma (142). Surface engineering techniques, such as layer-by-layer polymer encapsulation and topographical modifications, also reduce microbial adhesion and biofilm formation (105,143).

Stent design modifications are critical adjuncts to coating strategies. Larger diameter stents (e.g., 10Fr versus 7Fr) are associated with lower protein content in biofilms and reduced occlusion rates (114). Designs that minimize side holes and optimize flow dynamics decrease microturbulence and areas of preferential biofilm formation (114). Anti-reflux plastic stents can prolong and reduce stent-related cholangitis compared to traditional designs, as demonstrated by longer median patency and delayed onset of cholangitis (144). However, not all anti-reflux designs have proven effective, and some may even shorten stent patency (145). Novel spiral or screw-shaped stents may improve anchoring and reduce migration, with some evidence of sustained patency in malignant hilar obstruction (104,146). However, shape alone does not consistently impact stent patency in short-term studies.

Dual-layer stents, such as those combining polyurethane with polytetrafluoroethylene, have shown reduced biofilm formation and enhanced patency, although clinical outcomes are comparable to conventional stents in some studies (131). The use of biodegradable polymers and advanced manufacturing technologies, including 3D printing, are emerging trends that may further improve stent performance and reduce biofilm-related complications (100,143).

The role of prohylactic administration of antibiotics remains controversial. While prolonged antibiotic exposure increases the risk of colonization with resistant organisms and fungal species, a recent meta-analysis of randomized controlled trials found that prophylactic administration of antibiotics significantly reduces the risk of post-ERCP cholangitis, bacteremia, and infectious complications in patients with radiologically confirmed biliary obstruction (147). These findings challenge current guidelines that recommend administration of antibiotics only in high-risk scenarios, suggesting that pre-procedural antibiotics should be considered to improve outcomes in select patients. In vitro studies support the use of ciprofloxacin and ceftazidime for reducing bacterial adherence to stents, but clinical efficacy in preventing stent occlusion is inconsistent (124). Empirical therapy should be guided by microbiological analysis of extracted stents and local resistance patterns (109).

Recent evidence from in vitro and in vivo studies demonstrates that plastic biliary stents with antimicrobial coatings significantly reduce bacterial adherence, biofilm formation, and pathogen load compared to conventional plastic stents. In vitro, polylactide-based coatings containing agents such as octenidine and citrate achieve the highest log reduction in key biliary pathogens (e.g., *Echerichia coli*, *Enterococcus faecalis*, *Candida albicans*), with sustained antimicrobial activity and favorable biocompatibility profiles (141). Silver nanoparticle coatings also show a 10 to 100 fold reduction in bacterial adherence in vitro, especially in the presence of bile. In vivo studies confirm prolonged stent patency and improved survival due to reduced microbial colonization and tissue reaction (148).

Other antimicrobial-impregnated polymers, such as benzalkonium chloride, and materials like polytetrafluoroethylene, further decrease microbial colonization and adherence compared to standard polyurethane and polyethylene stents in vitro (149). Bismuth dimercaprol inhibits both bacterial growth and adherence at sufficient concentrations (150). Antibiotic perfusion (e.g., ciprofloxacin, ceftazidime) reduces bacterial attachment to stent surfaces in vitro, but clinical efficacy in preventing occlusion remains inconsistent (124).

Dual-layer stents with polytetrafluoroethylene inner layers may reduce biofilm formation, but have not demonstrated significant differences in patency or recurrent biliary obstruction rates compared to conventional stents (131). Multifunctional and trilayered stents show promise in preclinical studies, but require further validation (142,143).

Despite these promising preclinical results, clinical studies indicate that while antimicrobial coatings and advance materials reduce biofilm formation and may prolong patency, no coating or material has completely prevented stent occlusion in vivo, and routine clinical adoption awaits further large-scale trials (124,141,149,150).

The most effective strategies to prevent or disrupt biofilm formation on plastic biliary stents are antimicrobial and multifunctional surface coatings, combined with optimized stent design. Prophylactic antibiotics may reduce infectious complications in select high-risk patients, but routine use is limited by antimicrobial resistance concerns. Ongoing research into advanced materials, surface modifications, and drug-eluting technologies are likely to further improve stent performance and patient outcomes. Clinical decision-making should be individualized, taking into account patient risk factors, stent characteristics, and local microbiological profiles (105,114,131,141–143,147). The inconsistent results of antimicrobial coated plastic stents efficacy in vivo and in vitro underpin the importance of other factors affecting biofilm formation and plastic biliary stent occlusion.

TASK I

Duration and predictive factors of plastic biliary stent patency

Endoscopic retrograde cholangiopancreatography (ERCP) with biliary stent placement is a mainstay of current management of patients with both malignant and benign biliary obstruction. While plastic stents are favoured for their ease of placement, removal, and cost effectiveness, their durability remains limited—typically maintaining patency for only 2 – 4 months, with reported medians ranging from ~55 days in malignant disease to ~110 days in benign conditions (1,2).

It has been long known that obstruction of plastic stents most commonly results from bacterial biofilm formation, proteinaceous sludge accumulation, and tumor or tissue ingrowth. These processes are influenced by both stent-related and patient-specific factors (3–5). Studies have shown that malignant obstruction, particularly perihilar, significantly shortens stent patency (2). Furthermore, clinical variables such as elevated bilirubin levels, multiple stents, and hypoalbuminemia have been shown to increase the risk of subsequent cholangitis (134,151,152). In one large retrospective cohort, patients with hilar malignancy were at a 3-fold increased risk of early stent dysfunction compared to those with distal strictures (153).

The mechanism of the biofilm formation on a plastic stent resulting in occlusion is well known, however, there remains a lack of comprehensive models that integrate procedure-related, stent-related, and patient variables to predict stent occlusion and complications. The aim of this study was to investigate the duration of plastic biliary stent patency and risk factors for stent occlusion.

Materials and methods

A retrospective analysis into prospectively collected database of ERCP procedures carried out between 2010 and 2019 in a single tertiary care hospital in Vilnius, Lithuania, was performed. Permission by the regional bioethics committee for the study was obtained (permission number 2023/10-1539-1006). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All procedures that resulted in a plastic biliary stent placement were included in the analysis of plastic biliary stent patency. Patients who did not require stent placement, such as patients after dilation of benign strictures, successful choledocholithiasis or patients who were stented with metal stents were excluded from the analysis.

Primary outcome of the study was the duration of the stent patency considered as the time elapsed between index stent placement and the subsequent re-stenting. Secondary outcomes were development of cholangitis upon repeated stenting and whether subsequent re-stenting was emergent. Re-stenting was considered as *emergent* if happened before the planned elective re-stenting date irrespective of indication (development of cholangitis, rising jaundice, suspected dislodgement etc.).

To evaluate the impact of different aetiology of biliary obstruction on stent patency, patients were divided into 4 groups: patients with strictures due to extrabiliary malignancy (pancreatic cancer, metastatic compression etc.), intrabiliary malignancy (cholangiocarcinoma), benign biliary strictures (chronic pancreatitis, post-cholecystectomy strictures etc.) and biliary strictures due to parasitic infestation (echinococcal infection). All patients received routine antibiotic prophylaxis according to the hospital guidelines on the day of ERCP. Administration of additional antibiotics upon hospitalization was considered as use of antibiotics. Patients were followed up until the subsequent stenting, surgery or death and included in the present study.

Differences between groups were evaluated using Kruskal-Wallis test for continuous variables, Pearson's Chi-squared test or Fisher's exact test for categorical variables. Effect size was calculated using Cramer's V adjusted (for nominal variables) or Rank epsilon squared (for interval variables) statistics. To estimate stent patency time (survival function) Kaplan-Meier curves were plotted that were compared using log-rank test. To assess risk factors for repeated stenting being performed as an emergency (non-elective) procedure and development of cholangitis multivariate Cox proportional hazards regression model was used. A two-sided p value of less than 0,05 indicated statistical significance. Statistical analyses were conducted using R software, version 4.5.0 (R Project for Statistical Computing).

Results

Patients Population And Characteristics

Between 2010 and 2019 a total of 5462 ERCP procedures were performed. Out of the total, 2659 ERCP procedures resulted in plastic biliary stent placement and were included in this study. 1452 (56,4%) of the patients were male and the average patient age was 64 ±15 years. The majority of biliary stent placements were indicated for extrabiliary malignancies (N= 1041, 39,2%). All of the baseline characteristic between biliary stricture's aetiology groups differed with a statistical significance (p<0.001). Patients with both extrabiliary and intrabiliary malignancies were older (67 ± 12 years and 68 ± 12 years respectively), compared to patients with benign strictures (60 ± 17 years and parasitic infestation 52 ± 16 years). The same trend was detected regarding presence of cholangitis, most often present in extrabiliary malignancy group (N=400, 38%), followed by intrabiliary malignancy group (N=318, 31%), benign stricture (N=243, 23%) and parasitic infestation group (N=81, 7,8%). The highest number of stents was placed in intrabiliary malignancy and parasitic infestation groups (1,55 ± 0,57 and 1,56 ± 0,55, respectively). Baseline characteristics of the patients are shown in Table 1.

Patients with malignant indication for biliary stenting had to undergo emergent re-stenting more often (N=243, 39%; N=294, 33%; N=175, 20% and N=73, 8% for extrabiliary and intrabiliary malignancy, benign stricture and parasitic infestation groups, respectively). Similar tendency regarding diagnosis of cholangitis during the subsequent re-stenting was observed, in groups of malignant indication for ERCP incidence being higher (N=287, 37%; N=293, 38%; N=125, 16% and N=69, 9% for extrabiliary and intrabiliary malignancy, benign stricture and parasitic infestation groups, respectively).

Table 1. Baseline characteristics of the patients.

Characteristic	Overall* N = 2659	Biliary stricture's aetiology group				p-value**	Effect size (ES) adjusted (95% CI)***
		Extrabiliary malignancy* N = 1041 (39%)	Intrabiliary malignancy* N = 565 (21%)	Benign stricture* N = 790 (30%)	Parasitic infestation* N = 263 (10%)		
Sex (male)	1452 (55%)	456 (44%)	271 (48%)	523 66%	202 77%	<0,001	0,24 (0,20, 1,0)
Age (years)^	64 (15)	67 (12)	68 (12)	60 (17)	52 (16)	<0,001	0,10 (0,08, 1,0)
Cholangitis⁺	1042 (39%)	400 (38%)	318 (31%)	243 (23%)	81 (7,8%)	<0,001	0,19 (0,16, 1,0)
Antibiotics°	1,533 (58%)	577 (38%)	400 (26%)	443 (29%)	113 (7,4%)	<0,001	0,15 (0,12, 1,0)
Cholecystectomy Δ	756 (28%)	196 (26%)	125 (17%)	405 (54%)	30 (4,0%)	<0,001	0,33 (0,30, 1,0)
Presence of gallbladder stones	570 (21%)	228 (40%)	145 (25%)	148 (26%)	49 (8,6%)	<0,001	0,24 (0,22, 1,0)
Presence of CBD stones	492 (19%)	88 (18%)	72 (15%)	243 (49%)	89 (18%)	<0,001	0,27 (0,24, 1,0)
N of stents^ placed	1.34 (0,55)	1.13 (0,36)	1,55 (0,57)	1,37 (0,63)	1,56 (0,55)	<0,001	0,13 (0,11, 1,0)
Cumulative stent diameter (Fr)±	12,0 (10,0, 17,0)	12,0 (10,0, 12,0)	14,0 (10,0, 17,0)	12,0 (10,0, 17,0)	14,0 (10,0, 17,0)	<0,001	0,04 (0,03, 1,0)
Stent patency time (days)±	63 (25, 96)	41 (17, 84)	54 (22, 84)	83 (38, 100)	98 (84, 136)	<0,001	0,12 (0,10, 1,0)
Stent patency >30 days	1,680 (63%)	509 (30%)	346 (21%)	589 (35%)	236 (14%)	<0,001	0,25 (0,22, 1,0)
Next re-stenting emergency	885 (33%)	343 (39%)	294 (33%)	175 (20%)	73 (8%)	<0,001	0,26 (0,22, 1,0)
Cholangitis during the next restenting	774 (29%)	287 (37%)	293 (38%)	125 (16%)	69 (9%)	<0,001	0,31 (0,28, 1,0)

Characteristic	**Overall* N = 2659**	**Biliary stricture's aetiology group**				**p-value****	**Effect size (ES) adjusted (95% CI)*****
		Extrabiliary malignancy* N = 1041 (39%)	Intrabiliary malignancy* N = 565 (21%)	Benign stricture* N = 790 (30%)	Parasitic infestation* N = 263 (10%)		
Survival						<0,001	0,21 (0,18, 1,0)
Alive	2021 (76%)	650 (32%)	421 (21%)	702 (35%)	248 (12%)		
Dead	348 (13%)	220 (63%)	85 (24%)	35 (10%)	8 (2,3%)		
Unknown	289 (11%)	171 (59%)	59 (20%)	52 (18%)	7 (2,4%)		

* n (%), **Kruskal-Wallis test; Pearson's Chi-squared test, Fisher's exact test, ***Cramer's V adjusted, Rank epsilon squared

∧ Continuous variable of normal distribution defined by mean and standard deviation

± Continuous variable of non-normal distribution defined by median and interquartile range

+ Cholangitis – diagnosed based on the diagnostic criteria upon time of hospitalization

° Antibiotics - administration of additional antibiotics upon hospitalization other than routine antibiotic prophylaxis for ERCP procedure

Δ Cholecystectomy – performance of cholecystectomy in patient history previous to hospitalization

Primary outcome

On average the plastic biliary stent was patent for 63 [25, 96] days. There were significant differences in stent patency duration between different indication for ERCP groups (Figure 1). Shortest stent patency time was observed in extrabiliary malignancy group 41 [17, 84] days, while the stent was patent the longest in cases of parasitic infestation - 98 [84, 136] days. Log-rank test confirmed that the difference in stent patency time between aetiological groups is statistically significant ($p<0,0001$).

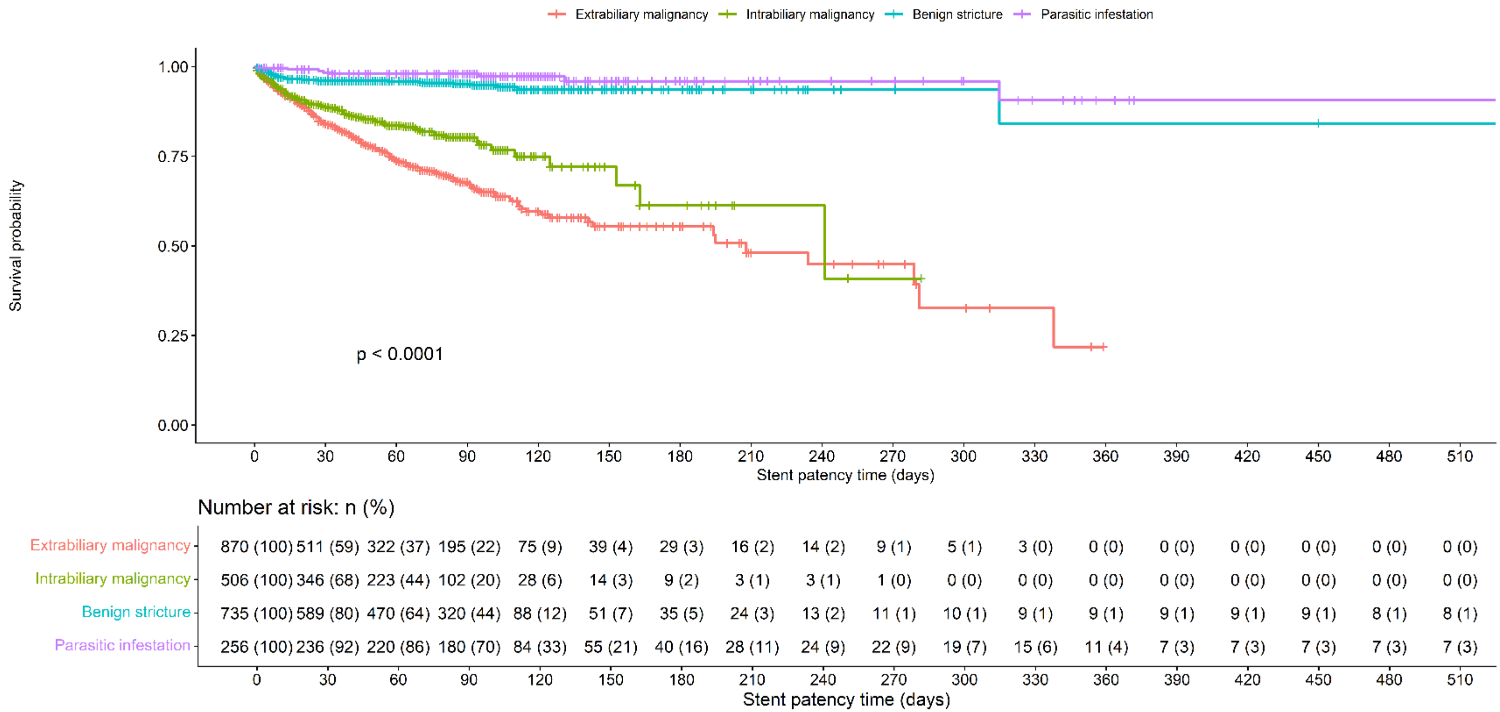

Figure 1. Plastic biliary stent patency time.

Secondary outcomes

Overall, cholangitis during the subsequent re-stenting was diagnosed in 774 cases (33%).

The strongest risk factors for the development of cholangitis upon the subsequent re-stenting was found to be cholangitis during the index ERCP (HR = 1,83; 95% CI: 1,48 – 2,27; p < 0.001), intrabiliary malignancy being the indication for stenting (HR = 1,34; 95% CI: 1,12 – 1,60; p < 0,001) and increasing number of stents being placed (HR = 1,73; 95% CI: 1,27 – 2,36; p < 0,001). The risk for the diagnosis of cholangitis during the subsequent re-stenting was also slightly increased in male patients (HR = 1,2, 95% CI: 1,04 – 1,40; p = 0,0150).

Two factors that were related to the reduced risk of subsequent diagnosis of cholangitis were identified: indication for biliary stenting being benign stricture (HR = 0,31; 95% CI: 0,24 – 0,39; p < 0,001) and parasitic infestation (HR = 0,30; 95% CI: 0,22 – 0,40; p < 0,001) (Figure 2).

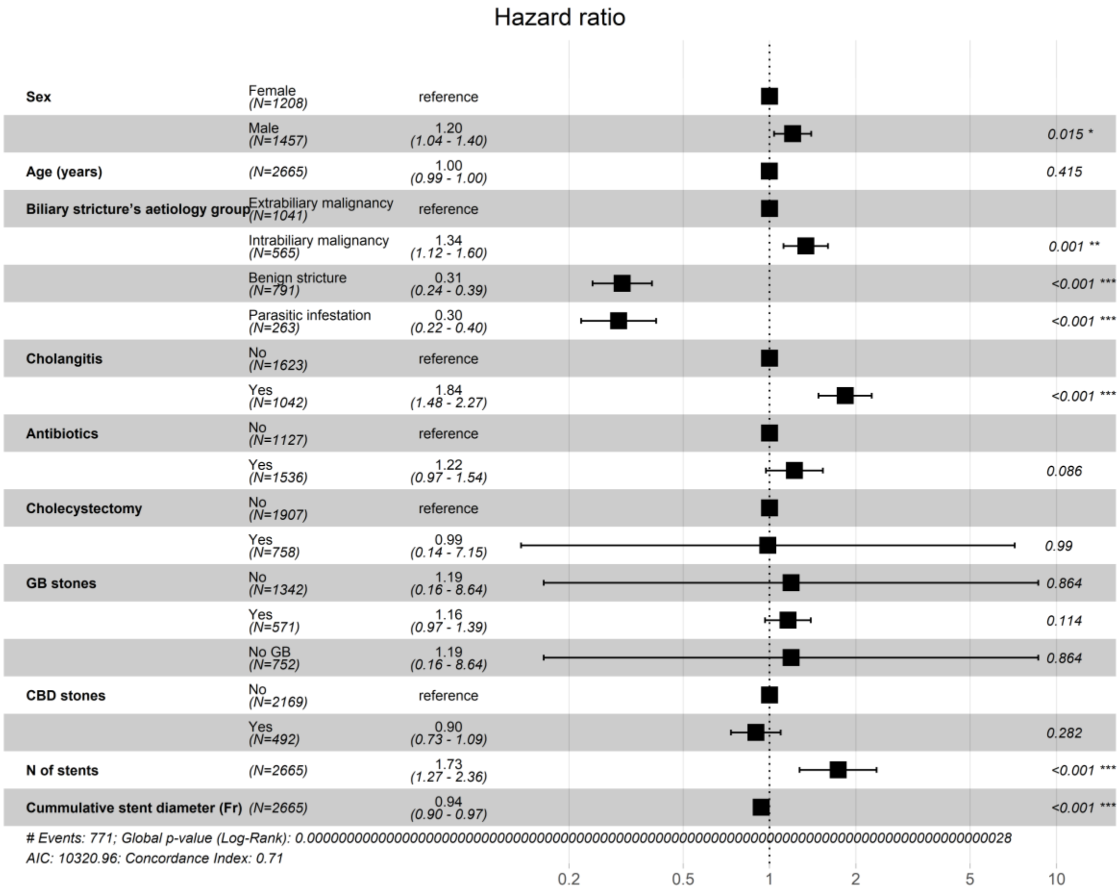

Figure 2. Risk factors for presenting with cholangitis during the subsequent re-stenting.

885 (33%) subsequent re-stentings were performed as an emergency procedure (non-elective). The strongest risk factors for successive ERCP being non-elective on multivariate Cox regression analysis were increasing number of biliary stents placed (HR = 1,49; 95% CI: 1,11 – 1,99; p < 0,001), prescription of antibiotics and presence of cholangitis during the index ERCP (HR = 1,45; 95% CI: 1,20 – 1,77; p < 0,001 and HR = 1,29; 95% CI: 1,07 – 1,55; p < 0,001, respectively). The risk was also increased in patients with intrabiliary malignancy (HR = 1,22; 95% CI: 1,03 – 1,45; p=0,02).

Two factors were significantly associated with a reduced risk of subsequent re-stenting being emergent on multivariate Cox regression analysis: indication for biliary stenting being benign stricture (HR = 0,39; 95% CI: 0,31 – 0,48; p < 0,001) and parasitic infestation (HR = 0,31; 95% CI: 0,23 – 0,41; p < 0,001). Increasing cumulative biliary stent diameter slightly decreased the risk of emergency re-stenting (HR = 0,94; 95% CI: 0,91 – 0,98; p < 0,001 (Figure 3).

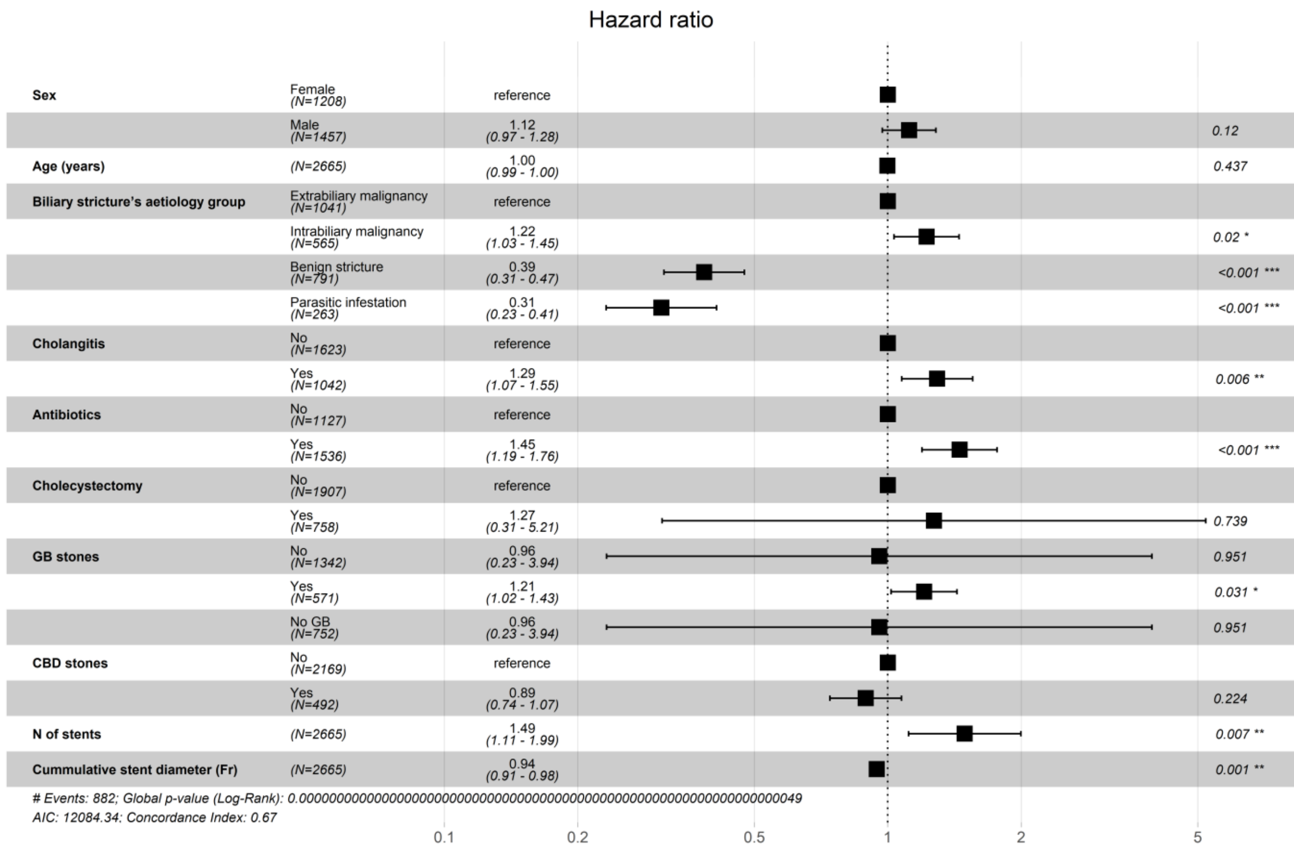

Figure 3. Risk factors for the subsequent re-stenting being emergent.

This study into plastic biliary stent patency and the risk factors affecting it is the biggest analysis of this question to date. It shows an average duration of stent patency of 63 days, with a significant impact of the indication for biliary stent placement on the stent patency. In addition, it identifies risk factors for complications, such as diagnosis of cholangitis at the index ERCP, increasing number of plastic stents placed.

Our results show that patients with a malignancy as an indication for biliary stent placement have a shorter plastic stent patency than those with a benign indication. This is concordant with previously published data reporting reduced stent patency time in patients with malignancy (106 versus 55 days for benign and malignant underlying disease, respectively) (2). This can be explained by the progressive course of disease in cases of malignancy and increased pressure of biliary tract.

Although it is known that the time of a plastic biliary stent patency is not sufficient to complete chemotherapy in a neoadjuvant setting (118), the effect of chemotherapy seems to prolong stent patency of metal stents in a palliative setting (154), likely resulting from tumor shrinkage and decreased biliary sludge.

