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Observations and Research

Does Timing of Ileal Pouch-Anal Anastomosis Matter in Patients With Primary Sclerosing Cholangitis and Orthotopic Liver Transplantation? A Systematic Review and Meta-analysis

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Introduction: Pouchitis is the most common complication in patients with ileal pouch-anal anastomosis (IPAA), which can develop in up to 66% of patients. There is limited data on the effect of orthoptic liver transplantation (OLT) on the risk of developing pouchitis. We aimed to objectively assess whether OLT itself significantly modifies the risk of developing pouchitis in patients with overlap PSC and inflammatory bowel disease (IBD).

Method: We searched Medline, Scopus, and Embase databases from inception through September 2023 for studies that describe the outcomes of IPAA in patients with PSC and IBD who also have a history of OLT. Pooled proportions, Odds Ratio (OR), and 95% confidence intervals (CI) for data were calculated utilizing a random effects model. Using the Freeman-Turkey double arcsine transformation (FTT) method, the pooled weight-adjusted estimate of event rates for clinical outcomes in each group was also calculated. Heterogeneity between studies was assessed using the Cochrane Q statistic (I^2).

Results: Seven studies with a total of 291 patients with a history of PSC, IBD, and OLT were identified. The pooled overall risk of pouchitis in PSC/IBD patients with a history of OLT was 65% (95% CI: 0.57–0.72), with no heterogeneity observed in the analysis (I^2 = 0%). In a subgroup analysis of patients who had IPAA followed by OLT, 3 studies with 28 patients were included; the pooled risk of pouchitis after IPAA and OLT was 83% (95% CI: 0.71–0.94; I^2 = 0%), which was significantly higher (P < .001) than the OLT followed by IPAA group (59%; 95 CI: 0.48–0.71; I^2 = 0%). There was no difference in the risk of pouchitis between OLT and non-OLT groups (OR = 1.36; 95% CI: 0.37–5.0).

Conclusions: Our meta-analysis revelaed that pouchitis is common in patients who underwent OLT for PSC, especially in those who had IPAA before the OLT. OLT before IPAA may reduce the risk of pouchitis. Further larger studies are warranted to reproduce this and investigate the reason behind this difference.

Lay Summary

After orthotopic liver transplantation (OLT), patients with concomitant primary sclerosing cholangitis and inflammatory bowel disease may still have a high risk of pouchitis, especially if they undergo ileal pouch-anal anastomosis (IPAA) before OLT. However, having OLT before IPAA might lower this risk.

Key Words: IPAA, pouchitis, PSC, liver, transplant

Introduction

Primary sclerosing cholangitis (PSC) is a rare disease of the biliary system characterized by idiopathic chronic inflammation, which causes cholestasis and progressive fibrosis with an increased risk of cirrhosis and mortality.[1] There is a strong association between PSC and inflammatory bowel diseases (IBD), particularly ulcerative colitis (UC), where 70%–80% of patients with PSC have concomitant UC.[2] To date, there is no effective medical treatment for PSC, and liver transplant (LT) remains the only definitive treatment option for patients with PSC.[3,4] However, post-LT, PSC recurrence is high and up to 25% of patients may require retransplantation.[5]

Approximately 25%–30% of patients with UC require surgery for medically refractory disease or complications such as malignancy. The most common restorative surgery after a total abdominal colectomy is the creation of an ileal

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pouch-anal anastomosis (IPAA), and in particular a J-pouch. There is some evidence that IPAA after LT may adversely affect graft survival.[6]

Pouchitis is the most common complication in patients with an ileal pouch, and this can occur in up to 66% of patients.[7] Patients with PSC and IBD are at a higher risk for developing pouchitis occurring in 60%–90% of non-transplanted patients with PSC/IBD.[8] In patients with a history of LT, immunosuppression may affect surgical outcomes, and in one study, previous LT may decrease the risk of pouchitis.[9] There is limited data on the effect of orthoptic liver transplantation (OLT) on the risk of developing pouchitis. Thus, we aim to objectively assess whether OLT itself significantly modifies the risk of developing pouchitis in patients with PSC/IBD who have an IPAA.