Our data shows slightly longer stent patency in intrabiliary malignancy group compared to extrabiliary malignancy. This is an unexpected finding since significant number of patients with intrabiliary malignancies had perihilar strictures, usually requiring placement of multiple smaller diameter plastic stents. It is also in contrast with currently published data. Ostrowski et al. (2) investigated differences in stent patency within malignancies, showing decreased stent patency for proximal stricture location (40 versus 76 days for perihilar and distal strictures, respectively). The longer stent patency time in intrabiliary malignancy group compared to extrabiliary malignancy group is also opposed by the finding that diagnosis of intrabiliary malignancy is a risk factor for the development of cholangitis. This discrepancy could have arisen due to a couple of reasons. Per our center's protocol, all patients undergoing ERCP and biliary stenting with plastic stents are scheduled for an elective re-stenting in 3 months. Any hospital admission and subsequent re-stenting, whether due to rising jaundice that could impede chemotherapy course or cholangitis was regarded as an emergent in this study. In the case of perihilar cholangiocarcinoma, dislodgement of longer stents is more common (155) and can result in localized biliary obstruction without cholangitis with subsequent decision to emergently re-stent. Moreover, considering patients with perihilar cholangiocarcinoma and stent placement in the left and/or right hepatic ducts, obstruction of one of the stents might result in focal cholangitis without apparent systemic symptoms of cholangitis.

Not surprisingly, the longest stent patency was observed in parasitic infestation group. Although rare, Echinococcal infection is endemic in certain parts of the world, and this study provides the most comprehensive analysis into outcomes of biliary stent patency in patiets with this parasitic infestation. The simplest explanation is that patients with parasitic infestations might require additional antibiotic therapy that targets Gram-negative bacteria, thus inhibiting one of the major mechanisms in biofilm formation and subsequent stent occlusion – bacterial colonization (3). A more hypothetical explanation could raise a question, whether destructive secretions of Echinococcus species that enable aggressive tissue invasion might affect the biofilm formation in plastic biliary stents.

We have found that the risk of cholangitis development was higher in patients with intrabiliary malignancies, presenting with cholangitis upon index procedure and increased with multiple stents being placed. These findings are similar to currently published data, showing that the diagnosis of malignancy, placement of multiple biliary stents, prior occlusion events and male gender are risk factor for development of cholangitis after plastic stent placement (1,151). In contrast to our findings, a dedicated study of 51 patients with hepatic alveolar echinococcosis undergoing ERCP, reported similar rate of cholangitis (9,1%) but identified placing a single plastic stent and a stent diameter >8,5Fr being risk factors of cholangitis (50).

In addition to the identified risk factors for development of cholangitis, the influence of quantity of plastic stents and their cumulative diameter was even higher considering risk for the subsequent re-stenting being non-elective. The risk of occlusion increases with number of plastic stents being placed and decreases as the cumulative stent diameter increases. Placing multiple smaller diameter plastic stents increases surface area of the stent for biofilm formation and decreases lumen diameter, resulting in earlier occlusion. This principle is clearly observed in the superior patency of larger diameter SEMS.

Recently published studies into cultural and metagenomic analysis of bile and biliary stentslead of plastic biliary stents identify possible specific microbial drivers of stent occlusion and hold promise for tailored approaches and plastic biliary stent innovations to prolong its patency (110,156).

Although being robust in patient inclusion, our study has several limitations, mostly due to the retrospective nature of the analysis. A tenth of our cohort patients, mostly with underlying malignancies, was lost to follow up resulting in a possible bias of the results. Another limitation is the crudeness of data collected in the database, not accounting for possible concomitant factors, possibly affecting stent patency, such as chemotherapy, laboratory work up, comorbidities, etc. This is important considering stent patency time in patients diagnosed with cholangiocarcinoma. Recent publications have shown that stent patency is significantly shorter in cases of perihilar cholangiocarcinoma compared to distal biliary cancer (157) but due to electronic database features, this subgroup analysis was not possible. Despite these shortcomings, significant number of patients in each patient cohort seem to indicate robust differences between the groups and provide reliable data on the factors analyzed.

Patients with an underlying malignancy, history of cholangitis and multiple biliary plastic stents are at an increased risk for stent occlusion and cholangitis. A more vigilant and tailored stent exchange interval, based on the underlying disease, previous occlusion events and procedural aspects is warranted to prevent complications.

TASK II

Endoscopic retrograde cholangiopancreatography-associated perforations

Endoscopic retrograde cholangiopancreatography (ERCP) is a pivotal minimally invasive therapeutic intervention in the management of biliary and pancreatic duct obstruction. Even with the advancements in endoscopic techniques, it remains one of the most technically challenging and complication-prone endoscopic interventions. The main complications of ERCP are post-ERCP pancreatitis, bleeding, cholangitis, cholecystitis, with perforation being among the most perilous adverse events. ERCP-associated perforation is the rarest of ERCP-related complications with overall incidence reported from 0,08% to 0,6% (54,158,159), compared to the most common – post-ERCP – pancreatitis, with the overall incidence of 3% to 10% (60,160), perforations can lead to significant morbidity and mortality if not promptly recognized and managed appropriately (67,161).

There are several mechanisms of ERCP-associated perforations: luminal perforation due to manipulation of the endoscope, extension of sphincterotomy cut beyond the intramural bile duct and extramural passage of guidewires or stent migration.

The risk factors for ERCP-associated perforations, such as sphincterotomy, precut techniques, difficult cannulation, and anatomical variations such as periampullary diverticula or altered surgical anatomy, have been identified and necessitate even more measured ERCP technique (64,69,162). The Stapfer classification, introduced in 2000, remains the most widely accepted system for categorizing ERCP-associated perforations, guiding both diagnosis and management. This classification distinguishes perforations based on anatomical localization and mechanism into four types, each with distinct clinical implications and prognostic significance (161,163).

Despite advances in imaging and endoscopic techniques, the mortality associated with ERCP-related perforations remains substantial. Population-based studies report overall ERCP mortality as high as 0,14%, with perforation-specific mortality ranging from 2% to over 20%, depending on the timing of diagnosis, the type of perforation, and the chosen management strategy (67,161). Timely identification and early intervention are critical to improving outcomes. Recent evidence suggests that intra-procedural diagnosis and endoscopic closure techniques may significantly reduce the need for surgery and shorten hospital stay (67,164).

This study aims to investigate the incidence, patterns of diagnosis, management and outcomes of ERCP-associated perforations in a high-volume center in the span of 10 years and reviews 2 illustrative clinical cases.

Materials and methods

A large prospectively collected database of ERCP procedures carried out between 2010 and 2019 was retrospectively analyzed for ERCP-associated perforations. All patients with a diagnosis of ERCP-associated perforation were included in the analysis. Permission by the Vilnius regional bioethics committee for the study was obtained (permission number 2023/10-1539-1006). The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients whose ERCP procedures were complicated by intraprocedural perforation were identified and demographic data, data regarding diagnostic workup and management of the perforations was collected. Incidences are provided as counts and percentages, whereas continuous data are presented as averages or medians for normally and non-normally distributed data, respectively.

Results

In the period between 2010 and 2019 years 5462 ERCP procedures were performed. 2665 ERCP procedure were carried out with an intention of biliary stent placement resulting in 20 perforations (0,75%). The average age of patients with ERCP-related perforations was 73,2±11,9 years, 7 of them being male (35%). All of the patients had risk factors for procedure associated perforation (N=20, 100%), and in 13 patients cannulation of the biliary tract was classified as "difficult" (65%). Perforations most often occurred in biliary tract (N=8, 40%). The most common perforation type was type III according to Stapfer (N=9, 45%) and type III according to Howard (N=10, 50%). Half of the patients with diagnosed ERCP-associated perforation underwent surgical interventions (N=10, 50%). Median duration of hospitalization for patients with ERCP-related perforations was 16,5 days and a quarter of the patients died (N=5, 25%).

During the period of the study, ERCP procedures were performed by 6 HPB-procedure dedicated endoscopist, 3 of whom performed ERCP procedures during the entirety of analyzed period. There was no significant time trend of decline in incidence of ERCP-associated perforations, that would suggest accumulating experience and remained in the range of 1 to 3 per year (Figure 4).

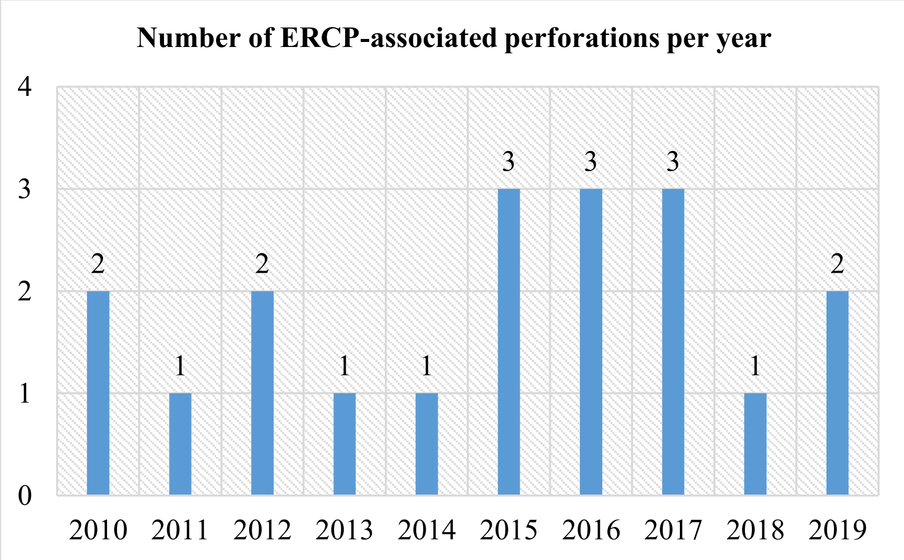

Figure 4. Number of ERCP-associated perforations per year.

Clinical presentation and diagnosis of ERCP-associated perforations

Out of 20 patients with ERCP-associated perforations, the complication was diagnosed during ERCP in 6 patients (30%), in the next 24 hours post the procedure in 10 (50%) and after 24 hours post the procedure in 4 (20%). In 13 patients (65%) principal complaint after the ERCP was severe pain and 9 (45%) developed clinical signs of peritonitis. In addition to ERCP-associated perforation, 13 patients (65%) were also diagnosed with post-ERCP pancreatitis.

In 5 patients (25%) ultrasound was the only and definitive imaging modality to diagnose an ERCP-associated perforation and guide further management. To establish definitive diagnosis 9 patients (45%) underwent contrast-enhanced computerized tomography (CT) and in all the cases the results were conclusive. In none of the cases X-ray was sufficient to identify free air in the abdomen.

Management and outcomes

Out of 20 patients with ERCP-associated perforations, all patients had clinical symptoms of a perforation. For 12 patients (60%) primary endoscopic management (stenting or clipping) was sufficient to resolve the perforation when noticed during the index procedure. Of note, all of the patients with successful primary endoscopic closure of perforation 7 (35%) (either clipping or stenting), had complete resolution of perforation and avoided additional interventions.

4 patients (20%) had to undergo surgical intervention, and 2 patients (10%) underwent combined endoscopic and surgical treatment. After careful evaluation of clinical status, laboratory and imaging work-up, 2 patients (10%) were observed with conservative management and had spontaneous resolution despite clinical and radiological signs of ERCP-associated perforation.

12 patients (60%) were admitted to ICU due to the ERCP-associated perforation for a median time of 6 days. For 5 patients (25%) ERCP-associated perforation resulted in death. For all of the patients with lethal outcomes of ERCP-associated perforations primary treatment modality of perforation closure was unsuccessful (N=5, 100%). Details of patient specific characteristics regarding clinical course of ERCP-associated perforation, diagnostic pathway and outcomes are provided in Table 2.

Table 2. ERCP associated perforations, clinical course and outcomes. *ICU: intensive care unit; CT: Computerized tomography.

Patient	Localization of the perforation	Perforation type according to Stapfer	Imaging performed	Modality of imaging confirming perforation	Primary treatment, effectiveness	Surgery performed	Hospitalization in ICU	Clavien-Dindo grade	Hospitalization time (days)
1	Duodenum	1			Endoscopic, yes		+	3b	13
2	Pancreatic duct	3			Endoscopic, no	Laparotomy	+	3b	33
3	Duodenum	1	+	CT	Surgery, no	Laparotomy	+	5	5
4	Duodenum	4	+	CT	Observation, yes			1	9
5	Biliary tract	3	+	CT	Endoscopic, no		+	5	4
6	Biliary tract	3	+	CT	Endoscopic + surgical, no	Laparoscopy	+	5	26
7	Biliary tract	4	+	Ultrasound	Observation, yes			3b	17
8	Duodenum	1	+	CT	Surgery, no	Laparotomy	+	5	5
9	Pancreatic duct	3	+	CT	Endoscopic, no	Laparotomy	+	4b	32
10	Biliary tract	3	+	Ultrasound	Endoscopic, no	Laparoscopy	+	3b	70
11	Biliary tract	3	+	CT	Endoscopic, yes		+	3b	24
12	Duodenum	2	+	CT	Endoscopic, no	Laparotomy	+	5	8
13	Pancreatic duct	3			Endoscopic, yes			1	13

Patient	Localization of the perforation	Perforation type according to Stapfer	Imaging performed	Modality of imaging confirming perforation	Primary treatment, effectiveness	Surgery performed	Hospitalization in ICU	Clavien-Dindo grade	Hospitalization time (days)
14	Duodenum	1	+	Ultrasound	Surgery, yes	Laparotomy		3b	20
15	Duodenum	3			Endoscopic, yes			2	23
16	Duodenum	1	+	Ultrasound	Endoscopic, yes			3b	15
17	Biliary tract	2			Endoscopic, yes			1	7
18	Biliary tract	2			Endoscopic, yes			3b	5
19	Duodenum	1	+	CT	Endosopic + surgical, yes	Laparotomy	+	3b	168
20	Biliary tract	3	+	Ultrasound	Surgery, yes	Laparotomy	+	3b	22

One instance of an immediate identification and successful primary endoscopic closure of an ERCP-associated perforation is the case of patient N1, a 76-year-old male, who underwent an ERCP for choledocholithiasis. During the procedure, multiple common bile duct (CBD) stones and a suspected distal CBD stricture were visualized. After performing a sphincterotomy, balloon dilation of the distal part of CBD was carried out. After extracting the majority of CBD stones with Dormia basket, mechanical lithotripsy for the remaining impacted stone was attempted. A perforation in the second part of duodenum occurred during mechanical lithotripsy and was successfully clipped with 3 endoscopic clips. A 12Fr plastic biliary stent was placed for the possible distal CBD stricture.

The patient was admitted to ICU for observation and conservative management. One day after the procedure a contrast-enhanced CT showed minor amount of free air in the retroperitoneal space with no further complications (Figure 5). 3 days after the initial procedure the patient underwent a second look ERCP that showed adequate closure of the perforation and an enteral tube below the perforation was placed for enteral nutrition.

The patient was discharged 12 days after the initial procedure with no further complications. After two months a follow up ERCP with biliary stent removal was performed, showing no signs of a CBD stricture. The patient underwent a cholecystectomy with no further biliary complications for the remainder of the follow-up.

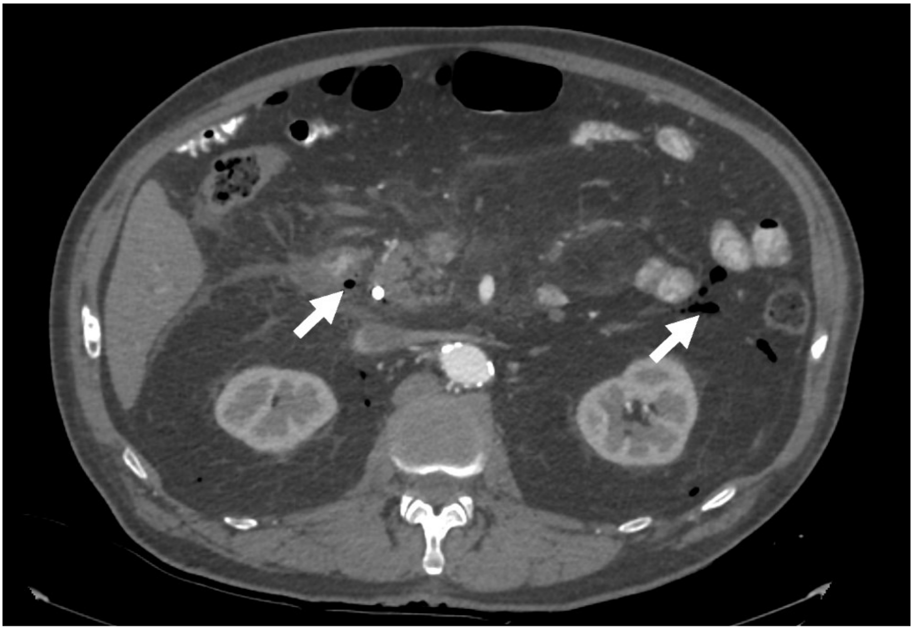

Figure 5. Axial oral and intravenous contrast-enhanced CT image shows free air in the retroperitoneal space (white arrows) after iatrogenic duodenal perforation during endoscopic retrograde cholangiopancreatography and bile duct stenting.

A much less straightforward diagnostic pathway and complex management of ERCP-associated perforation is evident considering patient N15, a 71-year-old male with a history of gallbladder carcinoma, cholecystectomy and liver resection, who underwent an ERCP for suspected mechanical cholestasis due to lymphadenopathy. During the procedure an opacity defect at the bifurcation region was identified with a slight dilation of the left hepatic duct. A sphincterotomy was performed and a plastic biliary stent in the left hepatic duct above the bifurcation was placed.

In the post-procedural period, the patient remained in pain, laboratory workup revealed elevation of α-amylase activity in the serum and post-ERCP pancreatitis was diagnosed.

2 days after the procedure a contrast-enhanced CT was performed that showed malignant hilar infiltration, intrahepatic cholestasis, and perihilar free fluid and air (Figure 6).

Figure 6. Axial intravenous contrast-enhanced CT image two days after common bile duct stenting shows free air and fluid (white arrow) posterior to the common bile duct and peripancreatic infiltration (white asterisk) likely due to bile duct perforation and pancreatitis.

Given the poor prognosis of an advanced malignant disease and no evidence of peritonitis, conservative treatment with broad-spectrum antibiotics, enteral nutrition via duodenal tube was commenced. Due to persistent elevation of inflammatory markers and intermittent febrility, 2 weeks after the initial ERCP the patient underwent a second contrast-enhanced CT. CT revealed multiple minute cystic lesions on the left liver lobe and peripancreatic infiltration. It was decided to continue with a conservative treatment, and the antibiotic therapy was escalated. In a course of one week the patient became afebrile, jaundice and inflammatory markers decreased. The patient was discharged 22 days after the index ERCP for palliative care and lost to follow-up.

Our analysis into a high-volume center's prospectively collected database regarding ERCP-associated perforations provides additional evidence with respect to incidence, diagnosis, management and outcomes of a rare, although potentially lethal procedural complication.

Our observed incidence of ERCP-related perforations (0,75%) is well within the reported bounds as low as 0,39% in a meta-analysis of 142847 patients by Bishay et al. (54) to as high as 0,9% reported in a study by Bray et al. (162). The varying data of the reported incidence of ERCP-associated perforations might arise due to differing numbers of ERCP performed in centers, as procedural volume is directly linked to the ERCP-related complications (165). However, the annual ERCP volume and resulting ERCP-associated perforations rate remained similar during the duration of the study. Considering our results, it should also be taken into account that only ERCP procedures resulting in biliary stenting were analyzed and the incidence of ERCP-associated perforations in an overall cohort might be lower and all patients had at least one risk factor for ERCP-associated perforation (166).

In half of the patients in our study (N=10, 50%) ERCP-associated perforation was diagnosed in the first 24 hours after the index procedure and in 4 (20%) after 24 hours with the main complaint being severe abdominal pain prompting further diagnostic workup.

Although the preferred modality for diagnosis of ERCP-associated perforation is CT scan with peroral contrast due to the highest sensitivity and specificity (167,168), interestingly, in our cohort, in 20% of the patients, ERCP-associated perforation was diagnosed definitively by the means of ultrasound prompting emergency surgery without further imaging studies. The reported ultrasound features of suspected perforation were free fluid or air around duodenal wall, periduodenal fat stranding. This underlines the importance of operator-dependent expertise to detect free air in the abdominal cavity utilizing widely available and fast imaging modality.

In our cohort of patients, the most common type of perforation was type III (distal bile duct) according to Stapfer (N=9). This is in contrast to the published data reporting type II ERCP-associated perforations (periampullary, sphincterotomy-related) to be the most common type. A pooled analysis of 562 perforations by Vezakis et al. (169) reported the incidence of II type perforations to be as high as 46% and a systematic review of 14 045 ERCPs by Bill et al. reported the incidence of type II perforations to be 38,1% (65). This could be explained by a long-standing tradition in our center to initiate treatment even of perihilar (Bismuth-Corlette type III and IV) mechanical obstruction by endoscopic means resulting in more difficult biliary access, hence, more perforations in biliary tract. Another explanation could be the repeated use of guidewires that become stiffer after the process of sterilization.

Interestingly, for 2 patients (10%), close clinical observation, repeated laboratory work-up and imaging was successful management plan that helped to avoid unnecessary interventional procedures. It could be hypothesized that diagnosis of perforation could have resulted from false-positive imaging findings when during an ERCP procedure air bubbles can sometimes move intramuscularly and simulate signs of perforation. However, both patients were symptomatic with mildly elevated inflammatory markers. Due to no overt signs of peritonitis and overall condition of the patients, cautious observation and treatment with broad-spectrum antibiotics, fasting and intravenous fluids was the chosen management approach. This is in accordance with ASGE recommendations for initial conservative management for ERCP-associated perforations without peritoneal signs or systemic inflammatory response (61). In carefully selected cases of ERCP-associated perforations, close clinical observation and repeated evaluation helps to prevent unnecessary interventional procedures, early surgery and associated complications (66). The importance of careful management plan has been proposed and assessed by Kumbhari et al., suggesting diagnostic and management algorithm in cases of Stapfer I and Stapfer II perforations (62). According to the findings of the study, out of 55 patients with postprocedural diagnosis of Stapfer II type perforation, only 4 patients (7%) failed medical management and required surgery, underpinning the importance of careful evaluation of clinical symptoms and evidence of systemic inflammation to avoid needless and potentially harmful interventions.

All of the patients with perforations diagnosed intra-procedurally were successfully treated with endoscopic means and later discharged concurring with the results of a large multicenter study by Emori et al. (67), emphasizing the importance of early detection and minimally invasive treatment options for better outcomes. In our study successful closure of a perforation was performed by the means of either clipping or placing a plastic biliary stent depending on perforation type. Unfortunately, for 7 patients (35%) the primary endoscopic closure was unsuccessful, and patients were referred to surgery. During the period of our study newer modalities for perforation closure, such as over-the-scope clips and fcSEMS were unavailable. Based on the recent evidence, it is reasonable to hypothesize, that having more advanced modalities for perforation closure could have lead to better outcomes (170,171).

Unfortunately, 5 (25%) patients with ERCP-associated perforations in our cohort had lethal outcomes. This is congruent with the reported data from the studies carried out in similar time frame such as Swedish GallRiks study (52140 ERCPs, 0,72% of perforations, 20% mortality) (161). Recent studies, such as Emori et al. (67), report mortality rate as low as 2%, that might be explained by the advances in minimally invasive treatment modalities, such as over-the-scope clips.

There are several limitations to our study. Firstly, due to the nature of retrospective analysis of the collected database some important factors, pertinent to the patient management and outcomes might have been not accounted for. Secondly, due to the rarity of ERCP-associated perforations, only 20 patients encountering this complication, clinical course was analyzed. However, we believe that detailed overview of diagnostic and management pathways provide additional and beneficial knowledge to clinical practice.

ERCP-associated perforation is a rare but potentially fatal procedural complication, necessitating prompt diagnosis, thorough workup and a multidisciplinary management plan. Emerging endoscopic management modalities provide possibilities for more efficacious intra-procedural treatment and careful post-procedural evaluation in cases of suspected ERCP-associated perforations with multidisciplinary approach lead to better patient outcomes.

TASK III

Interaction of biliary microbiome and plastic biliary stent patency

Endoscopic retrograde cholangiopancreatography (ERCP) and plastic biliary stent placement is an essential therapeutic modality for managing both benign and malignant biliary obstruction. However, plastic biliary stent utility is fundamentally constrained by the inevitable development of biofilm-mediated occlusion. The pathophysiology of stent dysfunction is a complex interplay between microbial colonization, biofilm matrix structure, and the physical properties of the stent itself.

Biofilm formation on plastic biliary stents follows a predictable temporal sequence, with initial colonization occurring predominantly through aerobic gram-positive bacteria and fungal species within the first 30 days of stent placement. This is followed by a progressive diversification to include aerobic gram-negative organisms and anaerobes after 60 days of stent indwelling time (3,113).

The microbiome of these biofilms demonstrate remarkable complexity, with polymicrobial colonization being predominant in more than 95% of retrieved stents (109). Enterococcus species emerge as the most prevalent colonizers, found in approximately 79% of stent biofilms, followed by Enterobacteriaceae in 74% and *Candida* species at 56% (109). Recent metagenomic analyses have identified additional key players in stent occlusion, including *Enterobacter* and *Lactobacillus* species, both recognized for their robust biofilm-forming capabilities (110). Notably, the abundance of *Bifidobacterium* species, particularly *Bifidobacterium animalis*, significantly correlates with occlusion severity independent of stent indwelling time (111).

The biofilm matrix itself comprises both proteinaceous and polysaccharide components, with protein concentrations significantly elevated in patients diagnosed with cholangitis and in smaller diameter stents (114). Longitudinal dissection studies reveal that biofilm formation initiates around stent side holes within 30 days, spreads to encompass the entire stent surface by 60 days, and progresses to complete occlusion by median of 90 days (3). This temporal progression explains the clinical observation that real life median stent patency ranges from 53 to 68 days, and is substantially shorter than the traditional 3 month stent exchange interval (118). The clinical consequences of stent occlusion extend beyond mechanical obstruction, with occluded stents showing a significantly increased risk of cholangitis (38,5% versus 9,1% in patent stents) (109).

Therapeutic strategies to prevent biofilm formation have yielded mixed results, with randomized trials of ursodeoxycholic acid and prophylactic antibiotics failing to demonstrate consistent benefit in prolonging stent patency or reducing mortality (126). However, emerging technologies including antimicrobial coatings incorporating octenidine-citrate combinations and drug-eluting polymers show promise in preclinical and early clinical studies (105,141).

The development of antibiotic resistance within stent biofilms represents an additional concern, with vancomycin-resistant enterococci, extended-spectrum beta-lactamase-producing Enterobacteriaceae, and azole-resistant *Candida* species accounting for 13,7%, 13,9%, and 32,9% of respective isolates (109).

Advances in sequencing technologies have transformed the study of the microbiome of plastic biliary stents, enabling comprehensive characterization of microbial communities and their role in stent occlusion. Early studies relied on culture-based methods, which underestimated microbial diversity and missed key anaerobic and fastidious organisms. The adoption of high-throughput 16S rRNA gene sequencing has allowed for detailed profiling of bacterial taxa, revealing patient-specific and hospital-specific community structures, and identifying previously unrecognized associations between specific genera (such as *Bifidobacterium*, *Enterobacter*, and *Lactobacillus*) and stent occlusion severity (110,111,115).

Metagenomic next-generation sequencing (mNGS) and whole-metagenome shotgun sequencing have further expanded the scope, enabling detection of novel biliary bacteria, functional gene analysis (e.g., biofilm formation, bile resistance), and the identification of metabolic pathways relevant to stent biofilm ecology (172,173). These approaches have also facilitated the study of fungal and viral components, as well as the spatial organization of biofilms using complementary imaging techniques (174).

Recent innovations, such as single-cell genome sequencing and simplified metagenomic methods (e.g., 2bRAD-M), offer improved resolution and efficiency for low-biomass samples typical of biliary stents, addressing challenges of contamination and heterogeneity (173). These advances support translational efforts to develop targeted antimicrobial therapies and anti-biofilm stent materials, and to establish standardized protocols for microbiome analysis in clinical practice (105,110,138).

Materials and methods

Study setting

This is an exploratory prospective cohort study into interaction between biliary microbiome and plastic biliary stent patency in a single tertiary care hospital in Vilnius, Lithuania. Permission by the Vilnius regional bioethics committee for the study was obtained (permission number 2021/9-1376-850, date of permission 2021-09-21). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Eligibility criteria

Patients undergoing ERCP with an intention of plastic biliary stent placement due to any aetiology of biliary tract stricture were eligible to be considered for inclusion into the study.

Inclusion criteria:

- Legally adult patients older than 18 years of age
- Patients signed informed consent form before undergoing ERCP
- Patients undergoing ERCP (including ERCP-naïve patients) due to a biliary tract stricture and a planned plastic biliary stent placement
- Patients with planned plastic biliary stent indwelling time of around 90 days

Exclusion criteria:

- Patients undergoing ERCP for choledocholithiasis and possible plastic biliary stent placement
- Patients with planned plastic biliary stent indwelling time shorter than 90 days
- Patients undergoing ERCP with planned SEMS placement

Intervention

All patients received routine antibiotic prophylaxis according to the hospital guidelines with cefazolin 1 gram twice a day intravenously on the day of ERCP. Administration of additional antibiotic medication upon hospitalization was considered as the use of antibiotics. The intake of antibiotic and probiotic medication was recorded before the collection of bile and stent specimens and was not considered as an exclusion criterion.

The sample size was selected according to Julious study "*Sample size of 12 rule of thumb for a pilot study*" (175).

ERCP procedures were performed by 4 experienced HPB-endoscopy dedicated endoscopists. Appropriate diameter and length stent was chosen from the same manufacturer in all cases to avoid stent material confounding. To avoid contamination the duodenoscope was introduced and positioned in front of the papilla without the use of suction. In cases of ERCP-naïve patients, the biliary tract was cannulated under sterile conditions and 5ml of bile suctioned. In cases of repeated ERCP, indwelling plastic biliary stent was carefully extracted using sterile snare, biliary tract was cannulated and 5ml of bile suctioned also under sterile conditions. Specimens of bile and plastic biliary stent were collected into sterile tubes, frozen immediately after collection (up to 30 minutes after the collection) and stored at − 80°C (sample A) in the study center.

Patients included in the study were followed up to the next elective or emergent re-stenting, surgery or death. Upon subsequent hospitalization clinical data was collected and patients underwent ERCP and re-stenting with bile and plastic stent collection (sample B) following the same methodology. Study procedure is summarized in Figure 7.

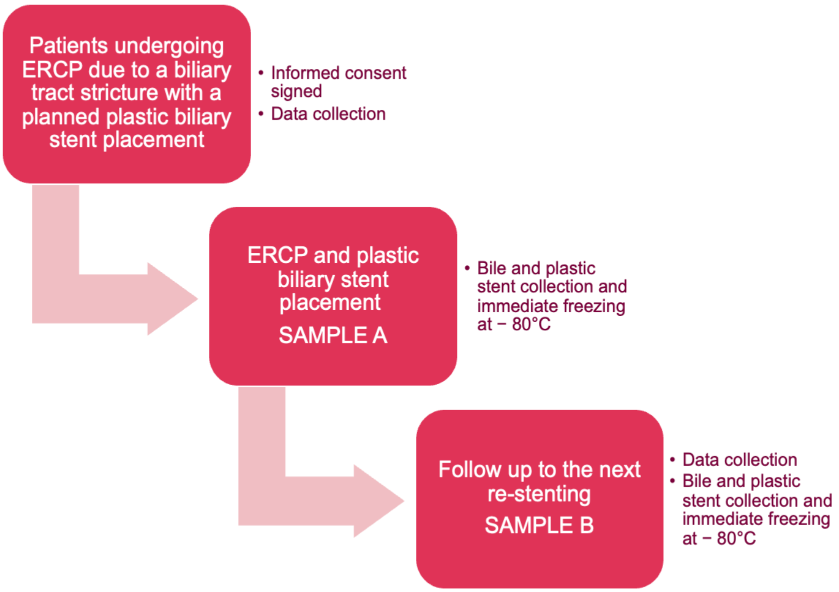

Figure 7. Flowchart of the study procedure.

Outcomes

Primary outcome of the study was bile and stent microbiome diversity. Secondary outcome was relative abundance of bacterial taxa in bile and stent samples.

Data analysis

Demographic and clinical differences between groups were evaluated using Fisher's exact test. A two-sided p value of less than 0,05 indicated statistical significance.

Raw reads from different sequencing batches were processed separately using QIIME2 (version 2025.10) with default settings, unless stated otherwise (176). Barcodes and adapters were trimmed using cutadapt, and untrimmed sequences were discarded (177). Poly-G artifacts arising from two-color Illumina chemistry were trimmed from the 3' end of reverse reads (R2). Read quality was assessed before and after trimming using MultiQC (178). Amplicon sequence variants (ASVs) were constructed using the DADA2 workflow (179). For 16S rRNA V3-V4 reads, sequences were truncated at the 5' and 3' ends. Decontamination was performed using q2-decontam with the frequency method, using DNA concentration measured after DNA extraction (180). After decontamination, the batch data was merged into one table and sequence collection. Sequences were aligned to build a phylogenetic tree using FastTree2 (181). Taxonomic classification was performed using the q2-feature-classifier plugin (182) with a Naive Bayes classifier trained on V3-V4 sequences using the SILVA v138.2 SSU Ref NR 99 database (183). After data preparation, 3,716,731 sequences were used for downstream analysis with an average of 72,877 reads.

All statistical analyses were performed using R (version 4.4.3) with the mia microbiome analysis framework. Rarefaction was performed by repeated subsampling (500 iterations) to the sequencing depth of the least abundant sample, and diversity values were averaged across iterations. Statistical significance was set at $\alpha = 0,05$. Taxonomic composition was summarized as median relative abundance with interquartile range (IQR) per group. For taxonomic summaries, taxa classified as *Incertae Sedis* were included in the remainder group during aggregation; diversity analyses used the full ASV table without taxonomic filtering. Alpha diversity was assessed at the ASV level using the Shannon diversity index and Faith's phylogenetic diversity (Faith PD) to capture abundance-weighted and phylogenetic aspects of community diversity. Differences between groups were evaluated using linear mixed models (LMMs) to account for repeated measures of patient samples, with post-hoc pairwise comparisons adjusted using the Benjamini-Hochberg procedure. Beta diversity was assessed using Jaccard (presence-absence) and Bray-Curtis (abundance-weighted) dissimilarity matrices, as well as unweighted and weighted UniFrac distances, computed on rarefied data with 500 repeated iterations. Ordination was performed using Principal Coordinates Analysis (PCoA), with variance explained by each axis derived from eigenvalue decomposition. Differences in community composition between groups were tested using permutational multivariate analysis of variance (PERMANOVA; 999 permutations), stratified by patient to account for repeated measures. Homogeneity of multivariate dispersions was assessed using the betadisper permutation test (999 permutations). For the identification of differences in specific taxa between groups, analysis using MaAsLin 3 was conducted. The Benjamini-Hochberg method was used for False Discovery Rate (FDR) correction; q-values of joint prevalence and abundance were reported.

Results

Patient population and characteristics

22 patients were included in the study between 2021 11 04 and 2025 01 09.

59% of the cohort patients were male (N=13) with an average age of 62,5 ± 11,4 years. Most prevalent aetiology of biliary stricture in the study cohort was extrabiliary malignancy (N=12, 54,6%) and only one patient underwent biliary stenting due to a benign pathology (portal biliopathy). 22,7% of the patients (N=5) were ERCP-naïve. Upon index ERCP 31,8% of the patients (N=7) had systemic signs of and were diagnosed with cholangitis, 54,5% (N=13) received antibiotics. 18% (N=4) of the patients died during the period of follow-up and one patient underwent Whipple procedure due to pancreatic ductal adenocarcinoma.

There were statistically significant differences in biliary stricture aetiologies (p=0,059) and stent patency time (p=0,006) between patients undergoing elective and emergent re-stenting.

Baseline patient characteristics are shown in Table 3.

Table 3. Baseline patient characteristics.

Characteristic	Overall N =18*	Next re-stenting		p-value**	Effect size (ES) adjusted (95% CI)***
		Elective N = 12*	Emergent N = 6*		
Gender	11 (61%)	7 (58%)	4 (67%)	>0,9	0,00 (0,00, 0,48)
Age (years; average (SD))	63 (12)	61 (12)	67 (12)	0,3	-0,31 (-0,71, 0,26)
Aetiological group				0,059	0,50 (0,00, 0,97)
Benign stricture	1 (5,6%)	1 (8.3%)	0 (0%)		
Extrabiliary malignancy	9 (50%)	7 (58%)	2 (33%)		
Intrabiliary malignancy	3 (17%)	0 (0%)	3 (50%)		
Parasitic infestation	5 (28%)	4 (33%)	1 (17%)		
ERCP-naïve patients	4 (22%)	4 (33%)	0 (0%)	0,2	0,30 (0,00, 0,83)
Cholangitis	4 (22%)	2 (17%)	2 (33%)	0,6	0,00 (0,00, 0,62)
Antibiotics	8 (44%)	4 (33%)	4 (67%)	0,3	0,21 (0,00, 0,76)
Stent patency (days; average (SD))	77 (20)	85 (19)	61 (11)	0,006	0,83 (0,55, 0,94)

Microbiome analysis

Bile versus stent microbiome

Taxonomic composition analysis identified the most abundant bacteria, which at the phylum level were *Pseudomonadota* at 47,5% [32,5-64,2%], *Bacillota* at 27 % [17,2-42,5], *Fusobacteria* at 4,3% [1,37-10,82] and *Bacteroidota* at 2,88% [0,81-10,56] of total relative abundance. Other less prevalent phyla detected were *Actinomycetota*, *Synergistota*, *Thermodesulfobacteriota* and *Campylobacterota* (Figure 8). Detailed relative abundance of phyla in bile and stent samples are shown in Table 4.

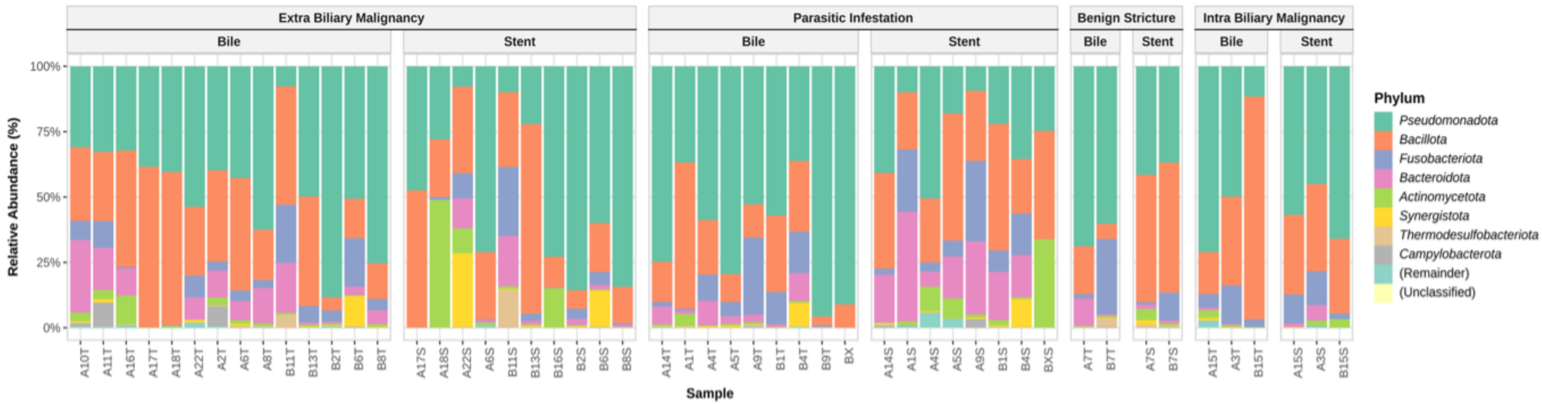

Figure 8. Phylum-level relative abundance composition across samples, grouped by disease group (Parasitic Infestation, Benign Stricture, Intrabiliary Malignancy, Extrabiliary Malignancy) and by sample type (Bile, Stent). Each bar represents one sample; colors indicate the eight most abundant phyla with remaining taxa grouped.

Table 4. Relative abundance of phyla in microbiome composition in bile and stent specimens (median [IQR]). Beta coefficients (± SE) represent log-fold differences in stentslead samples compared to bile.

Phylum	Bile	Stent	Beta coeficient (± SE)
Pseudomonadota	51,71% [39,73-69,37]	40,88% [21,84-58,38]	-0,56 ± 0,25
Bacillota	26,37% [14,73-36,46]	28,63% [21,97-48,47]	0,40 ± 0,26
Fusobacteriota	4,73% [1,74-10,72]	3,86% [1,14-10,83]	-0,19 ± 0,5
Bacteroidota	3,08% [0,70-10,36]	1,82% [0,90-15,92]	0,77 ± 0,56
Actinomycetota	0,72% [0,31-1,07]	1,19% [0,38-6,02]	1,18 ± 0,59
Synergistota	0,23% [0,02-0,60]	0,16% [0,02-0,51]	0,87 ± 0,85
Thermodesulfobacteriota	0,08% [0,05-0,18]	0,09% [0,00-0,22]	-0,52 ± 0,74
Campylobacterota	0,07% [0,04-0,26]	0,08% [0,01-0,17]	0,05 ± 0,71
(Remainder)	0,05% [0,01-0,33]	0,02% [0,00-0,07]	

MaAsLin3 differential abundance analysis at the genus level identified several taxa with nominally significant differences between bile and stentslead specimens, though none remained statistically significant after FDR correction (all q > 0,05). The most notable differences were observed in *Clostridium* (q = 0,109), which showed lower relative abundance in stent specimens and *Dialister* (q = 0,09), which showed higher relative abundance in stentslead specimens (Table 5 and Figure 9).

Table 5. Selected genera with lowest MaAsLin3 q-values for sample type comparison (Stent versus Bile). Relative abundance shown as median [IQR] (%). Coefficients (β ± SE) represent log-fold change in stent relative to bile (reference). Models were adjusted for disease group, sex, antibiotic use, sampling timepoint, sample type, and sequencing batch, with patient as a random intercept.

Genus	Bile	Stent	Coefficient Stent versus Bile (β ± SE)	p-value	q-value (FDR)
Clostridium	2,63% [1,10-6,75]	0,74% [0,16-2,24]	-2,07 ± 0,47	< 0,001	0,109
Aeromonas	1.07% [0,33-4,12]	0,27% [0,08-1,07]	-1,98 ± 0,60	0,004	0,436
Dialister	0,11% [0,03-0,21]	0,37% [0,12-1,95]	3,01 ± 0,60	< 0,001	0,090
Paeniclostridium	0,05% [0,02-0,15]	0,02% [0,00-0,10]	-1,20 ± 0,39	0,002	0,265
Anaeroglobus	0,02% [0,01-0,04]	0,12% [0,03-0,20]	2,50 ± 0,69	0,004	0,418
Limosilactobacillus	0,00% [0,00-0,00]	0,01% [0,00-0,08]	0,87 ± 0,84	0,492	1,000

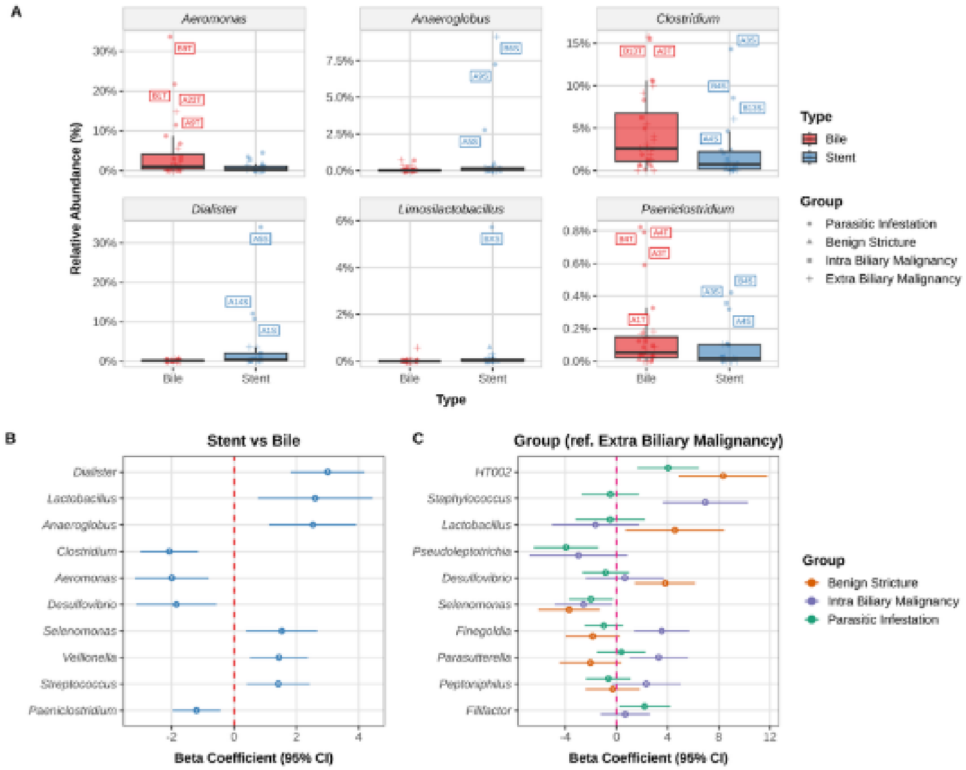

Figure 9. (A) Selected genera relative abundance by sample type (Bile versus Stent). Genera shown are those with the lowest MaAsLin3 q-values for sample type: *Aeromonas*, *Anaeroglobus*, *Clostridium*, *Dialister*, *Limosilactobacillus*, and *Paeniclostridium*. (B) Differentially abundant taxa in stent samples with bile as the reference group, ordered by the beta coefficient. (C) Differentially abundant taxa in sample groups, with Extrabiliary Malignancy as the reference group, ordered by beta coefficient. Lines indicate standard error. Models were adjusted for covariates as described in Table 5. Exact q-values reported in Table 5.

Microbiome composition analysis of bile and stent samples exhibited no significant difference in alpha diversity applying Shannon (p = 0,474) and Faith PD indices (p = 0,480) (Figure 10).

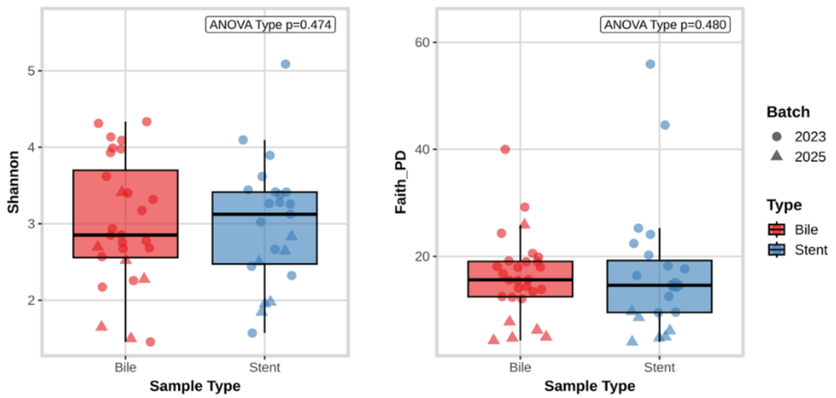

Figure 10. Alpha diversity of bile and stent samples measured by Shannon index (left) and Faith's phylogenetic diversity (right). Statistical significance of sample type was evaluated using linear mixed models adjusted for disease group, sex, antibiotic use, sampling timepoint and sequencing batch, with patient as a random effect and Satterthwaite's approximation for degrees of freedom.

Beta diversity analysis revealed a significant difference in community composition between bile and stent specimens by Bray-Curtis dissimilarity (PERMANOVA q = 0,012), while weighted UniFrac distance showed a trend that did not reach statistical significance (q = 0,057). Ordination by principal coordinates is illustrated in Figure 11.

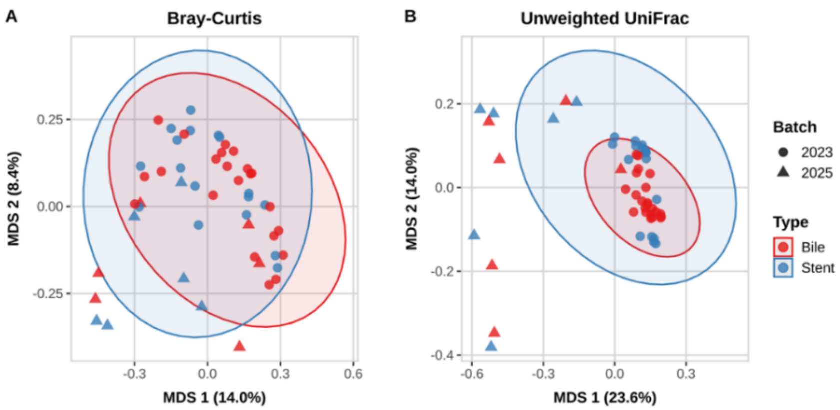

Figure 11. Beta diversity ordination by sample type using Bray-Curtis (left) and unweighted UniFrac (right) distance metrics. Ellipses represent 95% confidence intervals for each sample type. Axes indicate proportion of variance explained.

Microbiome diversity in sequential stenting

Alpha diversity of collective microbiome in samples at the index procedure (Sample A) and subsequent re-stenting (Sample B) were compared.

Shannon diversity was significantly higher in A samples versus in B cases (estimated difference + 0,9, 95% CI: 0,542 – 1,258, p<0,001), as well as Faith PD (estimated difference + 6,53, 95% CI: 1,27 – 11,78, p=0,014). These differences are illustrated in Figure 12.

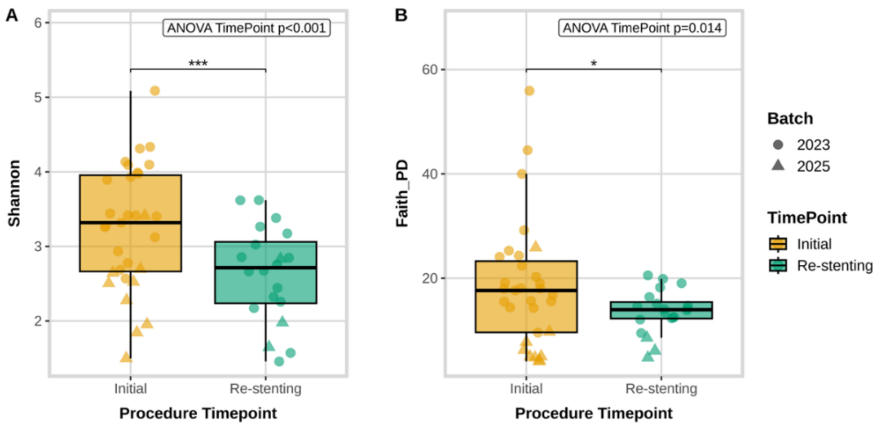

Figure 12. Alpha diversity by sampling timepoint (A: index procedure versus B: re-stenting) measured by Shannon index (left) and Faith's phylogenetic diversity (right). Shapes indicate sequencing batch. Statistical significance was evaluated using linear mixed models adjusted for sex, antibiotic use, disease group, sample type and sequencing batch, with patient as a random effect.

Differential abundance analysis between samples A and B identified *Citrobacter*, *Escherichia-Shigella*, *Fusobacterium* and *HT002* as the genera with lowest Q-values, however none reached statistical significance after FDR correction and are illustrated in Figure 13.

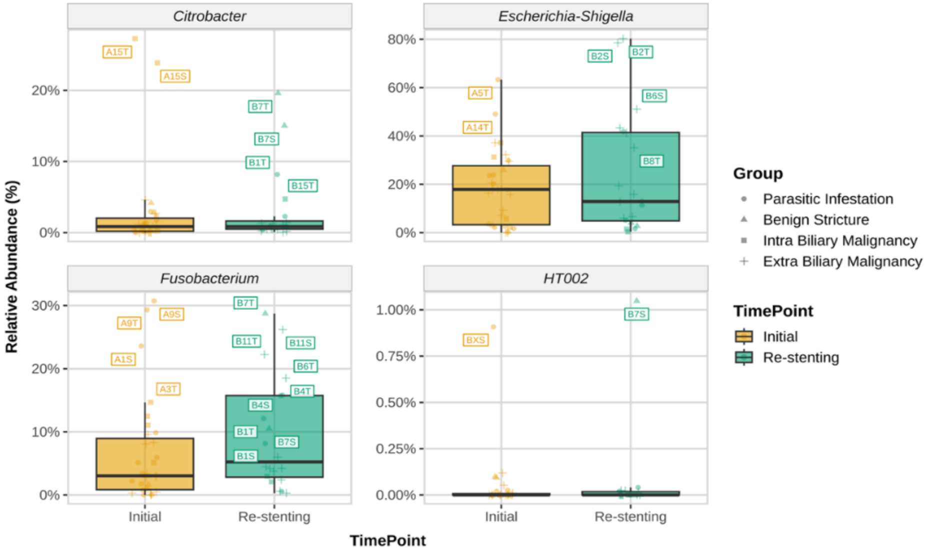

Figure 13. Selected genera relative abundance by sampling timepoint (A versus B). Genera shown are those with the lowest MaAsLin3 q-values for timepoint comparison: *Citrobacter*, *Escherichia-Shigella*, *Fusobacterium*, and *HT002*. Models were adjusted for disease group, sex, antibiotic use, sample type, and sequencing batch, with patient as a random intercept.

Elective versus emergency stenting

Differential abundance analysis revealed no statistically significant differences at the genus level between patients undergoing elective and emergent re-stenting. The most notable differences were observed in *Fusobacterium, Anaeroglobus, Desulfovibrio and Enterocloster*, none of which reached statistical significance after FDR correction (Figure 14). Notably, *Fusobacterium* showed higher relative abundance in patients undergoing emergent ERCP, though this finding should be interpreted with caution given the small sample size.