Methods

Search Strategy and Study Eligibility

Two independent reviewers (S.A. and M.A.) identified studies published prior to September 30, 2023, that reported the outcomes of IPAA in PSC/IBD patients with a history of OLT. The online MEDLINE, Embase, Web of Science, and Scopus databases were systematically searched using keywords in different combinations: (Liver transplant or Liver transplantation or organ transplantation) and (primary sclerosing cholangitis or PSC) and (UC or Crohn's disease or IBD) and (IPAA or ileal pouch-anal anastomosis or pouch). In addition, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), we screened the reference lists of the articles and corresponded with study investigators as needed.[10] There was no restriction based on language as long as study outcomes were mentioned in the text. A third reviewer (F.J.) resolved any disagreement.

Study Inclusion and Exclusion

We used the following criteria to include studies in this analysis: prospective or retrospective studies (1) for the study population, patients with PSC and history of OLT; (2) for intervention, IPAA; and (3) for outcomes, incidence of pouchitis.

The study was excluded if: (1) patients did not have a history of OLT; (2) case reports, animal studies, editorial, meta-analyses, and review articles; or (3) if studies lacked relevant clinical data on outcomes.

Data Extraction and Quality Assessment

All relevant data were extracted independently by S.A. and M.A. according to a predefined table. The following parameters were extracted: First author, year of publication, country, study design, patient demographics, and outcomes of interest. Using the Newcastle-Ottawa Scale, the methodological quality of the included cohort studies was assessed independently by 2 investigators (S.A. and F.J.). In case of discrepancy, a third independent individual (M.A.) was consulted.

Outcomes

The primary outcome of interest was the pooled incidence rates of pouchitis in PSC/IBD patients with a history of OLT. Additionally, a subgroup analysis was made based on the timing of OLT (before vs after IPAA). We also compared the pooled incidence rate of pouchitis between patients with and without a history of OLT.

Data Synthesis and Statistical Analysis

We used R, version 3.2.3 (R Project for Statistical Computing), with Meta and Metaprop packages for all analyses. Using the Freeman-Turkey Double Arcsine Transformation (FTT) method, the pooled, weight-adjusted event rate estimate for the clinical outcomes in each group was calculated using the Metaprop package. Between-study heterogeneity was assessed using the Cochrane Q-statistic (I^2), which represents the percentage of total between-study variation that cannot be attributed solely to chance. Between-study heterogeneity was rated as low if $25\% < I^2 \leq 50\%$, moderate if $50\% < I^2 \leq 75\%$, and high if $I^2 > 75\%$1. A leave-out meta-analysis was performed to assess the influence of the outcome by excluding each study and identifying influential studies that may contribute to heterogeneity. A subgroup analysis was performed based on the time of OLT. Statistical tests were 2-sided and used a significance threshold of $P < .05$. The assessment of publication bias was investigated by evaluation of funnel plot asymmetry and sensitivity analysis. In addition to the ethical standards of the competent institution for human subjects, this meta-analysis was conducted in compliance with the Helsinki Declaration.[11]

Results

Literature Search and Study Characteristics

A total of 561 unique records were identified according to the above search strategy. Finally, 7 studies with a total of 291 patients were included in the study. PRISMA flowchart illustrates our selection process, as shown in Figure 1. Table 1 shows the baseline characteristics of the included studies and their quality analysis. Most studies were from North America. The study design was retrospective in most studies, and most were single-center studies. Among the included studies, 3 were of good, and 4 were of fair quality. Table 2.

Incidence of Pouchitis in PSC/IBD Patients With a History of OLT

Seven studies reported on the outcomes of pouchitis in patients with a history of PSC/IBD and OLT. The pooled overall risk of pouchitis in PSC/IBD patients with a history of OLT was 65% (95% CI: 0.57–0.72), with no heterogeneity observed in the analysis (I2 = 0%). The forest plot is shown in Figure 2. On a single study exclusion/sensitivity analysis, the pooled incidence ranged between 55 and 79%. The funnel plot was symmetrical, which indicates the absence of study selection bias.

Comparison of Incidence Rate of Pouchitis Based on OLT Timing

In a subgroup analysis of patients who had IPAA-then-OLT, the pooled risk of pouchitis was 83% (95% CI: 0.71–0.94), which was significantly higher ($P < .001$) than the OLT-then-IPAA group (59%; 95 CI: 0.48–0.71). There was no heterogeneity observed in the analysis ($I^2 = 0\%$). The forest plot is shown in Figure 3.