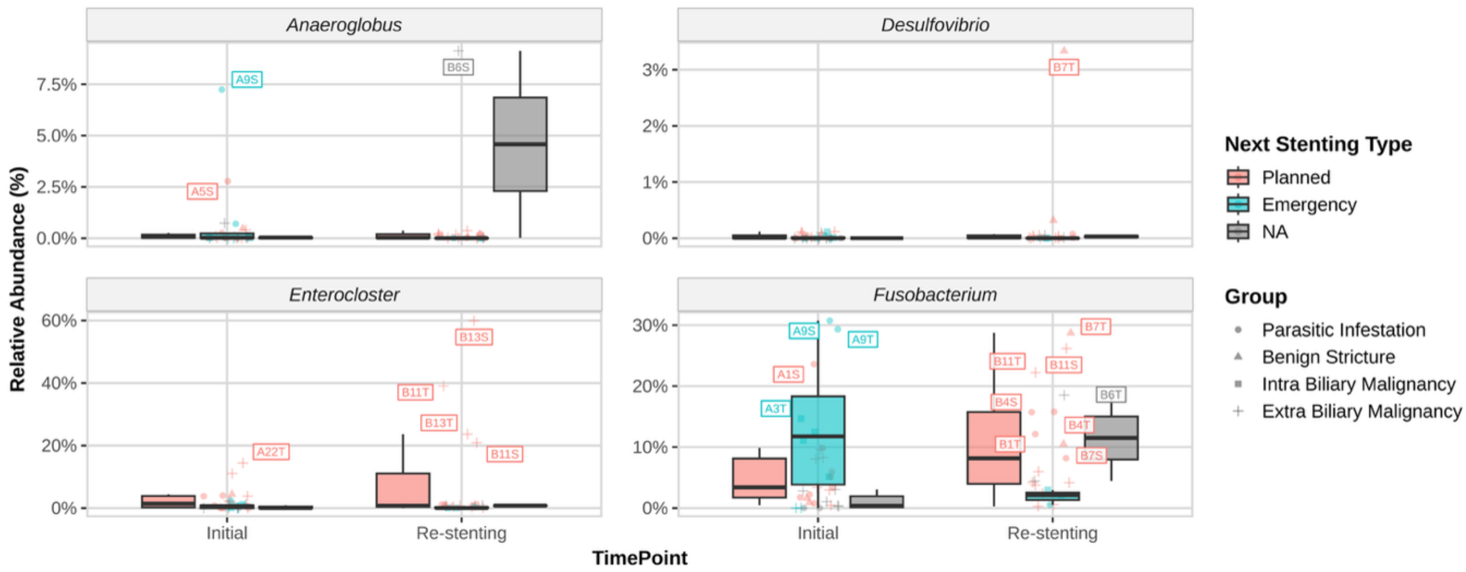

Figure 14. Selected genera relative abundance by next re-stenting type (Elective, Emergent, NA). Individual samples are colored by next re-stenting type and shaped by disease group. Genera shown were selected based on lowest MaAsLin3 q-values for re-stenting type: *Anaeroglobus*, *Desulfovibrio*, *Enterocloster*, and *Fusobacterium*.

Indication for ERCP and microbiome

Comparison of microbiome composition according to the indication for ERCP has shown no statistically significant differences in relative abundance, however there were non-statistically significant trends when samples were compared to extrabiliary malignancy group, as the most robust comparator. *Desulfovibrio* and *Lactobacillus* genera were more abundant in cases of benign structures, *Finegoldia* genus was more abundant in cases of intrabiliary malignancy, *HT002* was more abundant in cases of benign structures and parasitic infestation and *Parasutterella*, *Monoglobus* genera were more abundant in cases of intrabiliary malignancy. These selected genera according to the biggest difference in relative abundance are shown in Figure 15.

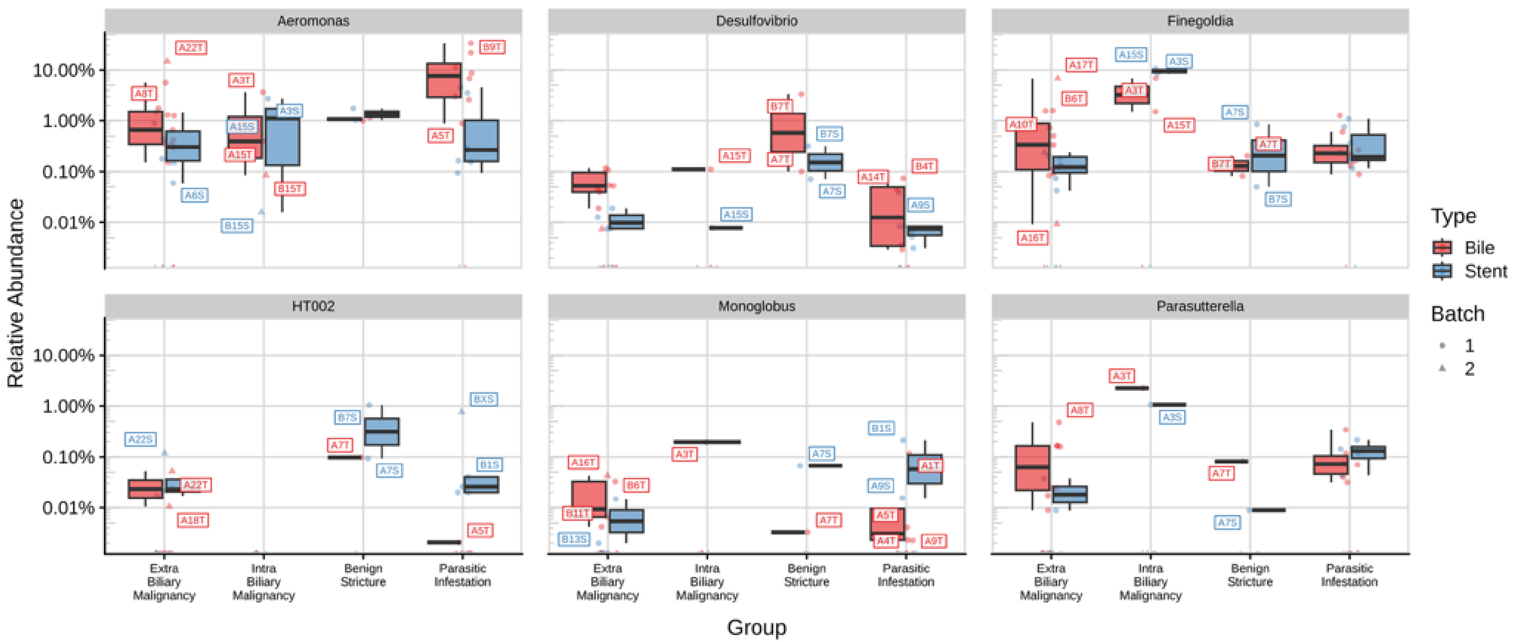

Figure 15. Selected genera relative abundance by indication for ERCP using extrabiliary malignancy indication as a reference.

Discussion

This prospective explorative study of biliary microbiome has shown nominally significant differences between bile and stentslead specimen composition, no alpha-diversity difference but a significant difference in community composition between bile and stent specimens. It has also revealed decreased alpha and beta diversity in sequential stenting specimens and no difference in differential abundance at a taxa level comparing samples from patients undergoing elective and emergency re-stenting.

Our findings are difficult to contextualize in the current literature landscape as there are only a few studies that investigate biliary microbiome in stented patients using metagenomic methods and earlier studies relied on culture-based methods, which underestimated microbial diversity and missed key anaerobic and fastidious organisms. Moreover, currently, there is only one study published investigating both bile and stent specimens (110).

In the samples of bile and stents the most relatively abundant bacteria at a phylum level were *Pseudomonadota* and *Bacillota*. After extrapolation these findings are congruent with the findings of Cacaci et al. that identified *Enterobacter* and *Lactobacillus* species as predominant in patients with benign biliary strictures at a genera level (110). This finding is further supported by previous culture-based studies, identifying *Enterobacter* (pertaining to *Peudomonadota* phylum) being associated with biofilm formation and stent occlussion (113–115). Our study showed statistically significant differences in microbiome composition at a genera level: *Dialister* ir *Anaeroglobus* genera were more abundant in stentslead specimens, whereas *Clostridium* genera were less abundant in stentslead specimens compared to bile specimens.

Comparison of the microbiome diversity at the index procedure and sequential re-stenting has shown statistically significant reduction in alpha diversity in specimens of the repeated procedures. Currently, there are no other studies investigating the effect of sequential stent placement on microbiome diversity. These findings have important clinical implications as repeated stent placement reduces microbiome diversity and predesposes patients to hospital-acquired infections.

Differential abundance analysis revealed no statistically significant differences at the genus level between patients undergoing elective and emergent re-stenting. There are no current studies using metagenomic methods to contextualize these results. However, the most notable differences were observed in *Fusobacterium, Anaeroglobus, Desulfovibrio and Enterocloster* genera. While *Fusobacterium* is not the predominant genus in biliary stent occlusion, its relative abundance in emergency-stenting setting underscores the importance of anaerobic bacteria in the pathogenesis of stent occlusion. The identification of *Fusobacterium* suggests that empirical antimicrobial strategies for stent-associated cholangitis should include coverage for anaerobes, in addition to aerobic bacteria (115).

There are limitations to our study. First of all, a small sample size of an exploratory study precludes wider generizibility of the results and most probably precipitates underestimation of true difference. Secondly, the metagenomic analysis was carried out in two separate batches, resulting in a significant ‘batch effect’. However, this was accounted for in the data analysis phase. Lastly, this study included non-homogeneous group of patients, with varied indications for ERCP and plastic biliary stent placement.

In conclusion, bile samples contain more diverse microbiome compared to biliary stents and should be used in clinical practice for microbiological investigations. Sequential stent placement reduces microbiome diversity, predisposing to hospital infections. Further more robust studies are needed to identify microbiome factors affecting biofilm formation and guide clinical and technological advancement.

CONCLUSIONS

- Actual average plastic biliary stent patency is lower than recommended in the guidelines for elective stent exchange, especially in patients with an underlying malignancy, history of cholangitis and multiple biliary plastic stents. A more vigilant and tailored stent exchange interval, based on the underlying disease, previous occlusion events and procedural aspects is warranted to prevent complications.
- Intra-procedural identification of ERCP associated perforations is essential for favourable patient outcomes and advanced measures should be taken while performing ERCP in patients at an increased risk.
- Bile samples contain more diverse microbiome compared to biliary stents and should be used in clinical practice for microbiological investigations. Sequential stent placement reduces microbiome diversity, predisposing patients to hospital-acquired infections. Underlying indication for ERCP affects biliary microbiome.

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SUMMARY

ĮŽANGA

Endoskopinės retrogradinės cholangiopankreatografijos (ERCP) metu atliekamas plastikinių tulžies latakų stentų įvedimas yra svarbi terapinė priemonė gydant tiek gerybinę, tiek piktybinę tulžies latakų obstrukciją. Tačiau šio metodo taikymą iš esmės riboja neišvengiamas bioplėvelės sukeltas stento užsikimšimas. Nors plastikiniai stentai dažnai pasirenkami dėl lengvesnio įvedimo ir pašalinimo bei mažesnių sąnaudų, jų ilgalaikis funkcinis patvarumas išlieka ribotas: stento praeinamumas paprastai išlieka tik 2–4 mėnesius, o literatūroje nurodoma, kad vidutinė jo trukmė svyruoja nuo maždaug 55 dienų sergant piktybine liga iki 110 dienų esant gerybinėms būklėms (1, 2). Plastikinių tulžies latakų stentų užsikimšimas reikšmingai blogina pacientų išeitis: didėja hospitalizacijų dažnis, vėluoja ar nutrūksta chemoterapija, taip pat didėja sunkių komplikacijų, tokių kaip cholangitas ir sepsis, rizika.

Stento disfunkcijos patofiziologija yra sudėtinga ir apima mikrobinės kolonizacijos, bioplėvelės matricos struktūros bei paties stento fizinių savybių tarpusavio sąveiką. Žinoma, kad plastikinių stentų obstrukciją dažniausiai lemia bakterinės bioplėvelės formavimasis, baltyminių nuosėdų kaupimasis, taip pat naviko ar audinių įaugimas. Šiuos procesus veikia tiek su stentu susiję, tiek pacientui būdingi veiksniai (3 – 5). Vis dėlto nevienareikšmiai antimikrobinėmis medžiagomis dengtų plastikinių stentų veiksmingumo rezultatai tiek in vivo, tiek in vitro sąlygomis pabrėžia ir kitų veiksnių svarbą bioplėvelės formavimuisi bei plastikinių tulžies latakų stentų užsikimšimui.

Bioplėvelės formavimasis prasideda nuo greitos bakterinės stento paviršiaus kolonizacijos, kuri įvyksta per kelias dienas po stento įvedimo. Šioje kolonizacijoje vyrauja polimikrobinė flora: dažniausiai aptinkami enterokokai, Enterobacteriaceae šeimos bakterijos ir *Candida* rūšys. Bioplėvelės formavimąsi skatina stento kontaktas su tulžimi ir dvylikapirštės žarnos turiniu, o šiam procesui daro įtaką anksčiau taikytas gydymas antibiotikais bei pagrindinė tulžies latakų patologija (6 – 8).

Sekoskaitos technologijų pažanga iš esmės pakeitė plastikinių tulžies latakų stentų mikrobiomo tyrimus, sudarydama galimybes išsamiai apibūdinti mikrobines bendrijas ir jų vaidmenį stentų užsikimšimo procese. Ankstyvieji tyrimai rėmėsi kultūriniais metodais, tačiau jie nepakankamai įvertino mikrobiologinę įvairovę ir neleido nustatyti svarbių anaerobinių bei sunkiai kultivuojamų mikroorganizmų.

Nors bioplėvelės formavimosi ant plastikinio stento mechanizmas, lemiantis jo užsikimšimą, yra gerai žinomas, vis dar trūksta išsamių modelių, kurie integruotų su procedūra, stentu ir pacientu susijusius kintamuosius, leidžiančius prognozuoti stento užsikimšimą ir komplikacijas.

Šios doktorantūros disertacijos **tikslas** – įvertinti su pacientu, pagrindine liga ir gydymu susijusius veiksnius, turinčius įtakos plastikinių tulžies latakų stentų funkcionavimui.

Uždaviniai:

1. Nustatyti faktinę plastikinių tulžies latakų stentų funkcionavimo trukmę bei su pacientu, pagrindine liga ir procedūra susijusius veiksnius, darančius jai įtaką.
2. Nustatyti su pacientu, procedūra ir gydymo taktika susijusius veiksnius, turinčius įtakos su ERCP susijusių perforacijų išeitims.
3. Įvertinti su pacientu, pagrindine liga ir procedūra susijusių veiksnių įtaką tulžies mikrobiomui.

Ginami teiginiai:

1. Vyriškoji lytis ir cholangitas pirminės ERCP metu yra su pacientu susiję veiksniai, turintys įtakos plastikinių tulžies latakų stentų funkcionavimui ir pacientų išeitims.
2. Piktybinė liga, ypač intrabiliarinė piktybinė patologija, yra su pagrindine liga susijęs veiksnys, turintis įtakos plastikinių tulžies latakų stentų funkcionavimui ir pacientų išeitims.
3. Antibiotikų skyrimas, didesnis įvedamų stentų skaičius, ankstyvas procedūrinių komplikacijų atpažinimas ir pakartotinis stentų keitimas yra su gydymu susiję veiksniai, turintys įtakos plastikinių tulžies latakų stentų funkcionavimui ir pacientų išeitims.

I UŽDAVINYS

Plastikinių tulžies latakų stentų funkcionavimo trukmė ir prognostiniai veiksniai

Endoskopinė retrogradinė cholangiopankreatografija (ERCP) ir tulžies latakų stentavimas yra vienas pagrindinių šiuolaikinio pacientų, sergančių tiek piktybine, tiek gerybine tulžies latakų obstrukcija, gydymo metodų. Nors plastikiniai stentai dažnai pasirenkami dėl lengvesnio įdėjimo ir pašalinimo bei mažesnės kainos, jų panaudojimas išlieka ribotas – stentų pratakumas paprastai išlieka tik 2–4 mėnesius, o literatūroje nurodomos medianos svyruoja nuo ~55 dienų esant piktybinei ligai iki ~110 dienų esant gerybinėms būklėms (122,149).

Žinoma, kad plastikinių stentų užsikimšimą dažniausiai lemia bakterinės bioplėvelės formavimasis, baltyminių nuosėdų kaupimasis bei naviko ar audinių įaugimas. Šiuos procesus veikia tiek su stentu susiję, tiek paciento individualūs veiksniai (109,112,150). Tyrimai parodė, kad piktybinė obstrukcija, ypač perihiliarinė, reikšmingai sutrumpina stento funkcionavimo trukmę (149). Be to, nustatyta, kad klinikiniai veiksniai, tokie kaip padidėjusi bilirubino koncentracija, kelių stentų įdėjimas ir hipoalbuminemija, didina cholangito riziką (132,151,152). Vienoje didelėje retrospektyvinėje kohortoje nustatyta, kad pacientams, sergantiems hiliarinės srities piktybininiais navikais, ankstyvos stento disfunkcijos rizika buvo tris kartus didesnė nei pacientams su distalinėmis striktūromis (153).

Bioplėvelės formavimosi ant plastikinio stento mechanizmas, sukeliantis jo okliuziją, yra gerai žinomas, tačiau vis dar trūksta išsamių modelių, kurie integruotų su procedūra, stentu ir pacientu susijusius veiksnius, leidžiančius prognozuoti stento užsikimšimą ir komplikacijas. Šio tyrimo tikslas buvo ištirti plastikinių tulžies stentų funkcionavimo trukmę ir stento okliuzijos rizikos veiksnius.

Metodai

Atlikta retrospektyvinė analizė, naudojant perspektyviai kauptos ERCP procedūrų duomenų bazės duomenis. Į analizę buvo įtrauktos procedūros, atliktos 2010–2019 m. vienoje tretinio lygio ligoninėje Vilniuje, Lietuvoje. Tyrimui gautas regioninio bioetikos komiteto leidimas (leidimo Nr. 2023/10-1539-1006). Tyrimas atliktas laikantis Helsinkio deklaracijos principų.

Į plastikinio tulžies latako stento funkcionavimo analizę buvo įtrauktos visos procedūros, kurių metu buvo įdėtas plastikinis tulžies latakų stentas. Iš analizės ekskliuduoti pacientai, kuriems stento įdėjimas nebuvo reikalingas, pavyzdžiui, pacientai po gerybinių striktūrų dilatacijos, sėkmingai atlikus choledocholitiazę, taip pat pacientai, kuriems buvo įdėti metaliniai stentai.

Pagrindinė tyrimo baigtis buvo stento funkcionavimo trukmė, apibrėžiama kaip laikotarpis nuo pirminio stento įdėjimo iki pakartotinio stentavimo. Antrinės baigtys buvo cholangito išsivystymas pakartotinio stentavimo metu ir tai, ar pakartotinis stentavimas buvo atliktas skubos tvarka. Pakartotinis stentavimas buvo laikomas skubiu, jei jis buvo atliktas anksčiau nei planuota pakartotinio stentavimo data, nepriklausomai nuo indikacijos (pvz., išsivystęs cholangitas, didėjanti gelta, įtariamas stento migravimas ir pan.).

Siekiant įvertinti skirtingos tulžies latakų obstrukcijos etiologijos įtaką stento funkcionavimui, pacientai buvo suskirstyti į 4 grupes: pacientai, su striktūromis dėl ekstrabiliarinės piktybinės ligos (kasos vėžys, spaudimas dėl metastazių ir kt.), intrabiliarinės piktybinės ligos (cholangiokarcinoma), pacientai su gerybinėmis tulžies latakų striktūromis (lėtinis pankreatitas, po cholecistektomijos atsiradusios striktūros ir kt.) bei pacientai su tulžies latakų striktūromis dėl parazitinės infestacijos (echinokokinė infekcija).

Visiems pacientams ERCP procedūros dieną buvo taikoma įprastinė antibiotikų profilaktika pagal ligoninės gaires. Papildomų antibiotikų skyrimas hospitalizacijos metu buvo laikomas antibiotikų vartojimu. Pacientai buvo stebimi iki pakartotinio stentavimo, chirurginio gydymo arba mirties ir buvo įtraukti į šį tyrimą.

Skirtumai tarp grupių buvo vertinami naudojant Kruskal–Wallis testą tolydiesiems kintamiesiems, o kategoriniams kintamiesiems – Pearsono χ^2 (chi kvadrato) testą arba Fišerio tikslųjį testą. Efekto dydis buvo apskaičiuotas naudojant koreguotą Cramerio V statistiką (nominaliesiems kintamiesiems) arba ranginį epsilon kvadrato (*Rank epsilon squared*) statistiką (intervaliniams kintamiesiems). Stento funkcionavimo laikui (išgyvenamumo funkcijai) įvertinti buvo sudarytos Kaplan–Meier kreivės, kurios buvo lyginamos naudojant log-rank testą. Siekiant įvertinti rizikos veiksnius, lemiančius pakartotinio stentavimo atlikimą skubos tvarka ir cholangito išsivystymą, buvo taikytas multivariacinis Cox proporcingų rizikų regresijos modelis. Dvipusė p reikšmė, mažesnė nei 0,05, buvo laikoma statistiškai reikšminga. Statistinė analizė atlikta naudojant R programinę įrangą, 4.5.0 versiją (R Project for Statistical Computing).

Pacientų populiacija ir charakteristikos

2010–2019 m. iš viso buvo atliktos 5462 ERCP procedūros. Iš jų 2659 procedūrų metu buvo įdėti plastikiniai tulžies latakų stentai, ir šios procedūros buvo įtrauktos į analizę. 1452 (56,4 %) pacientų buvo vyrai, o vidutinis pacientų amžius buvo 64 ± 15 metų. Didžiausia dalis tulžies latakų stentavimų buvo atlikta dėl ekstrabiliarinių piktybinių navikų (N = 1041, 39,2 %). Visos pradinės pacientų charakteristikos tarp skirtingos tulžies latakų striktūrų etiologijos grupių statistiškai reikšmingai skyrėsi (p < 0,001). Pacientai, sergantys ekstrabiliariniais ir intrabiliariniais piktybiniais navikais, buvo vyresni (atitinkamai 67 ± 12 m. ir 68 ± 12 m.) lyginant su pacientais, stentuotais dėl gerybinių striktūrų (60 ± 17 m.) ar parazitinės kilmės striktūrų (52 ± 16 m.). Panaši tendencija nustatyta ir vertinant cholangito dažnį – jis dažniausiai buvo nustatomas ekstrabiliarinių piktybinių navikų grupėje (N = 400, 38 %), po to sekė intrabiliarinių piktybinių navikų grupė (N = 318, 31 %), gerybinių striktūrų grupė (N = 243, 23 %) ir parazitinės infestacijos grupė (N = 81, 7,8 %). Didžiausias stentų skaičius vienos procedūros metu buvo įdėtas intrabiliarinės piktybinės ligos ir parazitinės infestacijos grupėse (atitinkamai 1,55 ± 0,57 ir 1,56 ± 0,55). Pacientų pradinės charakteristikos pateiktos 1 lentelėje.

Pacientams, kuriems tulžies latakų stentavimas buvo atliktas dėl piktybinės ligos, pakartotinis stentavimas skubos tvarka buvo reikalingas dažniau (N = 243, 39 %; N = 294, 33 %; N = 175, 20 % ir N = 73, 8 % atitinkamai ekstrabiliarinės ir intrabiliarinės piktybinės ligos, gerybinių striktūrų ir parazitinės infestacijos grupėse). Panaši tendencija nustatyta ir vertinant cholangito diagnozę pakartotinio stentavimo metu – pacientams, kuriems ERCP buvo atlikta dėl piktybinės indikacijos, cholangito dažnis buvo didesnis (N = 287, 37 %; N = 293, 38 %; N = 125, 16 % ir N = 69, 9 % atitinkamai ekstrabiliarinės ir intrabiliarinės piktybinės ligos, gerybinių striktūrų ir parazitinės infestacijos grupėse).

1 lentelė. Pradinės pacientų charakteristikos.

Characteristic	**Overall* N = 2659**	**Biliary stricture's aetiology group**				**p-value****	**Effect size (ES) adjusted (95% CI)*****
		Extrabiliary malignancy* N = 1041 (39%)	Intrabiliary malignancy* N = 565 (21%)	Benign stricture* N = 790 (30%)	Parasitic infestation* N = 263 (10%)		
Sex (male)	1452 (55%)	456 (44%)	271 (48%)	523 66%	202 77%	<0,001	0,24 (0,20, 1,0)
Age (years)^	64 (15)	67 (12)	68 (12)	60 (17)	52 (16)	<0,001	0,10 (0,08, 1,0)
Cholangitis⁺	1042 (39%)	400 (38%)	318 (31%)	243 (23%)	81 (7,8%)	<0,001	0,19 (0,16, 1,0)
Antibiotics°	1,533 (58%)	577 (38%)	400 (26%)	443 (29%)	113 (7,4%)	<0,001	0,15 (0,12, 1,0)
Cholecystectomy $^{\Delta}$	756 (28%)	196 (26%)	125 (17%)	405 (54%)	30 (4,0%)	<0,001	0,33 (0,30, 1,0)
Presence of gallbladder stones	570 (21%)	228 (40%)	145 (25%)	148 (26%)	49 (8,6%)	<0,001	0,24 (0,22, 1,0)
Presence of CBD stones	492 (19%)	88 (18%)	72 (15%)	243 (49%)	89 (18%)	<0,001	0,27 (0,24, 1,0)
N of stents^ placed	1.34 (0,55)	1.13 (0,36)	1,55 (0,57)	1,37 (0,63)	1,56 (0,55)	<0,001	0,13 (0,11, 1,0)
Cumulative stent diameter (Fr) $^{\pm}$	12,0 (10,0, 17,0)	12,0 (10,0, 12,0)	14,0 (10,0, 17,0)	12,0 (10,0, 17,0)	14,0 (10,0, 17,0)	<0,001	0,04 (0,03, 1,0)
Stent patency time (days) $^{\pm}$	63 (25, 96)	41 (17, 84)	54 (22, 84)	83 (38, 100)	98 (84, 136)	<0,001	0,12 (0,10, 1,0)
Stent patency >30 days	1,680 (63%)	509 (30%)	346 (21%)	589 (35%)	236 (14%)	<0,001	0,25 (0,22, 1,0)
Next re-stenting emergency	885 (33%)	343 (39%)	294 (33%)	175 (20%)	73 (8%)	<0,001	0,26 (0,22, 1,0)

Characteristic	Overall* N = 2659	Biliary stricture's aetiology group				p-value**	Effect size (ES) adjusted (95% CI)***
		Extrabiliary malignancy* N = 1041 (39%)	Intrabiliary malignancy* N = 565 (21%)	Benign stricture* N = 790 (30%)	Parasitic infestation* N = 263 (10%)		
Cholangitis during the next re-stenting	774 (29%)	287 (37%)	293 (38%)	125 (16%)	69 (9%)	<0,001	0,31 (0,28, 1,0)
Survival						<0,001	0,21 (0,18, 1,0)
Alive	2021 (76%)	650 (32%)	421 (21%)	702 (35%)	248 (12%)		
Dead	348 (13%)	220 (63%)	85 (24%)	35 (10%)	8 (2,3%)		
Unknown	289 (11%)	171 (59%)	59 (20%)	52 (18%)	7 (2,4%)		

* n (%), **Kruskal-Wallis test; Pearson's Chi-squared test, Fisher's exact test, ***Cramer's V adjusted, Rank epsilon squared

^ Continuous variable of normal distribution defined by mean and standard deviation

± Continuous variable of non-normal distribution defined by median and interquartile range

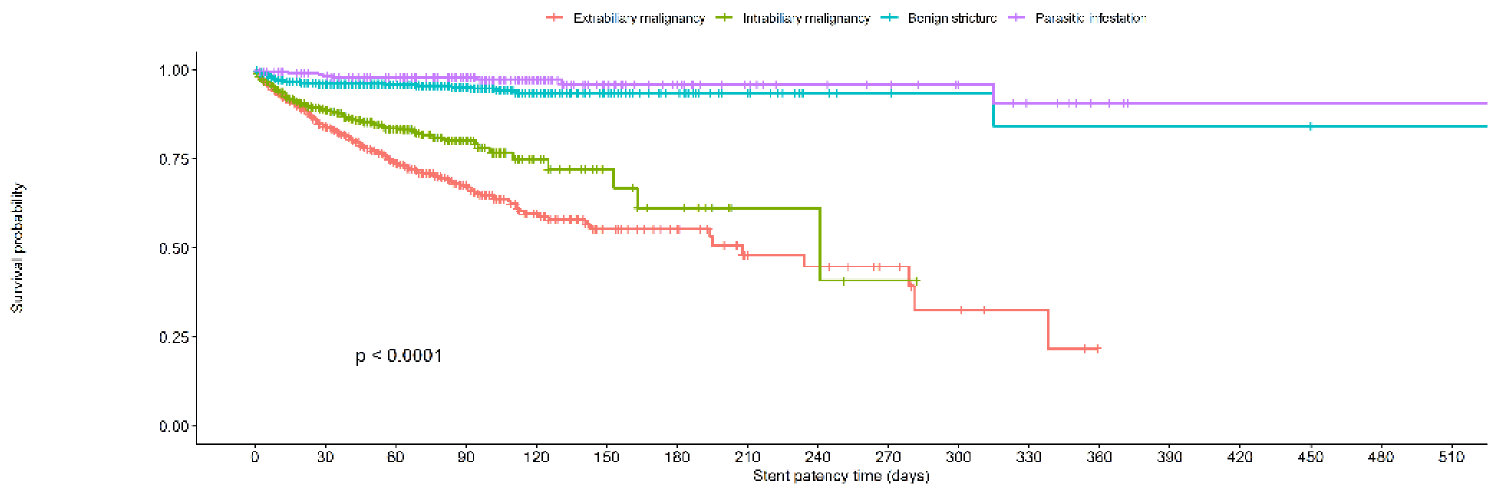
+ Cholangitis – diagnosed based on the diagnostic criteria upon time of hospitalization

° Antibiotics - administration of additional antibiotics upon hospitalization other than routine antibiotic prophylaxis for ERCP procedure

Δ Cholecystectomy – performance of cholecystectomy in patient history previous to hospitalization

Pirminė baigtis

Vidutiniškai plastikinis tulžies latako stentas funkcionavo 63 [25, 96] dienas. Nustatyti statistiškai reikšmingi stento funkcionavimo trukmės skirtumai tarp skirtingų indikacijos ERCP grupių (1 paveikslas). Trumpiausias stento funkcionavimo laikas buvo nustatytas ekstrabiliarinės piktybinės ligos grupėje – 41 [17, 84] diena, o ilgiausiai stentas išliko funkcionuojantis parazitinės infestacijos atvejais – 98 [84, 136] dienas. Log-rank testas patvirtino, kad stento funkcionavimo trukmės skirtumai tarp etiologinių grupių yra statistiškai reikšmingi ($p < 0,0001$).



Number at risk: n (%)

	0	30	60	90	120	150	180	210	240	270	300	330	360	390	420	450	480	510
Extrabiliary malignancy	870 (100)	511 (59)	322 (37)	195 (22)	75 (9)	39 (4)	29 (3)	16 (2)	14 (2)	9 (1)	5 (1)	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Intrabiliary malignancy	506 (100)	346 (68)	223 (44)	102 (20)	28 (6)	14 (3)	9 (2)	3 (1)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Benign stricture	735 (100)	589 (80)	470 (64)	320 (44)	88 (12)	51 (7)	35 (5)	24 (3)	13 (2)	11 (1)	10 (1)	9 (1)	9 (1)	9 (1)	9 (1)	9 (1)	8 (1)	8 (1)
Parasitic infestation	256 (100)	236 (92)	220 (86)	180 (70)	84 (33)	55 (21)	40 (16)	28 (11)	24 (9)	22 (9)	19 (7)	15 (6)	11 (4)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)

Stent patency time (days)

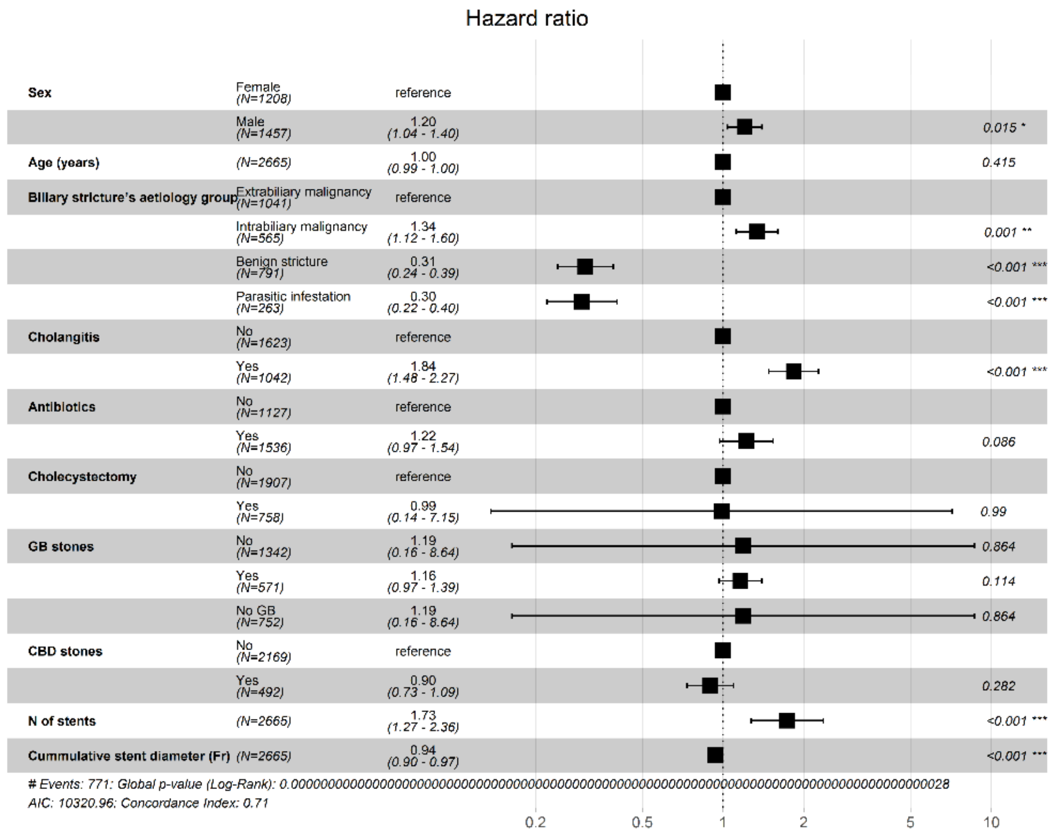
1 paveikslas. Plastikinio tulžies latakų stento funkcionavimo laikas.

Antrinės baigtys

Cholangitas pakartotinio stentavimo metu buvo diagnozuotas 774 atvejais (33 %).

Stipriausi cholangito išsivystymo rizikos veiksniai pakartotinio stentavimo metu buvo cholangitas pirminės ERCP procedūros metu (HR = 1,83; 95 % CI: 1,48–2,27; p < 0,001), intrabiliarinė piktybinė liga kaip stentavimo indikacija (HR = 1,34; 95 % CI: 1,12–1,60; p < 0,001) ir didėjantis įdėtų stentų skaičius (HR = 1,73; 95 % CI: 1,27–2,36; p < 0,001). Taip pat nustatyta šiek tiek didesnė cholangito diagnozės rizika pakartotinio stentavimo metu vyrams (HR = 1,2; 95 % PI: 1,04–1,40; p = 0,015).

Nustatyti ir du veiksniai, susiję su mažesne cholangito diagnozės rizika pakartotinio stentavimo metu: gerybinė tulžies latakų striktūra (HR = 0,31; 95 % CI: 0,24–0,39; p < 0,001) ir parazitinė infestacija (HR = 0,30; 95 % CI: 0,22–0,40; p < 0,001) kaip stentavimo indikacija (2 paveikslas).



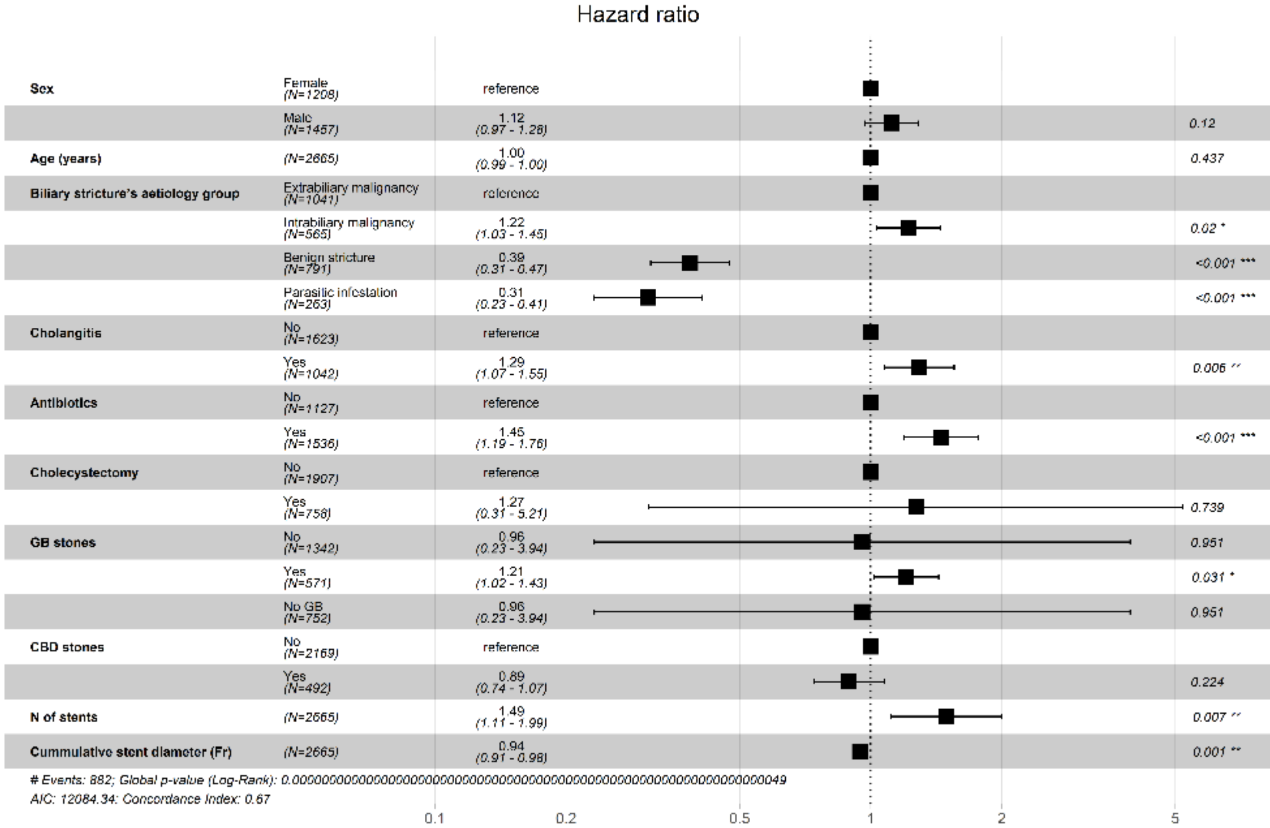
2 paveikslas. Rizikos veiksniai, susiję su cholangito diagnoze pakartotinio stentavimo metu.

885 (33 %) pakartotiniai stentavimai buvo atlikti skubos tvarka (neelektyviai).

Multivariacinės Cox proporcingų rizikų regresijos analizės duomenimis, stipriausi rizikos veiksniai, lemiantys, kad vėlesnė ERCP procedūra atliekama skubos tvarka, buvo didėjantis įdėtų plastikinių tulžies latakų stentų skaičius (HR = 1,49; 95 % CI: 1,11–1,99; p < 0,001), antibiotikų skyrimas ir cholangito diagnozė pirminės ERCP metu (atitinkamai HR = 1,45; 95 % CI: 1,20–1,77; p < 0,001 ir HR = 1,29; 95 % CI: 1,07–1,55; p < 0,001). Padidėjusi rizika taip pat nustatyta pacientams, sergantiems intrabiliarine piktybine liga (HR = 1,22; 95 % CI: 1,03–1,45; p = 0,02).

Du veiksniai buvo reikšmingai susiję su mažesne tikimybe, kad pakartotinis stentavimas bus neelektyvus: gerybinė tulžies latakų striktūra (HR = 0,39; 95 % CI: 0,31–0,48; p < 0,001) ir parazitinė infestacija (HR = 0,31; 95 % CI: 0,23–0,41; p < 0,001) kaip stentavimo indikacija.

Taip pat nustatyta, kad didėjantis bendras (kumulacinis) tulžies latakų stentų diametras šiek tiek mažino skubaus pakartotinio stentavimo riziką (HR = 0,94; 95 % CI: 0,91–0,98; p < 0,001) (3 paveikslas).



3 paveikslas. Rizikos veiksniai, susiję su pakartotiniu stentavimu skubos tvarka.

Šis tyrimas, nagrinėjantis plastikinių tulžies latakų stentų funkcionavimą ir jam įtaką darančius veiksnius, yra iki šiol klausimo analizė. Tyrimas parodė, kad vidutinė stento funkcionavimo trukmė yra 63 dienos, o stentavimo indikacija turi reikšmingą įtaką stento funkcionavimui. Be to, buvo nustatyti komplikacijų rizikos veiksniai, tokie kaip cholangito diagnozė pirminės ERCP metu ir didėjantis įdėtų plastikinių stentų skaičius.

Tyrimo rezultatai rodo, kad pacientams, kuriems tulžies latakai stentuojami dėl piktybinės ligos, plastikinio stento funkcionavimo trukmė yra trumpesnė nei pacientams, kuriems stentavimas atliekamas dėl gerybinių priežasčių. Tai sutampa su anksčiau publikuotais duomenimis, kurie taip pat rodo trumpesnį stento funkcionavimo laiką pacientams, sergantiems piktybinėmis ligomis (106 dienos, palyginti su 55 dienomis atitinkamai gerybinių ir piktybinių ligų atvejais) (149). Tai gali būti paaiškinama progresuojančia ligos eiga piktybinių susirgimų atvejais ir padidėjusiu spaudimu tulžies latakuose.

Nors žinoma, kad plastikinio tulžies latako stento funkcionavimo trukmė nėra pakankama užbaigti chemoterapinį gydymą neoadjuvantiniame etape (115), atrodo, kad chemoterapija paliatyvioje situacijoje gali prailginti metalinių stentų funkcionavimo laiką (154). Manoma, kad tai greičiausiai susiję su naviko tūrio sumažėjimu ir sumažėjusiu tulžies nuosėdų susidarymu.

Šio tyrimo duomenys rodo šiek tiek ilgesnę stento funkcionavimo trukmę intrabiliarinės piktybinės ligos grupėje, lyginant su ekstrabiliarinės piktybinės ligos grupe. Tai netikėtas radinys, nes nemažai pacientų, sergančių intrabiliarinėmis piktybinėmis ligomis, turėjo perihiliarines striktūras, kurių gydymas paprastai reikia kelių mažesnio diametro plastikinių stentų. Šis rezultatas taip pat prieštarauja šiuo metu publikuotiems duomenims. Pavyzdžiui, Ostrowski ir kt. (149) tyrė stentų funkcionavimo skirtumus tarp skirtingų piktybinių ligų lokalizacijų ir nustatė trumpesnę stento funkcionavimo trukmę esant proksimalinei striktūros lokalizacijai (atitinkamai 40 ir 76 dienos perihiliarinėms ir distalinėms striktūroms). Ilgesnė stento funkcionavimo trukmė intrabiliarinės piktybinės ligos grupėje, palyginti su ekstrabiliarinės piktybinės ligos grupe, taip pat prieštarauja radiniui, kad intrabiliarinės piktybinės ligos diagnozė yra cholangito išsivystymo rizikos veiksnys. Šis neatitikimas galėjo atsirasti dėl kelių priežasčių. Pagal mūsų centro protokolą visiems pacientams, kuriems ERCP metu stentuojami tulžies latakai plastikiniais stentais, planuojamas elektyvus pakartotinis stentavimas po 3 mėnesių. Bet koks hospitalizavimas ir pakartotinis stentavimas, nepriklausomai nuo priežasties (pavyzdžiui, didėjanti gelta, galinti sutrikdyti chemoterapijos skyrimą, ar cholangitas), šiame tyrime buvo laikomas skubiu. Perihiliarinės cholangiokarcinomos atveju ilgesnių stentų pasislinkimas pasitaiko dažniau (155) ir gali sukelti lokalią tulžies latakų obstrukciją be cholangito, dėl kurios priimamas sprendimas atlikti skubų pakartotinį stentavimą. Be to, pacientams, sergantiems perihiliarine cholangiokarcinoma, kai stentai įdedami į kairįjį ir (arba) dešinįjį kepenų latakus, vieno iš stentų užsikimšimas gali sukelti lokalų cholangitą, kuris gali nepasireikšti akivaizdžiais sisteminiais cholangito simptomais.

Nenuostabu, kad ilgiausia stento funkcionavimo trukmė buvo nustatyta parazitinės infestacijos grupėje. Nors tai retas susirgimas, echinokokinė infekcija yra endeminė kai kuriose pasaulio dalyse, o šis tyrimas pateikia išsamiausią iki šiol atliktą tulžies latakų stentų funkcionavimo rezultatų analizę sergant šia parazitine infekcija. Paprasčiausias paaiškinimas galėtų būti, kad pacientams, sergantiems parazitinėmis infekcijomis, gali būti dažniau skiriama papildoma antibiotikoterapija, veikianti gramneigiamas bakterijas, kuri slopina vieną iš pagrindinių bioplėvelės formavimosi ir stento užsikimšimo mechanizmų – bakterinę kolonizaciją (109). Kita, labiau hipotetinė, prielaida galėtų kelti klausimą, ar *Echinococcus* rūšių išskiriamos audinius ardančios medžiagos, leidžiančios parazitui agresyviai plisti į audinius, galėtų daryti įtaką bioplėvelės formavimuisi ant plastikinių tulžies latakų stentų.

Nustatėme, kad cholangito išsivystymo rizika buvo didesnė pacientams, sergantiems intrabiliarinėmis piktybinėmis ligomis, taip pat pacientams, kuriems cholangitas buvo diagnozuotas pirminės procedūros metu, ir didėjo didėjant įdėtų stentų skaičiui. Šie rezultatai sutampa su šiuo metu publikuotais duomenimis, rodančiais, kad piktybinės ligos diagnozė, kelių tulžies stentų įdėjimas, ankstesni stento užsikimšimo epizodai ir vyriškoji lytis yra cholangito išsivystymo rizikos veiksniai po plastikinio tulžies latakų stento įdėjimo (122,151). Priešingai nei mūsų tyrime, viename dedikuotame tyrime, į kurį įtrauktas 51 pacientas, sergantis kepenų alveoline echinokokoze ir kuriems buvo atlikta ERCP, buvo nustatytas panašus cholangito dažnis (9,1 %), tačiau kaip cholangito išsivystymo rizikos veiksniai buvo įvardyti vieno plastikinio stento įdėjimas ir stento diametras >8,5 Fr (42).

Be nustatytų cholangito išsivystymo rizikos veiksnių, plastikinių stentų skaičiaus ir jų kumuliacinio diametro įtaka buvo dar didesnė vertinant riziką, kad pakartotinis stentavimas bus atliekamas skubos tvarka. Okliuzijos rizika didėja didėjant įdėtų plastikinių stentų skaičiui ir mažėja didėjant bendram (kumulaciniam) stentų diametrui. Kelių mažesnio diametro plastikinių stentų įdėjimas padidina stento paviršiaus plotą, tinkamą bioplėvelės formavimuisi, ir sumažina spindžio skersmenį, todėl stentas užsikemša anksčiau. Šis principas aiškiai iliustruojamas ilgesniu didesnio diametro savaime išsiplečiančių metalinių stentų (SEMS) funkcionavimu.

Neseniai publikuoti tyrimai, kuriuose atliekama tulžies ir tulžies latakų stentų mikrobiologinė (kultūrinė) bei metagenominė analizė, leidžia nustatyti galimus specifinius mikrobiologinius agentus, lemiančius plastikinių tulžies stentų okliuziją. Šie tyrimai teikia vilčių individualizuotoms gydymo strategijoms ir plastikinių tulžies stentų technologinėms inovacijoms, kurios galėtų pailginti jų funkcionavimo trukmę (105,156).

Nors į tyrimą įtrauktas labai didelis pacientų skaičius, jis turi kelis trūkumus, daugiausia sąlygojamus retrospektyvios analizės pobūdžio. Apie dešimtadalis kohorto pacientų, daugiausia sergančių piktybinėmis ligomis, buvo prarasti stebėjimo metu, ir tai galėtų daryti įtaką rezultatų šališkumui. Kitas apribojimas – duomenų bazėje surinktos informacijos paprastumas, neatsižvelgiant į papildomus veiksnius, galinčius daryti įtaką stento funkcionavimui, tokius kaip chemoterapija, laboratorinių tyrimų rezultatai, gretutinės ligos ir panašiai. Tai ypač svarbu vertinant stento funkcionavimo laiką pacientams, sergantiems cholangiokarcinoma. Neseniai publikuoti duomenys rodo, kad stento funkcionavimo trukmė yra žymiai trumpesnė perihiliarinės cholangiokarcinomos atvejais, palyginti su distalinio tulžies latakų vėžio atvejais (157), tačiau dėl elektroninės duomenų bazės ypatumų šio pacientų pogrupio analizė nebuvo įmanoma. Nepaisant šių trūkumų, didelis pacientų skaičius kiekvienoje kohortos grupėje leidžia manyti, kad nustatyti skirtumai tarp grupių yra reikšmingi ir pateikia patikimus duomenis apie analizuotus veiksnius.

Pacientai, sergantys piktybine liga, sirgę cholangitu ir stentuoti daugiau nei vienu plastikiniu tulžies latakų stentu, yra padidėjusios rizikos grupėje ankstyvam stento užsikimšimui ir cholangitui. Siekiant išvengti komplikacijų, rekomenduojama dėmesinga ir individualizuota stentų keitimo taktika, pritaikyta atsižvelgiant į pagrindinę ligą, ankstesnius okliuzijos epizodus ir procedūrinius aspektus.

II UŽDAVINYS

Su endoskopine retrogradine cholangiopankreatografija susijusios perforacijos

Endoskopinė retrogradinė cholangiopankreatografija (ERCP) yra svarbi minimaliai invazinė terapinė intervencija, naudojama tulžies ir kasos latakų obstrukcijos gydymui. Nepaisant endoskopinių technologijų pažangos, ji išlieka viena iš techniškai sudėtingiausių ir rizikingiausių endoskopinių intervencijų. Pagrindinės ERCP komplikacijos yra po ERCP išsivystantis pankreatitas, kraujavimas, cholangitas ir cholecistitas, o perforacija laikoma vienu pavojingiausių nepageidaujamų įvykių. Su ERCP susijusi perforacija yra rečiausia šios procedūros komplikacija – bendras jos dažnis svyruoja nuo 0,08 % iki 0,6 % (46,158,159). Palyginimui, dažniausia komplikacija – po ERCP išsivystantis pankreatitas – pasireiškia 3–10 % atvejų (52,160). Nepaisant komplikacijos retumo, perforacijos gali sukelti reikšmingą sergamumą ir mirštamumą, jei nėra laiku atpažįstamos ir tinkamai gydomos (59,161).

Yra keli su ERCP susijusių perforacijų mechanizmai: spindžio perforacija dėl endoskopo manipuliacijos, sfinkterotomijos pjūvio plitimas už intramuralinio tulžies latako ribų bei ekstramuralinis vielos pravedimas arba stento migracija.

Yra nustatyti ERCP sukeltų perforacijų rizikos veiksniai, tokie kaip sfinkterotomija, '*precut*' technikos, sudėtinga kaniuliacija ir anatominiai ypatumai, pavyzdžiui, periampuliniai divertikulai ar pakitusi pooperacinė anatomija, kurių buvimas reikalauja dar atsargesnės ERCP atlikimo technikos (56,61,162). 2000 m. pristatyta Stapfer klasifikacija išlieka plačiausiai naudojama sistema ERCP sukeltoms perforacijoms klasifikuoti, padedanti tiek diagnostikai, tiek gydymo taktikos parinkimui. Ši klasifikacija perforacijas pagal anatominę lokalizaciją ir mechanizmą skirsto į keturis tipus, kurių kiekvienas pasižymi skirtingomis klinikinėmis pasekmėmis ir prognostine reikšme (161,163).

Nepaisant vaizdinimo ir endoskopinių technologijų pažangos, su ERCP susijusių perforacijų mirštamumas išlieka reikšmingas. Populiaciniai tyrimai rodo, kad bendras mirštamumas po ERCP gali siekti iki 0,14 %, o su perforacija susijęs mirštamumas svyruoja nuo 2 % iki daugiau nei 20 %, priklausomai nuo diagnozės nustatymo laiko, perforacijos tipo ir pasirinktos gydymo taktikos (59,161). Laiku nustatyta diagnozė ir ankstyva intervencija yra esminiai veiksniai, gerinantys gydymo rezultatus. Naujausi duomenys rodo, kad perforacijos nustatymas procedūros metu ir endoskopiniai perforacijos užvėrimo metodai gali reikšmingai sumažinti chirurginio gydymo poreikį bei sutrumpinti hospitalizacijos trukmę (59,164).

Šio tyrimo tikslas – ištirti su ERCP susijusių perforacijų dažnį, diagnostikos ypatumus, gydymo taktiką ir gydymo rezultatus didelės apimties centre per 10 metų laikotarpį bei apžvelgti du iliustratyvius klinikinius atvejus.

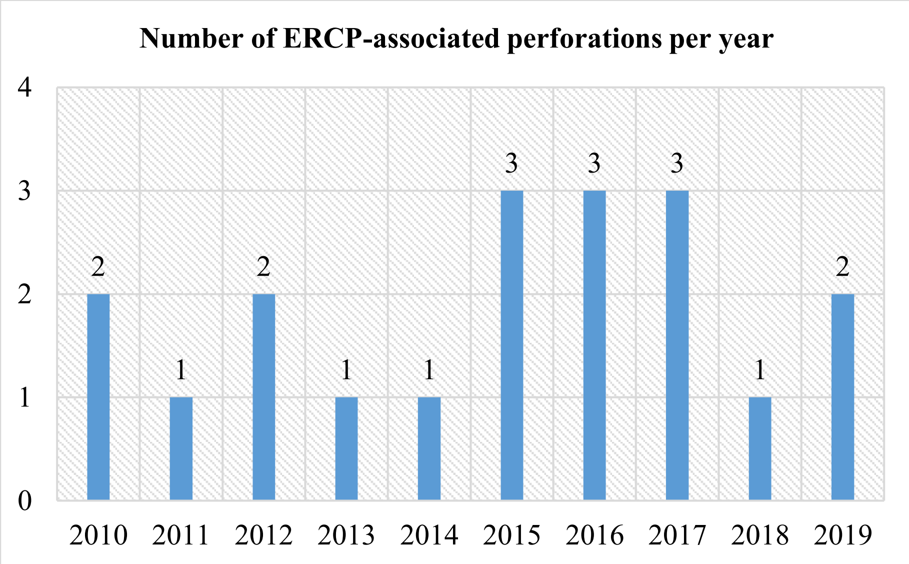
Metodai

Šio tyrimo metu analizuota didelė perspektyviai rinkta ERCP procedūrų, atliktų 2010–2019 m., duomenų bazė, siekiant įvertinti su ERCP susijusias perforacijas. Į analizę buvo įtraukti visi pacientai, kuriems nustatyta su ERCP susijusi perforacija. Tyrimui gautas Vilniaus regioninio bioetikos komiteto leidimas (leidimo Nr. 2023/10-1539-1006). Tyrimas atliktas laikantis Helsinkio deklaracijos principų. Buvo identifikuoti pacientai, kurių ERCP procedūros metu įvyko intraprocedūrinė perforacija, ir surinkti demografiniai duomenys bei kilinikinė informacija apie perforacijų diagnostiką ir gydymą. Kategorinių kintamųjų dažnis pateikiamas kaip atvejų skaičius ir procentai, o tolydieji duomenys – kaip vidurkiai arba medianos, atitinkamai normaliai ir nenormaliai pasiskirsčiusiems duomenims.