Comparison of Incidence Rate of Pouchitis Between Patients With and Without History of OLT

When patients with a history of OLT for PSC were compared to patients without, there was no difference in risk of developing pouchitis between the 2 groups (OR = 1.36; 95% CI: 0.37–5.0). There was no heterogeneity observed in the analysis ($I^2 = 0\%$). The forest plot is shown in Figure 4.

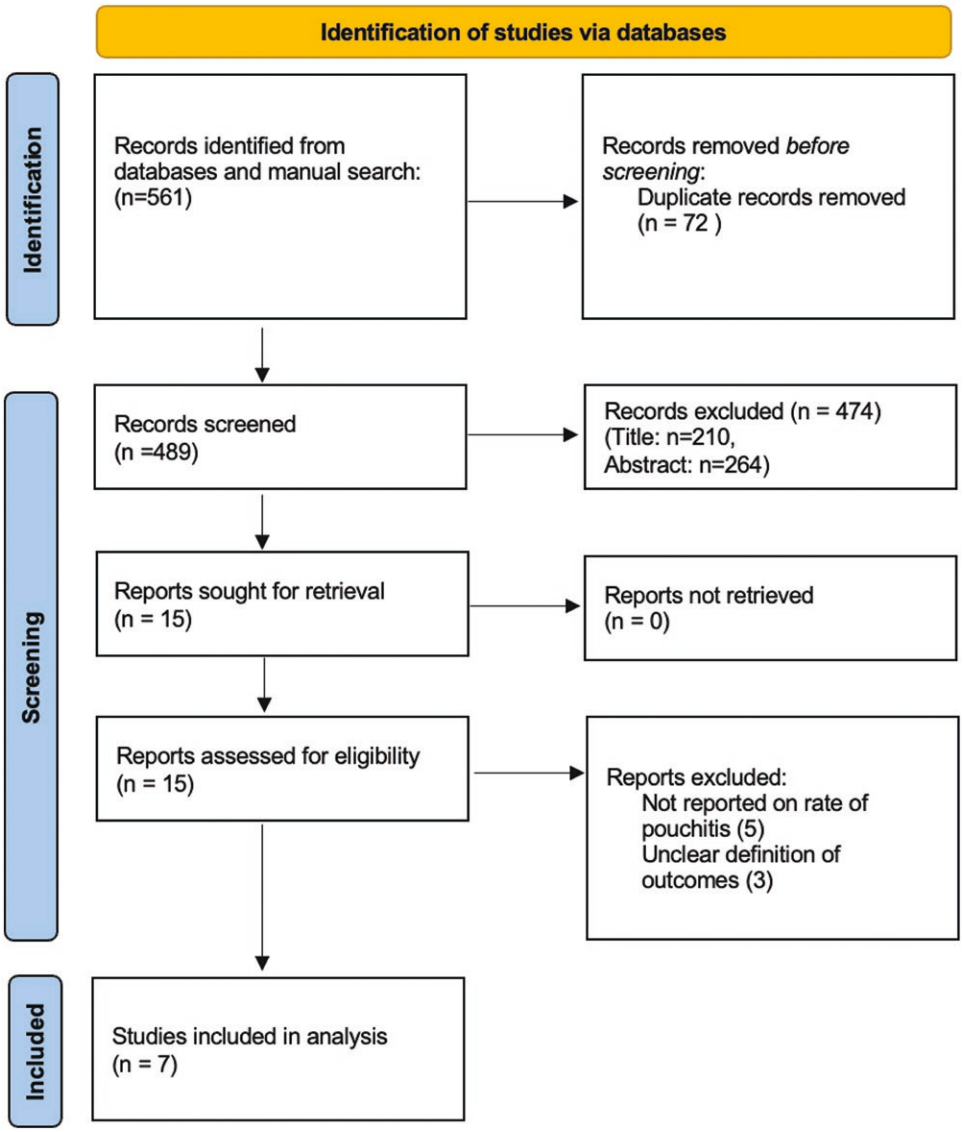

Figure 1. PRISMA chart.

Table 1. Baseline characteristics of included studies.