Rezultatai

2010–2019 m. laikotarpiu buvo atliktos 5462 ERCP procedūros. Iš jų 2665 ERCP procedūros buvo atliktos siekiant stentuoti tulžies latakus plastikiniu stentu ir jų metu nustatyta 20 perforacijų (0,75 %). Pacientų, kuriems nustatytos su ERCP susijusios perforacijos, vidutinis amžius buvo 73,2 ± 11,9 metų, iš jų 7 buvo vyrai (35 %). Visi pacientai turėjo su procedūra susijusių perforacijos rizikos veiksnių (N = 20, 100 %), o 13 pacientų tulžies latako kaniuliacija buvo klasifikuota kaip „sudėtinga“ (65 %). Perforacijos dažniausiai įvyko tulžies latakuose (N = 8, 40 %). Dažniausias perforacijos tipas buvo III tipas pagal Stapfer klasifikaciją (N = 9, 45 %) ir III tipas pagal Howard klasifikaciją (N = 10, 50 %). Pusei pacientų, kuriems diagnozuota su ERCP susijusi perforacija, prireikė chirurginio gydymo (N = 10, 50 %). Hospitalizacijos trukmės mediana pacientams, patyrusiems su ERCP susijusias perforacijas, buvo 16,5 dienos, o ketvirtadalis pacientų mirė (N = 5, 25 %).

Tyrimo laikotarpiu ERCP procedūras atliko 6 hepatopankreatobiliarinės (HPB) endoskopijos specialistai, iš kurių 3 ERCP procedūras atliko viso analizuojamo laikotarpio metu. Reikšmingos su ERCP susijusių perforacijų dažnio mažėjimo laiko tendencijos, kuri rodytų besikaupiančią patirtį, nenustatyta – jų skaičius išliko panašus ir svyravo nuo 1 iki 3 atvejų per metus (4 paveikslas).



4 paveikslas. Su ERCP susijusių perforacijų skaičius per metus.

Su ERCP susijusių perforacijų klinikinis pasireiškimas ir diagnostika

Iš 20 pacientų, kuriems nustatyta su ERCP susijusi perforacija, komplikacija buvo diagnozuota ERCP metu 6 pacientams (30 %), per pirmąsias 24 valandas po procedūros – 10 pacientų (50 %), o praėjus daugiau nei 24 valandoms po procedūros – 4 pacientams (20 %). 13 pacientų (65 %) pagrindinis nusiskundimas po ERCP buvo stiprus skausmas, o 9 pacientams (45 %) išsivystė klinikiniai peritonito požymiai. Be su ERCP susijusios perforacijos, 13 pacientų (65 %) taip pat buvo diagnozuotas post–ERCP pankreatitas.

5 pacientams (25 %) ultragarsinis tyrimas buvo vienintelis ir definityvus vaizdinimo metodas, leidęs nustatyti su ERCP susijusią perforaciją ir parinkti tolesnę gydymo taktiką. Galutinei diagnozei patvirtinti 9 pacientams (45 %) buvo atlikta kontrastinė kompiuterinė tomografija (KT), ir visais atvejais jos rezultatai galutinai patvirtino diagnozę. Nė vienu atveju rentgenologinio tyrimo nepakako laisvam orui pilvo ertmėje nustatyti.

Gydymas ir baigtys

Iš 20 pacientų, kuriems nustatyta su ERCP susijusi perforacija, visiems pasireiškė klinikiniai perforacijos simptomai. 12 pacientų (60 %) pirminis endoskopinis gydymas (stentavimas arba klipavimas) buvo pakankamas perforacijai užverti, kai ji buvo pastebėta pirminės procedūros metu.

Pažymėtina, kad visiems pacientams, kuriems pirminis endoskopinis perforacijos uždarymas buvo sėkmingas – 7 pacientams (35 %) (atliekant klipavimą arba stentavimą) – pasiekta visiška perforacijos rezoliucija ir papildomų intervencijų neprireikė.

4 pacientams (20 %) teko taikyti chirurginį gydymą, o 2 pacientams (10 %) buvo taikytas kombinuotas endoskopinis ir chirurginis gydymas. Išsamiai įvertinus klinikinę būklę, laboratorinių ir vaizdinių tyrimų duomenis, 2 pacientai (10 %) buvo gydyti konservatyviai, ir, nepaisant klinikinių bei radiologinių su ERCP susijusios perforacijos požymių, jiems perforacija užgijo savaime.

12 pacientų (60 %) dėl su ERCP susijusios perforacijos buvo gydyti intensyviosios terapijos skyriuje, kur jų gydymo laiko mediana buvo 6 dienos. 5 pacientams (25 %) su ERCP susijusi perforacija baigėsi mirtimi. Visiems pacientams, kurių baigtys buvo letalios, pirminė perforacijos uždarymo gydymo taktika buvo nesėkminga (N = 5, 100 %). Išsamūs pacientų duomenys apie su ERCP susijusios perforacijos klinikinę eigą, diagnostikos kelią ir baigtis pateikiami 2 lentelėje.

2 Lentelė. Su ERCP susijusios perforacijos, klinikinė eiga ir baigtys.

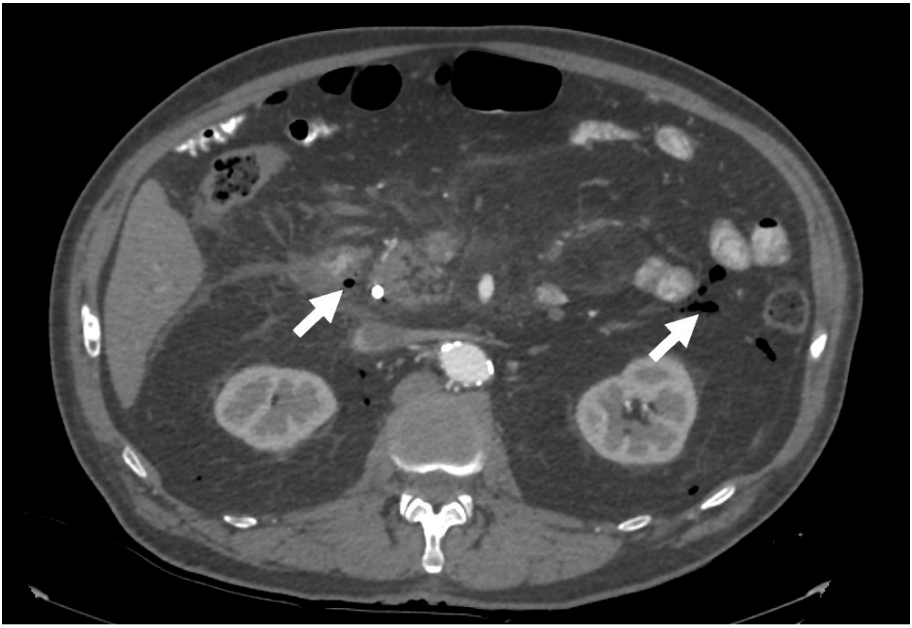
Patient	Localization of the perforation	Perforation type according to Stapfer	Imaging performed	Modality of imaging confirming perforation	Primary treatment, effectiveness	Surgery performed	Hospitalization in ICU	Clavien-Dindo grade	Hospitalization time (days)
1	Duodenum	1			Endoscopic, yes		+	3b	13
2	Pancreatic duct	3			Endoscopic, no	Laparotomy	+	3b	33
3	Duodenum	1	+	CT	Surgery, no	Laparotomy	+	5	5
4	Duodenum	4	+	CT	Observation, yes			1	9
5	Biliary tract	3	+	CT	Endoscopic, no		+	5	4
6	Biliary tract	3	+	CT	Endoscopic + surgical, no	Laparoscopy	+	5	26
7	Biliary tract	4	+	Ultrasound	Observation, yes			3b	17
8	Duodenum	1	+	CT	Surgery, no	Laparotomy	+	5	5
9	Pancreatic duct	3	+	CT	Endoscopic, no	Laparotomy	+	4b	32
10	Biliary tract	3	+	Ultrasound	Endoscopic, no	Laparoscopy	+	3b	70
11	Biliary tract	3	+	CT	Endoscopic, yes		+	3b	24

Patient	Localization of the perforation	Perforation type according to Stapfer	Imaging performed	Modality of imaging confirming perforation	Primary treatment, effectiveness	Surgery performed	Hospitalization in ICU	Clavien-Dindo grade	Hospitalization time (days)
12	Duodenum	2	+	CT	Endoscopic, no	Laparotomy	+	5	8
13	Pancreatic duct	3			Endoscopic, yes			1	13
14	Duodenum	1	+	Ultrasound	Surgery, yes	Laparotomy		3b	20
15	Duodenum	3			Endoscopic, yes			2	23
16	Duodenum	1	+	Ultrasound	Endoscopic, yes			3b	15
17	Biliary tract	2			Endoscopic, yes			1	7
18	Biliary tract	2			Endoscopic, yes			3b	5
19	Duodenum	1	+	CT	Endosopic + surgical, yes	Laparotomy	+	3b	168
20	Biliary tract	3	+	Ultrasound	Surgery, yes	Laparotomy	+	3b	22

Vienas iš skubaus su ERCP susijusios perforacijos nustatymo ir sėkmingo pirminio endoskopinio užvėrimo pavyzdžių yra paciento Nr. 1, 76 metų vyro, atvejis, kuriam dėl choledocholitiazės buvo atlikta ERCP. Procedūros metu buvo nustatyti daugybiniai bendrojo tulžies latako (BTL) akmenys ir įtarta distalinės BTL dalies striktūra. Atlikus sfinkterotomiją, buvo atlikta distalinės BTL dalies balioninė dilatacija. Pašalinus didžiąją dalį BTL konkrementų *Dormia* krepšeliu, buvo mėginta atlikti mechaninę litotripsiją likusiam įstrigusiam akmeniui pašalinti. Mechaninės litotripsijos metu įvyko dvylikapirštės žarnos antrosios dalies perforacija, kuri buvo sėkmingai užverta 3 endoskopiniais klipais. Dėl galimos distalinės BTL striktūros tulžies latakas stentuotas 12Fr plastikiniu stentu.

Pacientas buvo hospitalizuotas į intensyviosios terapijos skyrių stebėjimui ir konservatyviam gydymui. Praėjus vienai dienai po procedūros, atlikus kontrastinę kompiuterinę tomografiją, nustatytas nedidelis kiekis laisvo oro retroperitoniniame tarpe, kitų komplikacijų nenustatyta (5 paveikslas). Praėjus 3 dienoms po pirminės procedūros, pacientui buvo atlikta kontrolinė ERCP, kurios metu nustatytas adekvatus perforacijos uždarymas, o enterinei mitybai užtikrinti žemiau perforacijos vietos buvo įvestas enterinis zondas.

Pacientas buvo išrašytas praėjus 12 dienų po pirminės procedūros, daugiau komplikacijų nenustatyta. Po dviejų mėnesių buvo atlikta pakartotinė ERCP, kurios metu pašalintas tulžies latako stentas; tyrimo metu bendrojo tulžies latako striktūros požymių nenustatyta. Vėliau pacientui atlikta cholecistektomija, o tolesnio stebėjimo laikotarpiu daugiau biliarinių komplikacijų nepasireiškė.



5 paveikslas. Ašinėje KT projekcijoje po geriamojo ir intraveninio kontrastavimo matomas laisvas oras retroperitoniniame tarpe (baltos rodyklės) po jatrogeninės dvylikapirštės žarnos perforacijos, įvykusios ERCP ir tulžies latako stentavimo metu.

Kur kas mažiau aiškus diagnostinis kelias ir sudėtingesnis su ERCP susijusios perforacijos gydymas matomas vertinant paciento Nr. 15, 71 metų vyro, atvejį. Pacientas sirgo tulžies pūslės karcinoma, jam buvo atlikta cholecistektomija ir kepenų rezekcija, o ERCP atlikta įtariant mechaninę cholestazę dėl limfadenopatijos. Procedūros metu bifurkacijos srityje nustatytas kontrastinės medžiagos užpildymo defektas bei nedidelė kairiojo kepenų latako dilatacija. Buvo atlikta sfinkterotomija ir kairysis kepenų latakas stentuotas plastikiniu stentu virš bifurkacijos.

Po procedūros išliekant skausmui, laboratoriniams tyrimams parodžius padidėjusį α-amilazės aktyvumą kraujo serume, buvo diagnozuotas post-ERCP pankreatitas.

Praėjus 2 dienoms po procedūros, atlikta kontrastinė kompiuterinė tomografija, kuri parodė piktybinę hiliarinę infiltraciją, intrahepatinę cholestazę bei laisvą skystį ir orą perihiliarinėje srityje (6 paveikslas).

6 paveikslas. Ašinėje KT projekcijoje po intraveninio kontrastavimo, praėjus dviems dienoms po bendrojo tulžies latako stentavimo, matomi laisvas oras ir skystis (balta rodyklė) už bendrojo tulžies latako bei peripankreatinė infiltracija (balta žvaigždutė), tikėtina, dėl tulžies latako perforacijos ir pankreatito.

Atsižvelgiant į blogą pažengusios piktybinės ligos prognozę ir nesant peritonito požymių, buvo pradėtas konservatyvus gydymas plataus spektro antibiotikais ir enterine mityba per nazoduodeninį zondą. Dėl išliekančių padidėjusių uždegiminių rodiklių ir protarpinio karščiavimo, praėjus 2 savaitėms po pirminės ERCP, pacientui atlikta pakartotinė kontrastinė kompiuterinė tomografija. KT metu kairiojoje kepenų skiltyje nustatyti daugybiniai smulkūs cistiniai židiniai ir peripankreatinė infiltracija. Nuspręsta tęsti konservatyvų gydymą, o antibiotikoterapija buvo eskaluota. Per vieną savaitę pacientas nustojo karščiuoti, sumažėjo gelta ir uždegiminiai rodikliai. Pacientas buvo išrašytas praėjus 22 dienoms po pirminės ERCP paliatyviai priežiūrai, o tolesnio stebėjimo duomenų negauta.

Mūsų atlikta perspektyviai kauptos didelės apimties centro duomenų bazės su ERCP susijusių perforacijų analizė pateikia papildomų įrodymų apie šios retos, tačiau potencialiai letalios procedūrinės komplikacijos dažnį, diagnostiką, gydymą ir išeitis.

Mūsų nustatytas su ERCP susijusių perforacijų dažnis (0,75 %) atitinka literatūroje nurodomas ribas – nuo 0,39 % Bishay ir bendraautorių metaanalizėje, įtraukusioje 142 847 pacientus (46), iki 0,9 % Bray ir bendraautorių tyrime (162). Skirtingi literatūroje pateikiami su ERCP susijusių perforacijų dažnio duomenys gali būti susiję su nevienodu centruose atliekamų ERCP procedūrų skaičiumi, nes atliekamų procedūrų skaičius yra tiesiogiai susijęs su ERCP komplikacijų dažniu (165). Vis dėlto mūsų tyrimo laikotarpiu metinė ERCP procedūrų apimtis ir dėl jų pasireiškusių perforacijų dažnis išliko panašūs. Vertinant mūsų rezultatus, taip pat svarbu atsižvelgti į tai, kad buvo analizuotos tik tos ERCP procedūros, kurių metu atliktas tulžies latakų stentavimas, todėl bendroje pacientų kohortoje su ERCP susijusių perforacijų dažnis galėjo būti mažesnis; be to, visi pacientai turėjo bent vieną su ERCP susijusios perforacijos rizikos veiksnį (166).

Pusei mūsų tyrimo pacientų (N = 10; 50 %) su ERCP susijusi perforacija buvo diagnozuota per pirmąsias 24 valandas po pradinės procedūros, o 4 pacientams (20 %) – praėjus daugiau kaip 24 valandoms; pagrindinis nusiskundimas buvo stiprus pilvo skausmas, paskatinęs tolesnį diagnostinį ištyrimą.

Nors dėl didžiausio jautrumo ir specifiškumo rekomenduojamas su ERCP susijusios perforacijos diagnostikos metodas yra kompiuterinė tomografija su peroraliniu kontrastavimu (167,168), įdomu tai, kad mūsų kohortoje 20 % pacientų ši komplikacija buvo definityviai diagnozuota ultragarsinio tyrimo metu, o tai lėmė skubų operacinį gydymą be papildomų vaizdinių tyrimų. Ultragarsinio tyrimo metu įtartinos perforacijos požymiai buvo laisvas skystis arba oras aplink dvylikapirštės žarnos sienelę bei periduodeninės srities riebalinio audinio infiltracija. Tai pabrėžia nuo operatoriaus patirties priklausančios kompetencijos svarbą nustatant laisvą orą pilvo ertmėje, pasitelkiant plačiai prieinamą ir greitą vaizdinimo metodą.

Mūsų pacientų kohortoje dažniausias perforacijos tipas pagal Stapfer klasifikaciją buvo III tipas (distalinio tulžies latako) (N = 9). Tai prieštarauja publikuotiems duomenims, pagal kuriuos dažniausiai nustatomos II tipo su ERCP susijusios perforacijos (periampulinės, susijusios su sfinkterotomija). Vezakis ir bendraautorių atlikta 562 perforacijų jungtinė analizė parodė, kad II tipo perforacijų dažnis siekė net 46 % (169), o Bill ir bendraautorių sisteminėje 14 045 ERCP procedūrų apžvalgoje nustatyta, kad II tipo perforacijos sudarė 38,1 % visų perforacijų (57). Šiuos skirtumus būtų galima paaiškinti ilgalaike mūsų centro praktika net ir perihiliarinę (Bismuth–Corlette III ir IV tipo) mechaninę obstrukciją pirmiausia gydyti endoskopiniais metodais, dėl to tulžies latakų prieiga tampa sudėtingesnė, o perforacijų tulžies latakuose dažnis didėja. Kita galima priežastis – pakartotinis stygų naudojimas, nes po sterilizacijos proceso jos tampa standesnės.

Įdomu tai, kad 2 pacientams (10 %) sėkminga gydymo taktika buvo atidus klinikinės būklės stebėjimas, atliekant pakartotinius laboratorinius ir vaizdinius tyrimus, leidęs išvengti nereikalingų intervencinių procedūrų. Galima kelti prielaidą, kad perforacijos diagnozę galėjo lemti klaidingai teigiami vaizdinių tyrimų radiniai, nes ERCP metu oro burbuliukai kartais gali plisti intramuraliai ir imituoti perforacijos požymius. Vis dėlto abu pacientai turėjo perforacijos klinikinių simptomų, jiems nustatyti nežymiai padidėję uždegiminiai rodikliai. Kadangi nebuvo akivaizdžių peritonito požymių, atsižvelgiant į bendrą pacientų būklę buvo pasirinkta atsargi stebėsena ir konservatyvus gydymas plataus veikimo spektro antibiotikais, badavimu bei intravenine skysčių terapija. Tai atitinka ASGE rekomendacijas, siūlančias pradinį konservatyvų su ERCP susijusių perforacijų gydymą tais atvejais, kai nėra pilvaplėvės dirginimo požymių ar sisteminės uždegiminės reakcijos (53). Kruopščiai atrinktais su ERCP susijusių perforacijų atvejais atidus klinikinės būklės stebėjimas ir vertinimas padeda išvengti nereikalingų intervencinių procedūrų, ankstyvos operacijos ir su tuo susijusių komplikacijų (58). Atsargios gydymo taktikos svarbą pabrėžė ir Kumbhari su bendraautoriais, pasiūlę diagnostikos ir gydymo algoritmą Stapfer I ir II tipo perforacijų atvejais (54). Remiantis šio tyrimo duomenimis, iš 55 pacientų, kuriems Stapfer II tipo perforacija buvo diagnozuota po procedūros, tik 4 pacientams (7 %) konservatyvus gydymas buvo neefektyvus ir prireikė chirurginio gydymo. Tai dar kartą pabrėžia kruopštaus klinikinių simptomų ir sisteminio uždegimo požymių vertinimo svarbą, siekiant išvengti nereikalingų ir potencialiai žalingų intervencijų.

Visi pacientai, kuriems perforacija buvo diagnozuota procedūros metu, buvo sėkmingai gydyti endoskopiniais metodais ir vėliau išrašyti iš ligoninės; tai sutampa su didelio daugiacentrio Emori ir bendraautorių tyrimo rezultatais (59), pažyminčiais ankstyvos diagnostikos ir minimaliai invazinių gydymo metodų svarbą siekiant geresnių išeičių. Mūsų tyrime sėkmingas perforacijos uždarymas buvo atliekamas naudojant klipus arba įvedant plastikinį tulžies latakų stentą, priklausomai nuo perforacijos tipo. Deja, 7 pacientams (35 %) pirminis endoskopinis perforacijos uždarymas buvo nesėkmingas, todėl jiems prireikė chirurginio gydymo. Tyrimo laikotarpiu naujesnės perforacijų uždarymo priemonės, tokios kaip *over-the-scope* klipai ir pilnai dengti savaime išsiplečiantys metaliniai stentai, nebuvo prieinamos. Remiantis naujausiais duomenimis, galima pagrįstai manyti, kad pažangesnių perforacijos uždarymo metodų prieinamumas galėtų lemti geresnes gydymo išeitis (170,171).

Deja, 5 pacientų (25 %), patyrusių su ERCP susijusias perforacijas mūsų kohortoje, išeitys buvo letalios. Tai atitinka panašiu laikotarpiu atliktų tyrimų duomenis, pavyzdžiui, Švedijoje atlikto GallRiks tyrimo (52 140 ERCP procedūrų, 0,72 % perforacijų, 20 % mirštamumas) (161). Naujesniuose tyrimuose, tokiuose kaip Emori ir bendraautorių analizė (59), nurodomas gerokai mažesnis – apie 2 % – mirštamumas, kuris galėtų būti aiškinamas minimaliai invazinių gydymo metodų, tokių kaip *over-the-scope* klipai, pažanga.

Mūsų tyrimas turi keletą trūkūmų. Pirma, dėl retrospektyvios surinktos duomenų bazės analizės pobūdžio kai kurie svarbūs veiksniai, reikšmingi pacientų gydymui ir išeitims, galėjo būti neįtraukti į tyrimą. Antra, dėl su ERCP susijusių perforacijų retumo buvo analizuota tik 20 pacientų, patyrusių šią komplikaciją, klinikinė eiga. Vis dėlto manome, kad išsami diagnostikos ir gydymo taktikos apžvalga suteikia papildomų ir klinikinei praktikai naudingų žinių.

Su ERCP susijusi perforacija yra reta, tačiau potencialiai mirtina procedūrinė komplikacija, todėl būtina skubi diagnostika, išsamus ištyrimas ir daugiadalykis gydymo taktikos parinkimas. Tobulėjančios endoskopinio gydymo galimybės sudaro prielaidas veiksmingesniam intraprocedūriniam gydymui, o kruopštus paciento būklės po procedūros vertinimas įtariamos su ERCP susijusios perforacijos atvejais bei daugiadalykis požiūris lemia geresnes pacientų išeitis.

III UŽDAVINYS

Tulžies mikrobiomo ir plastikinių tulžies latakų stentų funkcionavimo sąveika

Endoskopinė retrogradinė cholangiopankreatografija (ERCP) ir tulžies latakų stentavimas plastikiniais stentais yra svarbus gydymo metodas tiek gerybinei, tiek piktybinei tulžies latakų obstrukcijai. Tačiau plastikinių tulžies latakų stentų naudojimą iš esmės riboja neišvengiamai išsivystantis bioplėvelės sukeltas stento spindžio užsikimšimas. Stento funkcijos praradimo patofiziologiją lemia sudėtinga sąveika tarp mikroorganizmų kolonizacijos, bioplėvelės matricos struktūros ir paties stento fizinių savybių.

Bioplėvelės susidarymas ant plastikinių tulžies latakų stentų vyksta pagal nuspėjamą laiko seką: per pirmąsias 30 dienų po stento įvedimo vyksta pirminė kolonizacija aerobinėmis gramteigiamomis bakterijomis ir grybelių rūšimis. Vėliau, po 60 dienų stento buvimo latake, mikrobiomas palaipsniui įvairėja ir įtraukia aerobinius gramneigiamus mikroorganizmus bei anaerobus (108,109).

Tulžies latakų stentų bioplėvelių mikrobiomas pasižymi išskirtiniu sudėtingumu: daugiau kaip 95 % pašalintų stentų nustatoma polimikrobinė kolonizacija (104). Enterococcus rūšys yra dažniausi kolonizatoriai, aptinkami maždaug 79 % stentų bioplėvelių, po jų seka Enterobacteriaceae – 74 % ir *Candida* rūšys – 56 % (104). Naujausios metagenominės analizės nustatė ir kitus svarbius stentų užsikimšimo veiksnius, įskaitant *Enterobacter* ir *Lactobacillus* rūšis, kurios pasižymi stipriu gebėjimu formuoti bioplėveles (105). Pažymėtina, kad *Bifidobacterium* rūšių, ypač *Bifidobacterium animalis*, gausa reikšmingai koreliuoja su užsikimšimo sunkumu, nepriklausomai nuo stento funkcionavimo trukmės (106).

Bioplėvelės matrica susideda iš baltyminių ir polisacharidinių komponentų; baltymų koncentracija yra reikšmingai padidėjusi pacientams, kuriems diagnozuotas cholangitas, taip pat mažesnio skersmens stentuose (110). Išilginės struktūros analizės tyrimai rodo, kad bioplėvelė pradeda formuotis aplink stento šonines angas per pirmąsias 30 dienų, per 60 dienų išplinta ir apima visą stento paviršių, o iki visiško užsikimšimo progresuoja per vidutiniškai 90 dienų (109). Ši laiko progresija paaiškina klinikinį pastebėjimą, kad realiomis sąlygomis vidutinė stento funkcionavimo trukmė svyruoja nuo 53 iki 68 dienų ir yra gerokai trumpesnė nei tradicinis 3 mėnesių stento keitimo intervalas (115). Klinikinės stento užsikimšimo pasekmės neapsiriboja vien mechanine obstrukcija: užsikimšę stentai yra susiję su reikšmingai didesne cholangito rizika (38,5 %, palyginti su 9,1 % funkcionuojančiais stentais) (104).

Gydymo strategijos, skirtos bioplėvelės susidarymo prevencijai, davė prieštaringų rezultatų: atsitiktinių imčių tyrimai, kuriuose buvo vertinama ursodeoksicholio rūgštis ir profilaktinis antibiotikų vartojimas, neparodė tvarios naudos nei stento funkcionavimo trukmės prailginimo, nei mirštamumo mažinimo aspektu (124). Tačiau naujos technologijos, įskaitant antimikrobines dangas su oktenidino ir citrato deriniais bei vaistus išskiriančius polimerus, ikiklinikiniuose ir ankstyvuosiuose klinikiniuose tyrimuose rodo vilčių teikiančius rezultatus (97,139).

Antibiotikams atsparių mikroorganizmų vystymasis stentų bioplėvelėse kelia papildomą susirūpinimą: vankomicinui atsparūs enterokokai, išplėstinio spektro beta laktamazes gaminančios Enterobacteriaceae ir azolams atsparios *Candida* rūšys sudaro atitinkamai 13,7 %, 13,9 % ir 32,9 % visų mėginių (104).

Sekoskaitos technologijų pažanga iš esmės pakeitė plastikinių tulžies latakų stentų mikrobiomo tyrimus, nes tapo įmanoma visapusiškai apibūdinti mikrobines bendrijas ir jų vaidmenį stentų užsikimšimo procese. Ankstyvieji tyrimai rėmėsi kultūriniais metodais, kurie nepakankamai įvertino mikrobiologinę įvairovę ir neatskleidė svarbių anaerobinių bei reikliųjų mikroorganizmų reikšmės. Pritaikius didelio pralaidumo 16S rRNR genų sekoskaitą, tapo įmanomas išsamus bakterinių taksonų profiliavimas; tai atskleidė pacientui specifines ir ligoninei būdingas mikrobiologinių bendrijų struktūras bei padėjo nustatyti anksčiau neatpažintas sąsajas tarp tam tikrų genčių, tokių kaip *Bifidobacterium*, *Enterobacter* ir *Lactobacillus*, ir stento užsikimšimo sunkumo (105,106,111).

Metagenominė naujos kartos sekoskaita (mNGS) ir viso metagenomo „*shotgun*“ sekoskaita dar labiau išplėtė tyrimų galimybes, leidama aptikti naujas biliarines bakterijas, analizuoti funkcinius genus, pavyzdžiui, susijusius su bioplėvelės formavimusi ir atsparumu tulžiai, bei nustatyti metabolinius kelius, svarbius stentų bioplėvelių ekologijai (172,173). Šie metodai taip pat sudarė galimybes tirti grybelinius ir virusinius komponentus, taip pat bioplėvelių erdvinę organizaciją, pasitelkiant papildomus vaizdinimo metodus (174).

Naujausios inovacijos, tokios kaip vienos ląstelės genomo sekoskaita ir supaprastinti metagenominiai metodai, pavyzdžiui, 2bRAD-M, suteikia didesnę rezoliuciją ir efektyvumą tiriant mažos biomasės mėginius, būdingus tulžies latakų stentams, ir padeda spręsti kontaminacijos bei heterogeniškumo problemas (173). Ši pažanga skatina transliacinius tyrimus, kuriais siekiama kurti tikslines antimikrobines terapijas ir bioplėvelių susidarymą slopinančias stentų medžiagas, taip pat nustatyti standartizuotus mikrobiomo analizės protokolus klinikinėje praktikoje (97,105,136).

Metodai

Tyrimo aplinka

Tai yra žvalgomasis perspektyvus kohortinis tyrimas, kurio metu vienoje tretinio lygio ligoninėje Vilniuje, Lietuvoje, tirta tulžies mikrobiomo ir plastikinių tulžies latakų stentų praeinamumo sąveika. Tyrimui buvo gautas Vilniaus regioninio biomedicininių tyrimų etikos komiteto leidimas (leidimo Nr. 2021/9-1376-850, leidimo data – 2021-09-21). Tyrimas atliktas laikantis Helsinkio deklaracijos principų.

Įtraukimo kriterijai

Į tyrimą galėjo būti įtraukti pacientai, kuriems atliekama ERCP ir planuojamas tulžies latakų stentavimas plastikiniu stentu dėl bet kokios etiologijos tulžies latakų striktūros.

Įtraukimo kriterijai:

- Vyresni nei 18 metų teisiškai pilnamečiai pacientai
- Pacientai, pasirašę informuoto sutikimo formą prieš atliekant ERCP
- Pacientai, kuriems dėl tulžies latakų striktūros atliekama ERCP (įskaitant pacientus, kuriems ERCP atliekama pirmą kartą) ir planuojamas plastikinio tulžies latako stento įvedimas
- Pacientai, kuriems planuojama apie 90 dienų trunkanti plastikinio tulžies latako stento laikymo trukmė

Neįtraukimo kriterijai:

- Pacientai, kuriems dėl choledocholitiazės atliekama ERCP ir galimas tulžies latakų stentavimas plastikiniu stentu
- Pacientai, kuriems planuojama trumpesnė nei 90 dienų plastikinio tulžies latako stento laikymo trukmė
- Pacientai, kuriems atliekama ERCP ir planuojamas savaime išsiplečiančio metalinio stento (SEMS) įvedimas

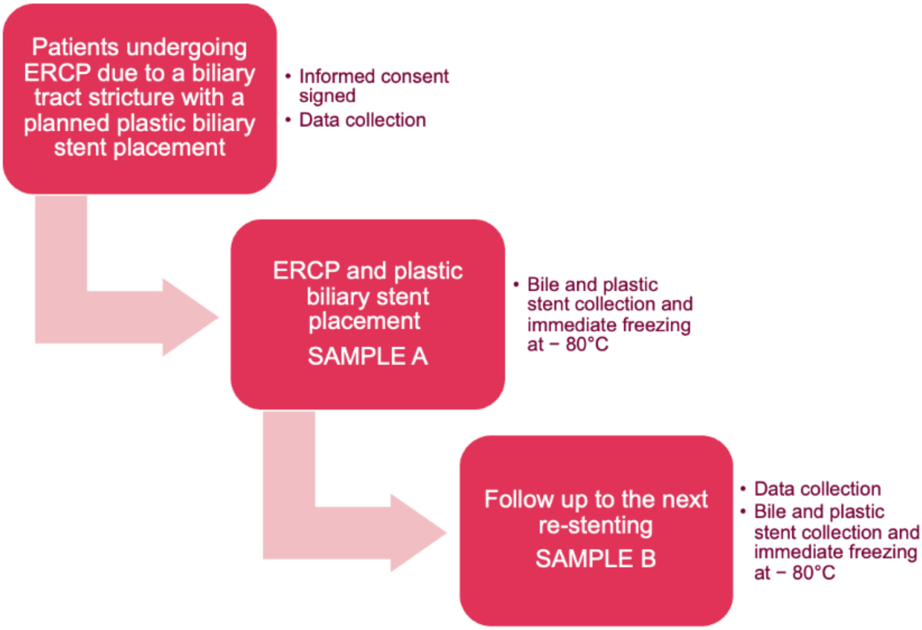
Intervencija

Visiems pacientams buvo taikyta įprastinė profilaktika antibiotikais pagal ligoninės gaires: ERCP dieną į veną buvo skiriama po 1 gramą cefazolino du kartus per parą. Papildomų antibiotikų skyrimas hospitalizacijos metu buvo laikomas antibiotikų vartojimu. Antibiotikų ir probiotikų vartojimas buvo registruojamas prieš surenkant tulžies ir stento mėginius ir nebuvo laikomas neįtraukimo kriterijumi.

Imties dydis buvo parinktas pagal Julious tyrimą „*12 tiriamųjų taisyklė bandomajam tyrimui*“ (175).

ERCP procedūras atliko 4 kvalifikuoti endoskopuotojai, patyrę HPB endoskopinių procedūrų atlikime. Visų procedūrų metu buvo parenkamas to paties gamintojo tinkamo skersmens ir ilgio stentas, siekiant išvengti stento medžiagos įtakos tyrimo rezultatams. Siekiant išvengti kontaminacijos, duodenoskopas buvo įvedamas ir pozicionuojamas priešais papilę nenaudojant siurbimo. Pacientams, kuriems ERCP buvo atliekama pirmą kartą, tulžies latakai buvo kaniuliuojami steriliomis sąlygomis ir atsiurbiama 5 ml tulžies. Kartotinės ERCP atvejais tulžies latakuose esantis plastikinis stentas buvo atsargiai pašalinamas sterilia kilpa, tulžies latakai buvo kaniuliuojami, ir 5 ml tulžies atsiurbiama steriliomis sąlygomis. Tulžies ir plastikinio tulžies stento mėginiai buvo surenkami į sterilius mėgintuvėlius, iškart po surinkimo užšaldomi (ne vėliau kaip per 30 minučių po surinkimo) ir laikomi −80 °C temperatūroje (A mėginys) tyrimo centre.

Į tyrimą įtraukti pacientai buvo stebimi iki kito planinio arba skubaus pakartotinio stentavimo, operacijos arba mirties. Vėlesnės hospitalizacijos metu buvo renkami klinikiniai duomenys, pacientams atliekama ERCP ir pakartotinis stentavimas, surenkant tulžies ir plastikinio stento mėginius (B mėginys) pagal tą pačią metodiką. Tyrimo procedūra apibendrinta 7 paveiksle.



7 paveikslas. Tyrimo procedūros schema.

Baigtys

Pirminė tyrimo baigtis buvo tulžies ir stento mikrobiomo įvairovė. Antrinė baigtis buvo bakterijų taksonų santykinis gausumas tulžies ir stento mėginiuose.

Duomenų analizė

Demografiniai ir klinikiniai skirtumai tarp grupių buvo vertinami taikant Fišerio tikslųjį testą. Dvipusė p reikšmė, mažesnė nei 0,05, buvo laikoma statistiškai reikšminga.

Neapdoroti skaitiniai iš skirtingų sekoskaitos partijų buvo apdorojami atskirai naudojant *QIIME2* (versija 2025.10) numatytaisiais nustatymais, jei nenurodyta kitaip (176). Brūkšniniai kodai ir adapteriai buvo pašalinti naudojant *cutadapt*, o neapkarpytos sekos atmestos (177). *Poly-G* artefaktai, atsirandantys dėl dviejų spalvų *Illumina* chemijos, buvo šalinami iš atvirkštinių skaitinių (R2) 3’ galo. Skaitinių kokybė prieš ir po apkarpymo buvo vertinama naudojant *MultiQC* (178). Amplikonų sekų variantai (ASV) buvo sudaryti taikant *DADA2* darbo seką (179). 16S rRNR V3–V4 skaitiniams sekos buvo trumpinamos 5’ ir 3’ galuose. Dekontaminacija buvo atliekama naudojant *q2-decontam* dažnio metodą, remiantis DNR koncentracija, išmatuota po DNR ekstrakcijos (180). Po dekontaminacijos partijų duomenys buvo sujungti į vieną lentelę ir sekų rinkinį. Sekos buvo sugretintos, siekiant sudaryti filogenetinį medį naudojant *FastTree2* (181). Taksonominė klasifikacija buvo atliekama naudojant *q2-feature-classifier* papildinį (182) su *Naive Bayes* klasifikatoriumi, apmokytu pagal V3–V4 sekas naudojant *SILVA v138.2 SSU Ref NR 99* duomenų bazę (183). Paruošus duomenis, tolesnei analizei buvo naudojama 3 716 731 seka, vidutiniškai po 72 877 skaitinius.

Visos statistinės analizės buvo atliktos naudojant R (versija 4.4.3) ir *mia* mikrobiomo analizės sistemą. Retinimas buvo atliekamas pakartotinio atsitiktinio atrinkimo būdu (500 iteracijų) iki mažiausią sekoskaitos gylį turėjusio mėginio lygio, o įvairovės reikšmės buvo vidurkinamos per visas iteracijas. Statistinio reikšmingumo lygmuo buvo nustatytas $\alpha = 0{,}05$. Taksonominė sudėtis apibendrinta kaip santykinio gausumo mediana su tarpkvartiliniu intervalu (IQR) kiekvienai grupei. Taksonominių suvestinių sudarymui taksonai, klasifikuoti kaip *Incertae Sedis*, agregavimo metu buvo įtraukiami į likučių grupę. Įvairovės analizėse buvo naudojama visa ASV lentelė be taksonominio filtravimo. Alfa įvairovė ASV lygmeniu buvo vertinama naudojant Shannon įvairovės indeksą ir Faith filogenetinės įvairovės rodiklį (Faith PD), siekiant atspindėti tiek gausumo svertus, tiek filogenetinius bendrijos įvairovės aspektus. Skirtumai tarp grupių buvo vertinami taikant tiesinius mišriuosius modelius (LMM), kad būtų atsižvelgta į pakartotinius pacientų mėginių matavimus, o *post hoc* poriniai palyginimai buvo koreguojami pagal *Benjamini–Hochberg* procedūrą. Beta įvairovė buvo vertinama naudojant *Jaccard* (buvimo–nebuvimo) ir *Bray–Curtis* (gausumo svertas) nepanašumo matricas, taip pat nesvertinius ir svertinius *UniFrac* atstumus, apskaičiuotus naudojant retintus duomenis su 500 pakartotinių iteracijų. Ordinacija buvo atlikta taikant pagrindinių koordinačių analizę (*PCoA*), o kiekvienos ašies paaiškinama dispersijos dalis buvo gauta iš savųjų reikšmių skaidymo. Bendrijos sudėties skirtumai tarp grupių buvo testuojami naudojant permutacinę daugiamatę dispersinę analizę (*PERMANOVA*; 999 permutacijos), stratifikuotą pagal pacientą, atsižvelgiant į pakartotinius matavimus. Daugiamatės dispersijos homogeniškumas vertintas naudojant *betadisper* permutacinį testą (999 permutacijos). Siekiant nustatyti specifinių taksonų skirtumus tarp grupių, analizei naudotas *MaAsLin 3* metodas. *False Discovery Rate* (FDR) korekcijai buvo taikytas *Benjamini–Hochberg* metodas ir pateiktos jungtinio paplitimo ir gausumo q reikšmės.

Pacientų populiacija ir charakteristikos

Į tyrimą 2021 11 04 – 2025 01 09 laikotarpiu buvo įtraukti 22 pacientai. 59 % tiriamosios kohortos pacientų buvo vyrai (N = 13), o vidutinis amžius siekė 62,5 ± 11,4 metų. Dažniausia tulžies latakų striktūros etiologija tiriamojoje kohortoje buvo ekstrabiliarinė piktybinė liga (N = 12; 54,6 %), ir tik vienam pacientui tulžies latakų stentavimas buvo atliktas dėl gerybinės patologijos (portinės biliopatijos). 22,7 % pacientų (N = 5) anksčiau nebuvo atlikta ERCP. Pirminės ERCP metu 31,8 % pacientų (N = 7) nustatyti sisteminiai cholangito požymiai ir diagnozuotas cholangitas, o 54,5 % (N = 13) buvo skirti antibiotikai. Stebėjimo laikotarpiu mirė 18 % pacientų (N = 4), o vienam pacientui dėl kasos vėžio buvo atlikta pankreatoduodeninė rezekcija.

Nustatyti statistiškai reikšmingi skirtumai tarp pacientų, kuriems pakartotinis stentavimas buvo atliktas planine ir skubia tvarka, vertinant tulžies latakų striktūros etiologiją (p = 0,059) ir stento funkcionavimo laiką (p = 0,006).

Pradinės pacientų charakteristikos pateiktos 3 lentelėje.

3 lentelė. Pradinės pacientų charakteristikos.

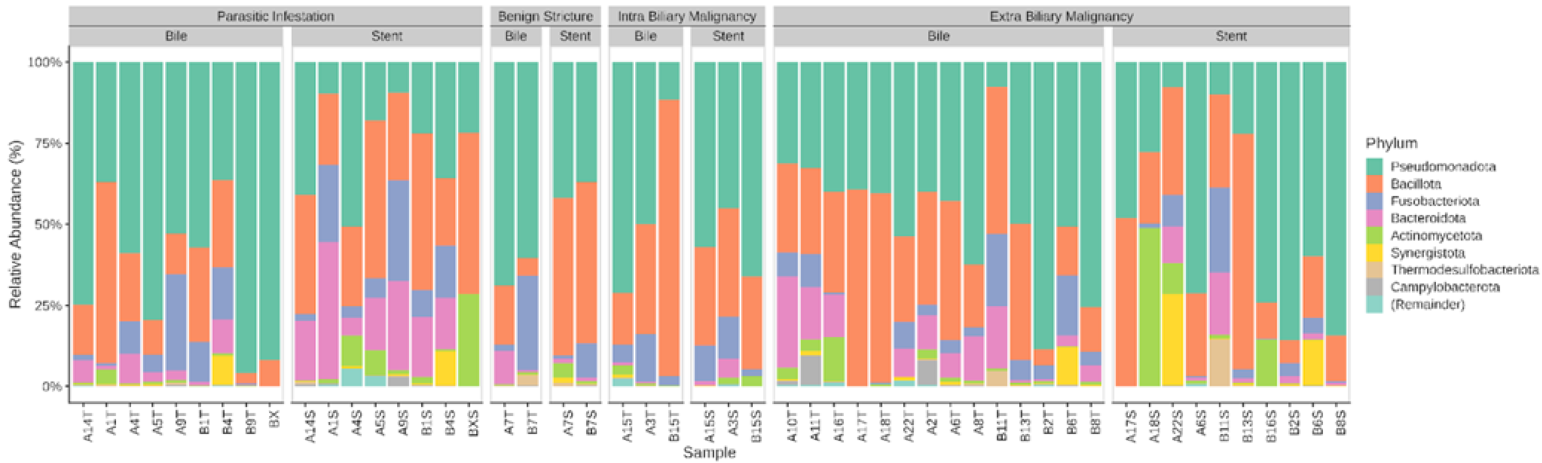
Charakteristika	Bendrai N =18*	Sekantis stentavimas		p reikšmė**	Efekto dydis (ES) koreguotas (95% CI)***
		Planinis N = 12*	Skubus N = 6*		
Lytis	11 (61%)	7 (58%)	4 (67%)	>0,9	0,00 (0,00, 0,48)
Amžius (metai)	63 (12)	61 (12)	67 (12)	0,3	-0,31 (-0,71, 0,26)
Etiologinė grupė				0,059	0,50 (0,00, 0,97)
Gerybinės striktūros	1 (5,6%)	1 (8.3%)	0 (0%)		
Ekstrabiliarinė piktybinė liga	9 (50%)	7 (58%)	2 (33%)		
Intrabiliarinė piktybinė liga	3 (17%)	0 (0%)	3 (50%)		
Parazitinė infestacija	5 (28%)	4 (33%)	1 (17%)		
1-ą kartą atliekama ERCP	4 (22%)	4 (33%)	0 (0%)	0,2	0,30 (0,00, 0,83)
Cholangitas	4 (22%)	2 (17%)	2 (33%)	0,6	0,00 (0,00, 0,62)
Antibiotikai	8 (44%)	4 (33%)	4 (67%)	0,3	0,21 (0,00, 0,76)

Charakteristika	**Bendrai N =18***	**Sekantis stentavimas**		**p reikšmė****	**Efekto dydis (ES) koreguotas (95% CI)*****
		Planinis N = 12*	**Skubus N = 6***		
Stento funkcionavimas (dienos)				0,006	0,83 (0,55, 0,94)
Vidurkis (SN)	77 (20)	85 (19)	61 (11)		

Mikrobiomo analizė

Tulžies ir stento mikrobiomas

Taksonominės sudėties analizė nustatė gausiausiai aptinkamas bakterijas, kurios tipo lygmeniu buvo: *Pseudomonadota* – 47,5 % [32,5–64,2 %], *Bacillota* – 27 % [17,2–42,5], *Fusobacteria* – 4,3 % [1,37–10,82] ir *Bacteroidota* – 2,88 % [0,81–10,56] viso santykinio gausumo. Taip pat buvo aptikta ir kitų, mažiau paplitusių tipų: *Actinomycetota*, *Synergistota*, *Thermodesulfobacteriota* ir *Campylobacterota* (8 pav.). Detalus bakterijų tipų santykinis gausumas tulžies ir stento mėginiuose pateiktas 4 lentelėje.



8 paveikslas. Bakterijų santykinio gausumo sudėtis visuose mėginiuose pagal ligos grupę (parazitinė infestacija, gerybinė striktūra, intrabiliarinė piktybinė liga, ekstabiliarinė piktybinė liga) ir pagal mėginio tipą (tulžis, stentas). Kiekviena juosta žymi atskirą mėginį; spalvos nurodo aštuonis gausiausius tipus, o likę taksonai sugrupuoti į vieną bendrą grupę.

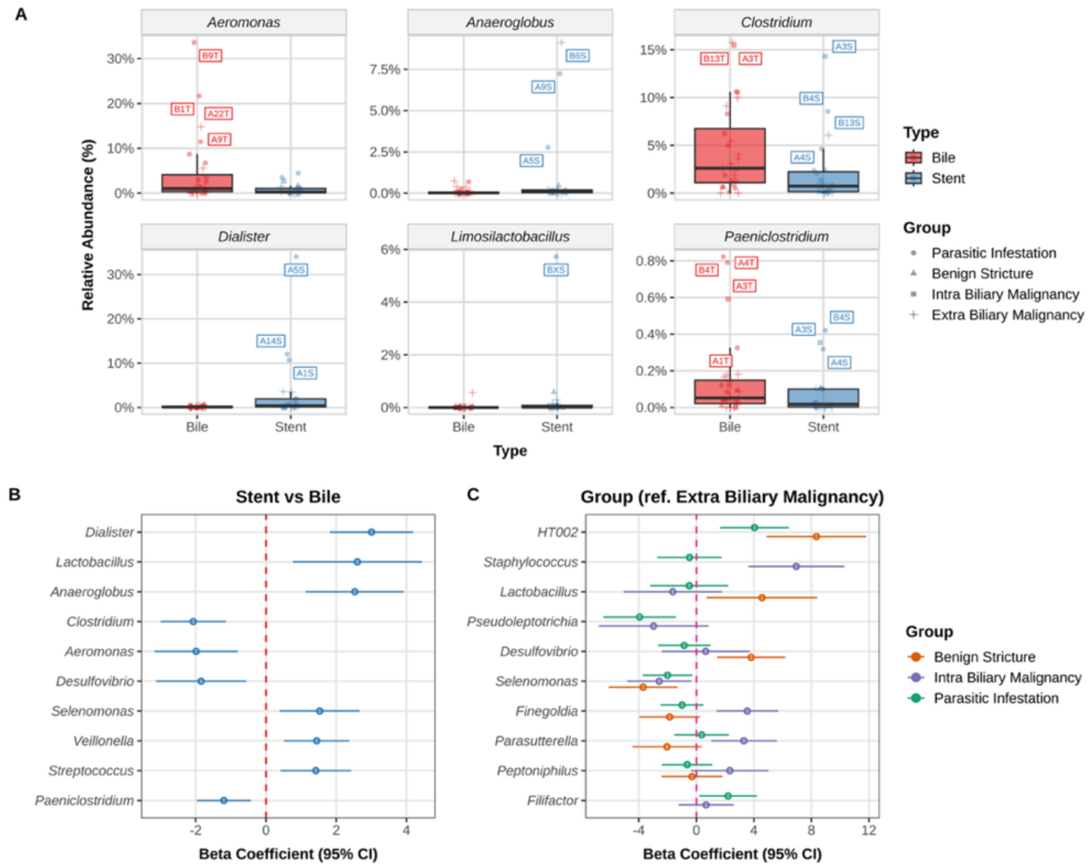
4 lentelė. Bakterijų tipų santykinis gausumas tulžies ir stento mėginių mikrobiomo sudėtyje (mediana [IQR]). Beta koeficientai (± SE) parodo logaritminius gausumo skirtumus stento mėginiuose, lyginant su tulžies mėginiais.

Tipas	Tulžis	Stentas	Beta koeficientas (± SE)
Pseudomonadota	51,71% [39,73-69,37]	40,88% [21,84-58,38]	-0,56 ±0,25
Bacillota	26,37% [14,73-36,46]	28,63% [21,97-48,47]	0,40 ± 0,26
Fusobacteriota	4,73% [1,74-10,72]	3,86% [1,14-10,83]	-0,19 ± 0,5
Bacteroidota	3,08% [0,70-10,36]	1,82% [0,90-15,92]	0,77 ± 0,56
Actinomycetota	0,72% [0,31-1,07]	1,19% [0,38-6,02]	1,18 ± 0,59
Synergistota	0,23% [0,02-0,60]	0,16% [0,02-0,51]	0,87 ± 0,85
Thermodesulfobacteriota	0,08% [0,05-0,18]	0,09% [0,00-0,22]	-0,52 ± 0,74
Campylobacterota	0,07% [0,04-0,26]	0,08% [0,01-0,17]	0,05 ± 0,71
(Likusios)	0,05% [0,01-0,33]	0,02% [0,00-0,07]	

MaAsLin3 diferencinio gausumo analizė genties lygmeniu nustatė kelis taksonus, kurių skirtumai tarp tulžies ir stento mėginių buvo nominaliai statistiškai reikšmingi, tačiau po FDR korekcijos nė vienas jų neišliko statistiškai reikšmingas (visos $q > 0,05$). Ryškiausi skirtumai nustatyti *Clostridium* ($q = 0,109$), kurios santykinis gausumas stento mėginiuose buvo mažesnis, ir *Dialister* ($Q = 0,09$), kurios santykinis gausumas stento mėginiuose buvo didesnis (5 lentelė ir 9 paveikslas).

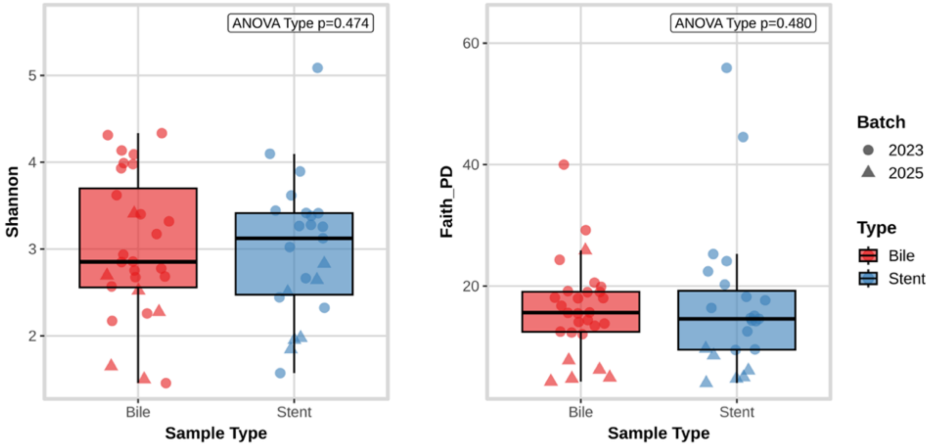
5 lentelė. Atrinktos gentys, turėjusios mažiausias MaAsLin3 q reikšmes lyginant mėginių tipus (stentas ir tulžis). Santykinis gausumas pateiktas kaip mediana [IQR] (%). Koeficientai ($\beta \pm SE$) parodo logaritminį gausumo pokytį stento mėginiuose, lyginant su tulžies mėginiais (referentinė grupė). Modeliai buvo koreguoti pagal ligos grupę, lytį, antibiotikų vartojimą, mėginių ėmimo laiką, mėginio tipą ir sekoskaitos partiją, o pacientas buvo įtrauktas kaip atsitiktinis efektas.