Study name, year	Country	Center	Design	Number of patients	Age (mean in Y)	Sex (M/F)	Quality
Freeman, 2008	USA	Single	Prospective	63	54	48/15	Good
Zins, 1995	USA	Single	Retrospective	7	N/A	3/4	Fair
Mathis, 2008	USA	Single	Retrospective	32	45	18/14	Good
Cho, 2008	USA	Multi-center	Retrospective	22	45	14/8	Fair
Rowely, 1995	UK	Single	Prospective	4	N/A	3/1	Fair
Bosso, 2009	Italy	Single	Retrospective	3	N/A	N/A	Fair
Maspero, 2023	USA	Single	Retrospective	48	39	N/A	Good

Assessment of Publication Bias and Sensitivity Analysis

A funnel plot of studies that reported on pouchitis rate in PSC/IBD patients with a history of OLT is presented in Figure 5. The influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time. The omission of any study resulted in no significant difference, indicating that our results were statistically reliable.

Table 2. Quality assessment of included studies using The Newcastle-Ottawa Scale.

First author and year	Selection				Comparability	Outcome			Quality	
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Score	Quality
Freeman, 2008	*	*	*		**	*	*	*	8	Good
Zins, 1995	*		*		*	*	*	*	6	Fair
Mathis, 2008	*		*	*	**	*	*	*	8	Good
Cho, 2008	*		*	*		*		*	5	Fair
Rowely, 1995	*		*			*	*	*	5	Fair
Bosso, 2009	*		*	*		*	*	*	6	Fair
Maspero, 2023	*	*	*	*	**	*	*	*	9	Good

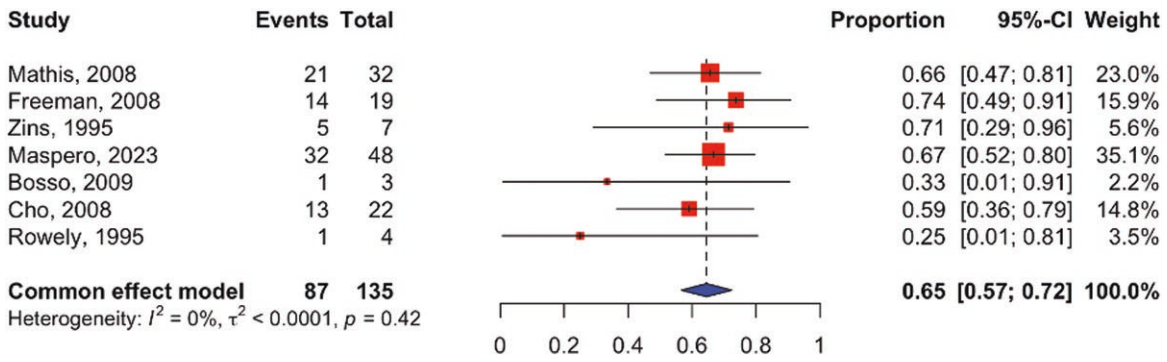

Figure 2. Forest plot of incidence of pouchitis in PSC/IBD patients with a history of orthoptic liver transplantation.

Discussion

The effect of OLT on the risk of development of pouchitis in patients with both PSC and IBD remains unclear. Our study showed that there is a high risk of developing pouchitis in PSC/IBD patients with a history of OLT with a pooled incidence rate of 65% (95% CI: 0.57–0.72). The incidence rate is higher in those with IPAA before OLT (83%) than in those with OLT-then-IPAA (59%). Additionally, there was no difference in risk of pouchitis between PSC/IBD OLT and non-OLT groups who required IPAA (OR = 1.36; 95% CI: 0.37–5.0).

Among the surgical options, IPAA is the most common restorative surgery in patients with medically refractory UC.[12] Pouchitis is a common complication after IPAA, which affects 48% of patients within the first 2 years after IPAA creation, with up to 80% of patients developing pouchitis symptoms at some point after IPAA.[13,14] PSC is an established risk factor for the development of pouchitis in patients with IPAA. The diagnosis of PSC has also been associated with antibiotic-refractory chronic pouchitis as well as postoperative pelvis sepsis and an overall higher long-term mortality.[15–18]