Gentis	Tulžis	Stentas	Koeficientas Stentas ir tulžis ($\beta \pm SE$)	P reikšmė	q reikšmė (FDR)
Clostridium	2,63% [1,10-6,75]	0,74% [0,16-2,24]	-2,07 ± 0,47	< 0,001	0,109
Aeromonas	1.07% [0,33-4,12]	0,27% [0,08-1,07]	-1,98 ± 0,60	0,004	0,436
Dialister	0,11% [0,03-0,21]	0,37% [0,12-1,95]	3,01 ± 0,60	< 0,001	0,090
Paeniclostridium	0,05% [0,02-0,15]	0,02% [0,00-0,10]	-1,20 ± 0,39	0,002	0,265
Anaeroglobus	0,02% [0,01-0,04]	0,12% [0,03-0,20]	2,50 ± 0,69	0,004	0,418
Limosilactobacillus	0,00% [0,00-0,00]	0,01% [0,00-0,08]	0,87 ± 0,84	0,492	1,000



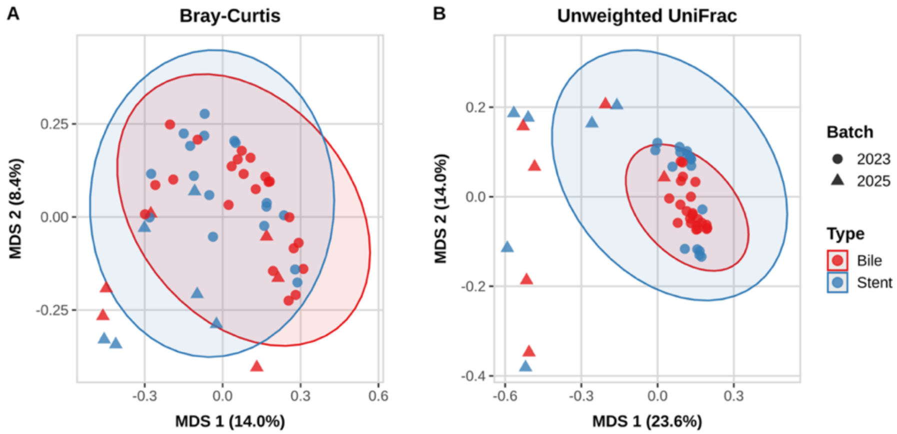
9 paveikslas. (A) Atrinktų genčių santykinis gausumas pagal mėginio tipą (tulžis ir stentas). Pavaizduotos gentys, turėjusios mažiausias MaAsLin3 q reikšmes pagal mėginio tipą: *Aeromonas*, *Anaeroglobus*, *Clostridium*, *Dialister*, *Limosilactobacillus* ir *Paeniclostridium*. (B) Diferencialiai gausūs taksonai pagal beta koeficientą stento mėginiuose, kai referentinė grupė yra tulžies mėginiai. (C) Diferencialiai gausūs taksonai pagal beta koeficientą mėginių grupėse, kai referentinė grupė yra ekstrabiliarinė piktybinė liga. Linijos žymi standartinę paklaidą. Modeliai buvo koreguoti pagal 5 lentelėje aprašytus kofaktorius. Tikslios q reikšmės pateiktos 5 lentelėje.

Tulžies ir stento mėginių mikrobiomo sudėties analizė neparodė statistiškai reikšmingų alfa įvairovės skirtumų, taikant Shannon (p = 0,474) ir Faith PD (p = 0,480) indeksus (10 paveikslas).



10 paveikslas. Tulžies ir stento mėginių alfa įvairovė, vertinant Shannon indeksą (kairėje) ir Faith filogenetinės įvairovės rodiklį (dešinėje). Mėginio tipo įtakos statistinis reikšmingumas buvo vertinamas taikant tiesinius mišriuosius modelius, koreguotus pagal ligos grupę, lytį, antibiotikų vartojimą, mėginių ėmimo laiką ir sekoskaitos partiją; pacientas buvo įtrauktas kaip atsitiktinis efektas, o laisvės laipsniams apskaičiuoti taikyta Satterthwaite aproksimacija.

Beta įvairovės analizė parodė reikšmingą bendrijų sudėties skirtumą tarp tulžies ir stento mėginių pagal *Bray–Curtis* nepanašumo metodą (*PERMANOVA* q = 0,012), o svertinis *UniFrac* atstumas rodė tendenciją, kuri nepasiekė statistinio reikšmingumo (q = 0,057). Ordinacija pagal pagrindines koordinates pavaizduota 11 paveiksle.

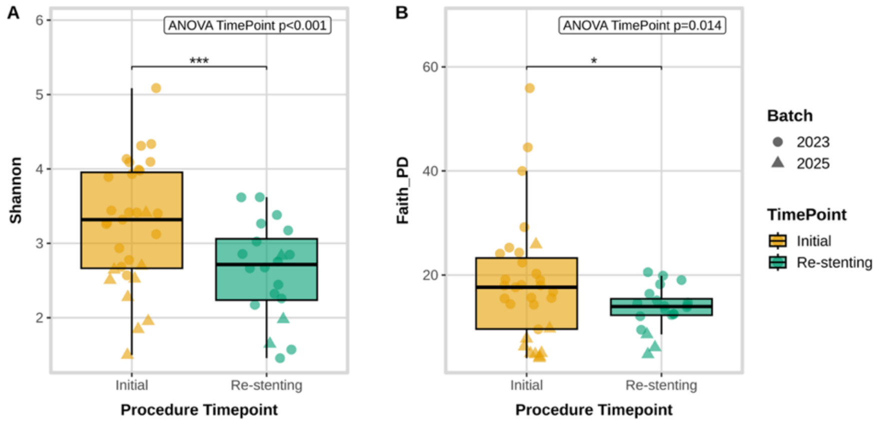


11 paveikslas. Beta įvairovės ordinacija pagal mėginio tipą, naudojant Bray–Curtis (kairėje) ir nesvertinio UniFrac (dešinėje) atstumo metodus. Elipsės žymi kiekvieno mėginio tipo 95 % pasikliautinuosius intervalus. Ašys nurodo paaiškinamos dispersijos dalį.

Mikrobiomo įvairovė sekančio stentavimo metu

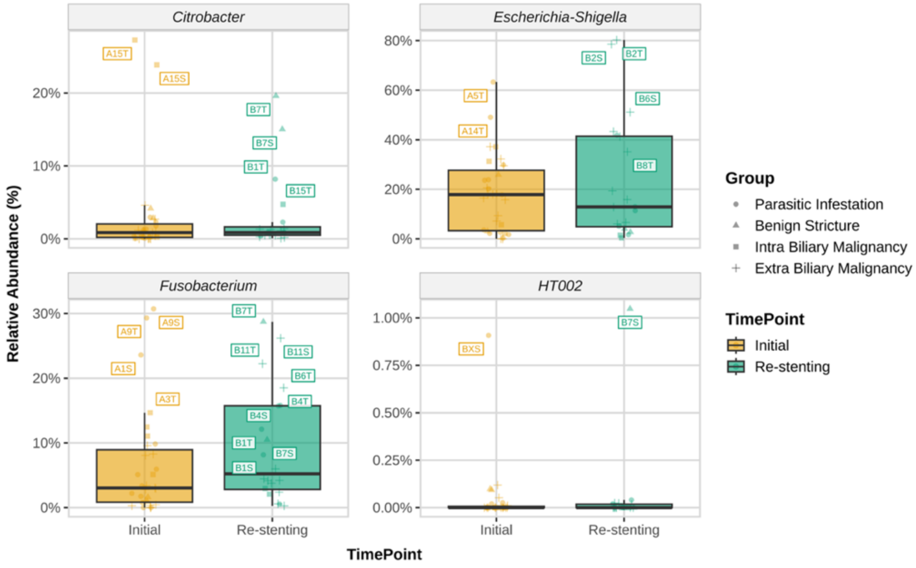
Alfa įvairovė bendrai tulžies ir stento mėginiuose buvo palyginta pradinės procedūros metu (A mėginys) ir pakartotinio restentavimo metu (B mėginys).

Shannon indeksu vertinta mikrobiomo įvairovė buvo statistiškai reikšmingai didesnė A mėginiuose, palyginti su B mėginiais (įvertintas skirtumas +0,9; 95 % CI 0,542–1,258; $p < 0,001$), taip pat ir Faith PD rodikliu (įvertintas skirtumas +6,53; 95 % CI 1,27–11,78; $p = 0,014$). Šie skirtumai pavaizduoti 12 paveiksle.



12 paveikslas. Alfa įvairovė pagal mėginių ėmimo laiką (A: pirminė procedūra, lyginant su B: pakartotiniu stentavimu), įvertinta pagal Shannon indeksą (kairėje) ir Faith filogenetinės įvairovės rodiklį (dešinėje). Skirtingos taškų formos žymi sekoskaitos partiją. Statistinis reikšmingumas buvo vertinamas taikant tiesinius mišriuosius modelius, koreguotus pagal lytį, antibiotikų vartojimą, ligos grupę, mėginio tipą ir sekoskaitos partiją; pacientas buvo įtrauktas kaip atsitiktinis efektas.

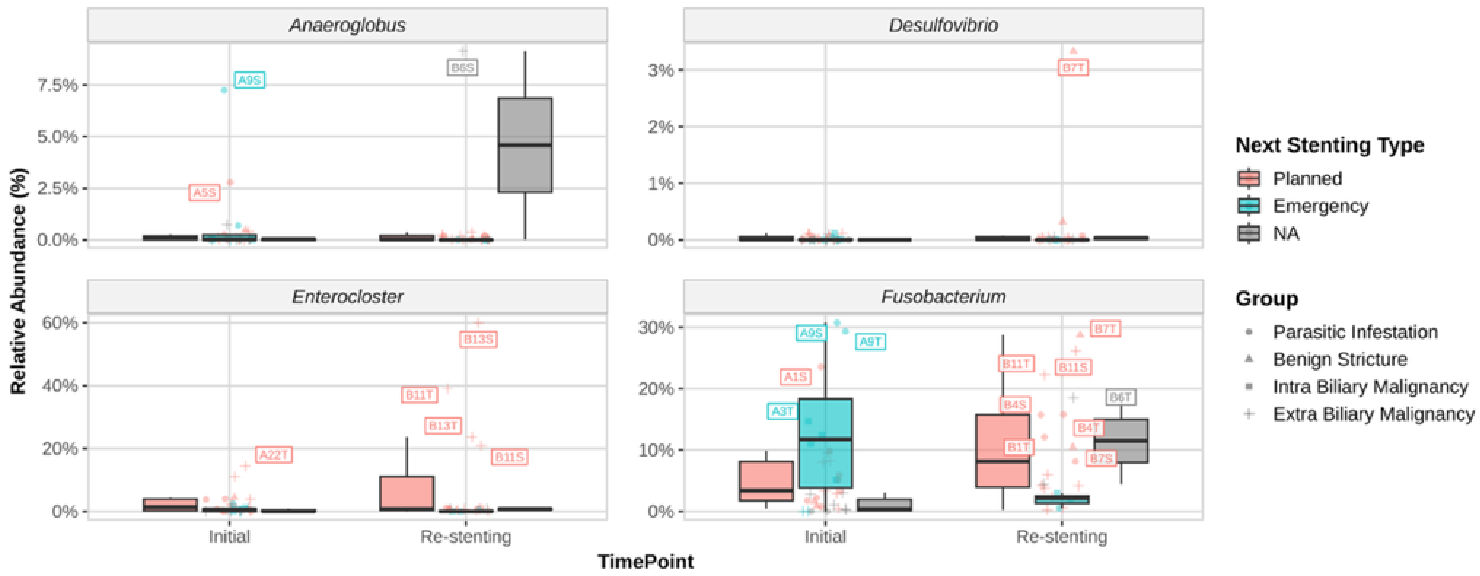
Diferencinio gausumo analizė tarp pirminių A mėginių ir pakartotinių B mėginių nustatė, kad mažiausias q reikšmes turėjo *Citrobacter*, *Escherichia-Shigella*, *Fusobacterium* ir *HT002* gentys, tačiau po FDR korekcijos nė viena jų nepasiekė statistinio reikšmingumo. Šie duomenys pavaizduoti 13 paveiksle.



13 paveikslas. Atrinktų genčių santykinis gausumas pagal mėginių ėmimo laiką (A ir B). Pavaizduotos gentys, turėjusios mažiausias MaAsLin3 q reikšmes: *Citrobacter*, *Escherichia-Shigella*, *Fusobacterium* ir *HT002*. Modeliai buvo koreguoti pagal ligos grupę, lytį, antibiotikų vartojimą, mėginio tipą ir sekoskaitos partiją; pacientas buvo įtrauktas kaip atsitiktinis efektas.

Planinis ir skubus restentavimas

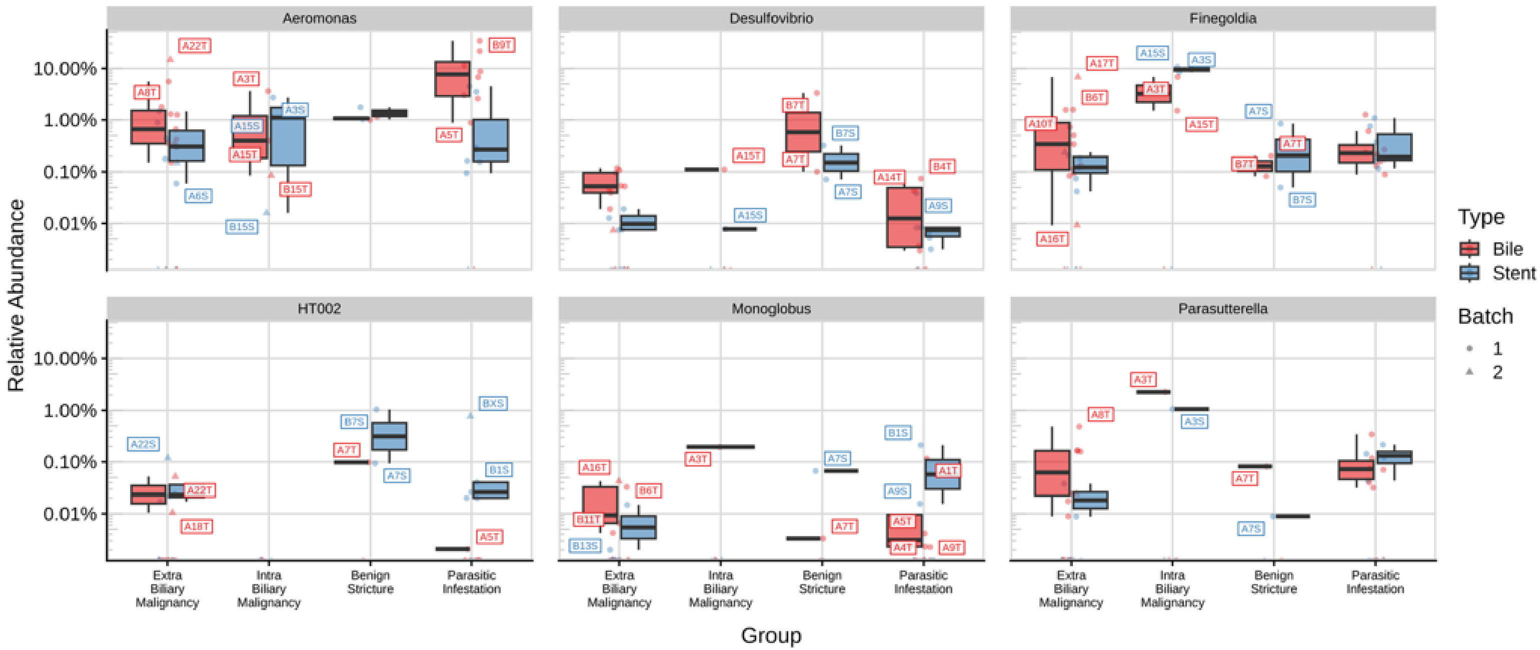
Diferencinio gausumo analizė neatskleidė statistiškai reikšmingų skirtumų genties lygmeniu tarp pacientų, kuriems pakartotinis stentavimas buvo atliktas planine ir skubos tvarka. Ryškiausi skirtumai nustatyti tarp *Fusobacterium*, *Anaeroglobus*, *Desulfovibrio* ir *Enterocloster* genčių, tačiau po FDR korekcijos nė vienas jų nepasiekė statistinio reikšmingumo (14 paveikslas). Pažymėtina, kad *Fusobacterium* santykinis gausumas buvo didesnis pacientų, kuriems ERCP atlikta skubos tvarka, mėginiuose, tačiau šį rezultatą reikėtų vertinti atsargiai dėl mažos tiriamųjų imties.



14 paveikslas. Atrinktų genčių santykinis gausumas pagal pakartotinio stentavimo tipą (planinis, skubus, NA). Atskiri mėginiai nuspalvinti pagal pakartotinio stentavimo tipą, o jų forma žymi ligos grupę. Pavaizduotos gentys buvo atrinktos pagal mažiausias MaAsLin3 q reikšmes, susijusias su pakartotinio stentavimo tipu: *Anaeroglobus*, *Desulfovibrio*, *Enterocloster* ir *Fusobacterium*.

Indikacija ERCP ir mikrobiomas

Lyginant mikrobiomo sudėtį pagal ERCP indikaciją, statistiškai reikšmingų santykinio gausumo skirtumų nenustatyta, tačiau, naudojant ekstrabiliarinės piktybinės ligos grupę kaip gausiausią palyginamąją grupę, buvo pastebėtos statistiškai nereikšmingos tendencijos. *Desulfovibrio* ir *Lactobacillus* gentys buvo gausesnės gerybinių striktūrų atvejais, *Finegoldia* gentis buvo gausesnė intrabiliarinės piktybinės ligos atvejais, *HT002* buvo gausesnė gerybinių striktūrų ir parazitinės infestacijos atvejais, o *Parasutterella* ir *Monoglobus* gentys buvo gausesnės intrabiliarinės piktybinės ligos atvejais. Šios atrinktos gentys, pasižymėjusios didžiausiais santykinio gausumo skirtumais, pavaizduotos 15 paveiksle.



15 paveikslas. Atrinktų genčių santykinis gausumas pagal ERCP indikaciją, kaip referentinę grupę naudojant ekstrabiliarinę piktybinę ligą.

Šis perspektyvusis žvalgomasis biliarinio mikrobiomo tyrimas parodė nominaliai statistiškai reikšmingus skirtumus tarp tulžies ir stento mėginių sudėties, nenustatė alfa įvairovės skirtumų, tačiau parodė reikšmingus bendrijų sudėties skirtumus tarp tulžies ir stento mėginių. Tyrimas taip pat atskleidė sumažėjusią alfa ir beta įvairovę pakartotinio stentavimo mėginiuose bei nenustatė taksonų diferencinio gausumo skirtumų, lyginant pacientų, kuriems pakartotinis stentavimas buvo atliktas planine ir skubia tvarka, mėginius.

Mūsų gautus rezultatus sunku įvertinti dabartinės literatūros kontekste, nes yra vos keli tyrimai, kuriuose stentuotų pacientų tulžies mikrobiomas nagrinėjamas taikant metagenominius metodus, o ankstesniuose tyrimuose remtasi mikrobiologinėmis kultūromis pagrįstais metodais, kurie nepakankamai įvertino mikrobiologinę įvairovę ir neaptiko svarbių anaerobinių bei reikliųjų mikroorganizmų. Be to, šiuo metu yra paskelbtas tik vienas tyrimas, kuriame tiriami ir tulžies, ir stento mėginiai (105).

Tulžies ir stento mėginiuose tipo lygmeniu santykinai gausiausios bakterijos buvo *Pseudomonadota* ir *Bacillota*. Ekstrapoliavus šiuos duomenis, mūsų rezultatai atitinka Cacaci ir kt., kurie genties lygmeniu parodė, kad pacientų, kuriems nustatytos gerybinės tulžies latakų striktūros, mėginiuose dominavo *Enterobacter* ir *Lactobacillus* rūšys (105). Šį rezultatą taip pat patvirtina ankstesni mikrobiologiniais pasėliais pagrįsti tyrimai, kuriuose nustatyta, kad *Enterobacter* (priklausanti *Pseudomonadota* tipui) yra susijusi su bioplėvelės formavimusi ir stento okliuzija (108, 110, 111). Mūsų tyrimas parodė statistiškai reikšmingus mikrobiomo sudėties skirtumus genties lygmeniu: *Dialister* ir *Anaeroglobus* gentys buvo gausesnės stento mėginiuose, o *Clostridium* genties bakterijų stento mėginiuose buvo mažiau, palyginti su tulžies mėginiais.

Palyginus mikrobiomo įvairovę pirminės procedūros metu ir pakartotinio stentavimo metu, nustatytas statistiškai reikšmingas alfa įvairovės sumažėjimas pakartotinių procedūrų mėginiuose. Šiuo metu nėra kitų tyrimų, nagrinėjančių pakartotinio stentavimo poveikį mikrobiomo įvairovei. Šie rezultatai turi svarbių klinikinių implikacijų, nes pakartotinis stentų įvedimas mažina mikrobiomo įvairovę ir didina pacientų riziką hospitalinėms infekcijoms.

Diferencinio gausumo analizė neatskleidė statistiškai reikšmingų skirtumų genties lygmeniu tarp pacientų, kuriems pakartotinis stentavimas buvo atliktas planine ir skubos tvarka. Šiuo metu nėra tyrimų, kuriuose, taikant metagenominius metodus, būtų galima šiuos rezultatus palyginti platesniame kontekste. Vis dėlto ryškiausi skirtumai buvo stebėti *Fusobacterium*, *Anaeroglobus*, *Desulfovibrio* ir *Enterocloster* genčių atveju. Nors *Fusobacterium* nėra dominuojanti gentis tulžies latakų stento okliuzijos atvejais, jos santykinis gausumas skubaus stentavimo situacijose pabrėžia anaerobinių bakterijų svarbą stento okliuzijos patogenezėje. *Fusobacterium* genties nustatymas leidžia manyti, kad empirinė antimikrobinė terapija stento sukeltam cholangitui turėtų aprėpti anaerobų, taip pat ir aerobinių bakterijų, spektrą (111).

Šis tyrimas turi tam tikrų ribotumų. Pirmiausia, nedidelė žvalgomojo pobūdžio tyrimo imtis riboja rezultatų platesnį pritaikymą ir, tikėtina, lemia realių skirtumų nepakankamą įvertinimą. Antra, metagenominė analizė buvo atlikta dviem atskiromis partijomis, todėl atsirado reikšmingas „partijos efektas". Vis dėlto į tai buvo atsižvelgta duomenų analizės etape. Galiausiai, į šį tyrimą buvo įtraukta nevienalytė pacientų grupė, turėjusi skirtingas ERCP ir plastikinio tulžies stento įvedimo indikacijas.

Apibendrinant galima teigti, kad tulžies mėginiuose mikrobiomas yra įvairesnis nei tulžies latakų stentuose, todėl klinikinėje praktikoje mikrobiologiniams tyrimams turėtų būti naudojami būtent tulžies mėginiai. Pakartotinis stentų įvedimas mažina mikrobiomo įvairovę ir didina riziką hospitalinėms infekcijoms. Reikalingi tolesni, didesnės imties tyrimai, siekiant nustatyti mikrobiomo veiksnius, turinčius įtakos bioplėvelės formavimuisi, ir skatinti klinikinę bei technologinę pažangą.

IŠVADOS

- Faktinis vidutinis plastikinių tulžies latakų stentų funkcionavimo laikas yra trumpesnis, nei rekomenduojama gairėse planiniam stentų keitimui, ypač pacientams, sergantiems piktybine liga, turėjusiems cholangito anamnezę ir esant keliems plastikiniams tulžies latakų stentams. Siekiant išvengti komplikacijų, būtinas atidus ir individualizuotas periodinio stentų keitimo protokolas, atsižvelgiant į pagrindinę ligą, ankstesnius okliuzijos epizodus ir procedūrinius aspektus.
- Su ERCP susijusių perforacijų nustatymas procedūros metu yra esminis faktorius siekiant palankių paciento baigčių, todėl atliekant ERCP pacientams, kuriems yra padidėjusi perforacijos rizika, būtina imtis išplėstinių atsargumo priemonių.
- Tulžies mėginiuose mikrobiomas yra įvairesnis nei plastikiniuose tulžies latakų stentuose, todėl klinikinėje praktikoje mikrobiologiniams tyrimams turėtų būti naudojami būtent tulžies mėginiai. Pakartotinis stentų įvedimas mažina mikrobiomo įvairovę ir didina hospitalinių infekcijų riziką. ERCP indikacija ir pagrindinė liga turi įtakos biliariniam mikrobiomui.

LIST OF PUBLICATIONS

1. Dieninyte E, Jasiunas E, Lemezis A, Kezeviciute E, Stanaitis J, Poskus T. Duration and Predictive Factors of Plastic Biliary Stent Patency: Results of a Large Prospective Database Analysis. J Clin Med. 2025 Dec 11;14(24):8788. doi: 10.3390/jcm14248788. PMID: 41464690; PMCID: PMC12733814.
2. Dieninyte E, Pliuskute K, Jarasunas J, Stanaitis J, Poskus T. Endoscopic retrograde cholangiopancreatography associated perforations: 10-year experience of a large volume center. World J Gastrointest Endosc 2026; In press

CURRICULUM VITAE

Eglė Dieninytė

Education

Mar 2023 - Jun 2023	Observer at Verona Pancreas Institute, Digestive Endoscopy Unit | Verona, Italy Basic diagnostics in HPB EUS
Oct 2020 - Apr 2026	PhD candidate | Vilnius university Plastic biliary stent patency: translational research into patient, procedure and microbiome factors
Sept 2020	UEG Clinical fellow at Cambridge university Addenbrooke's hospital, Upper GI unit | Cambridge, UK
Sept 2018 - June 2021	Resident physician at Vilnius University Hospital Santaros Klinikos | Vilnius, Lithuania Gastroenterology and hepatology
Sept 2016 - June 2018	Resident physician at Vilnius University Hospital Santaros Klinikos | Vilnius, Lithuania Internal medicine
Sept 2009 – June 2016	Vilnius university | Vilnius, Lithuania Masters degree in Medicine

Professional Experience

Jan 2026 - now	Lecturer | Vilnius university - Evidence based medicine course for II year medical students
Oct 2021 - now	Lecturer | Vilnius university - gastroenterology course for IV year medical students
July 2021 - now	Attending gastroenterologist - endoscopist at Vilnius University Hospital Santaros Klinikos| Vilnius, Lithuania
July 2021 - June 2022	Gastroenterologist at Republic Vilnius University Hospital | Vilnius, Lithuania
Aug 2020 - 2023	Program coordinator at National Colorectal Cancer Screening Program | Vilnius, Lithuania - updating and implementing a new national colorectal cancer screening program
Feb 2018 - Sept 2020	Clinical research specialist at Vilnius University Hospital Santara Clinics | Vilnius, Lithuania
Feb 2017 - Apr 2019	Medical doctor at Vilnius city clinical hospital | Vilnius, Lithuania
Feb 2016 – March 2016	Medical intern at UMCG, Centre of Kidney Transplantation | Groningen, the Netherlands

Voluntary work and projects

Jun 2025 - now	Vice-chair, Education committee | European pancreatic club
Jun 2023 - now	Team lead | European Guidelines for Rational Prophylactic PPI prescription Development of UEG grant supported multisociety endorsed guidelines
Jun 2023 - now	UEG Podcast | Host Education podcast of United European Gastroenterology
May 2022 - now	National representative to the Meeting of the Members | United European Gastroenterology
Jan 2021 - now	Young Talent Group member | United European Gastroenterology Representative to the Quality of Care Task Force
Jun 2018 – Jul 2018	Volunteer doctor at Lake Clinic | Siem Reap, Cambodia - Worked as a primary care physician in mobile clinics on water - Gave lectures on current medical practice and provided hands-on training for local doctors

Language and IT Skills

Languages:

- English: full professional proficiency
- German: limited professional proficiency
- Italian: limited professional proficiency
- Lithuanian: native professional proficiency
- Russian: limited professional proficiency

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- Very good command of SPSS
- Basics in R program

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