A proposed hypothesis as to why PSC is a risk factor for pouchitis is that advanced liver disease typically associated with PSC leads to a change in the luminal bile acid content which may in turn contribute to the findings associated with pouchitis.[19] Given the implications of advanced liver disease and the role of the liver in maintaining homeostasis, metabolic function, production of bile salts, and its potential contribution to maintaining a diverse microbiome, it is not surprising that the association between PSC and pouchitis exists. The deficiency of short-chain fatty acids has long been known to lead to changes in the colonic mucosa in those undergoing fecal diversion due to a change in microbiota. There is evidence that liver disease impacts the microbiome substantially.[20] Cirrhosis can lead to a decrease in the number of commensal bacteria and an increase in the number of pathogenic and pathogenic microorganisms, also known as pathobionts. This can lead to a disruption of the intestinal barrier due to increased intestinal permeability and cause a host of downstream effects, including worsening the liver disease itself through hepatic exposure of bacterial endotoxins.[21] Thus, this association between PSC and pouchitis may actually reflect the underlying burden that PSC places on the liver function of patients and how reversing this cycle with OLT may lead to improved outcomes in those who subsequently underwent IPAA after OLT.

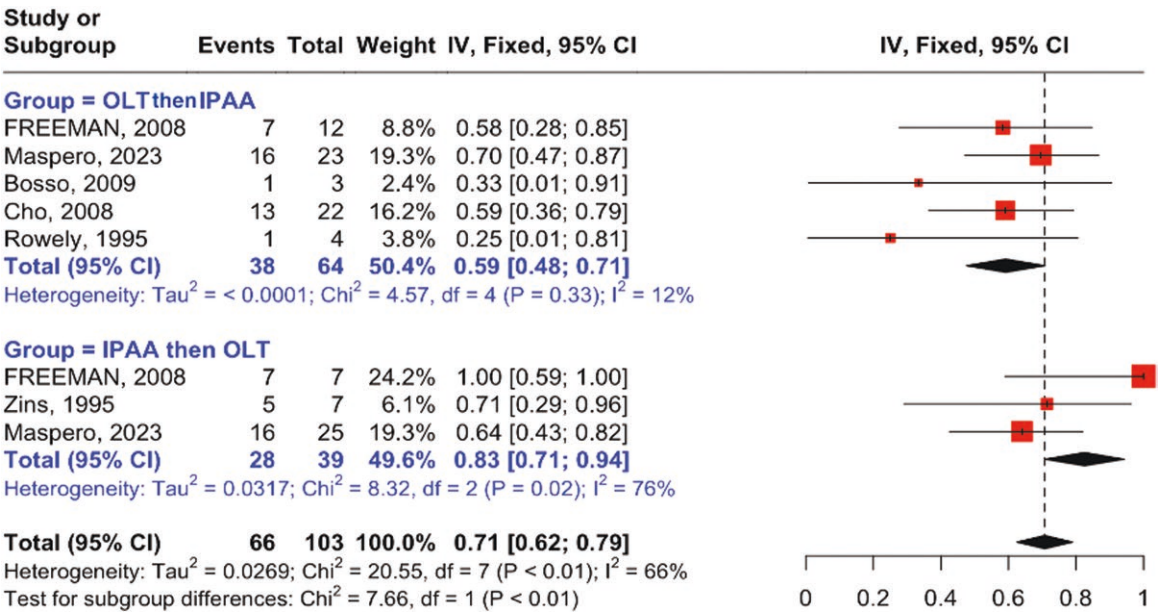

Figure 3. Forest plot of comparison of the incidence rate of pouchitis based on orthoptic liver transplantation timing.

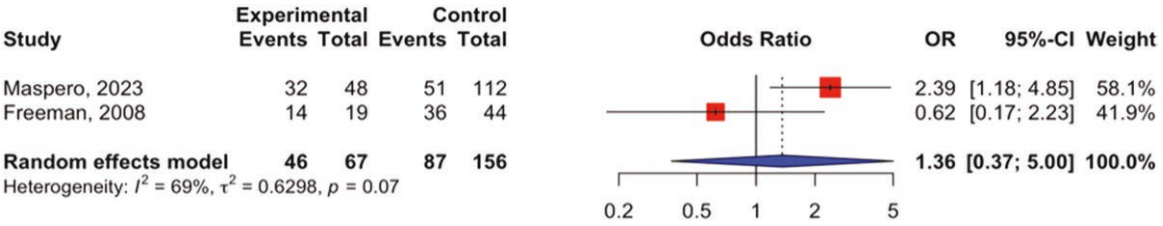

Figure 4. Forest plot of comparison of the incidence rate of pouchitis between patients with and without a history of orthoptic liver transplantation.

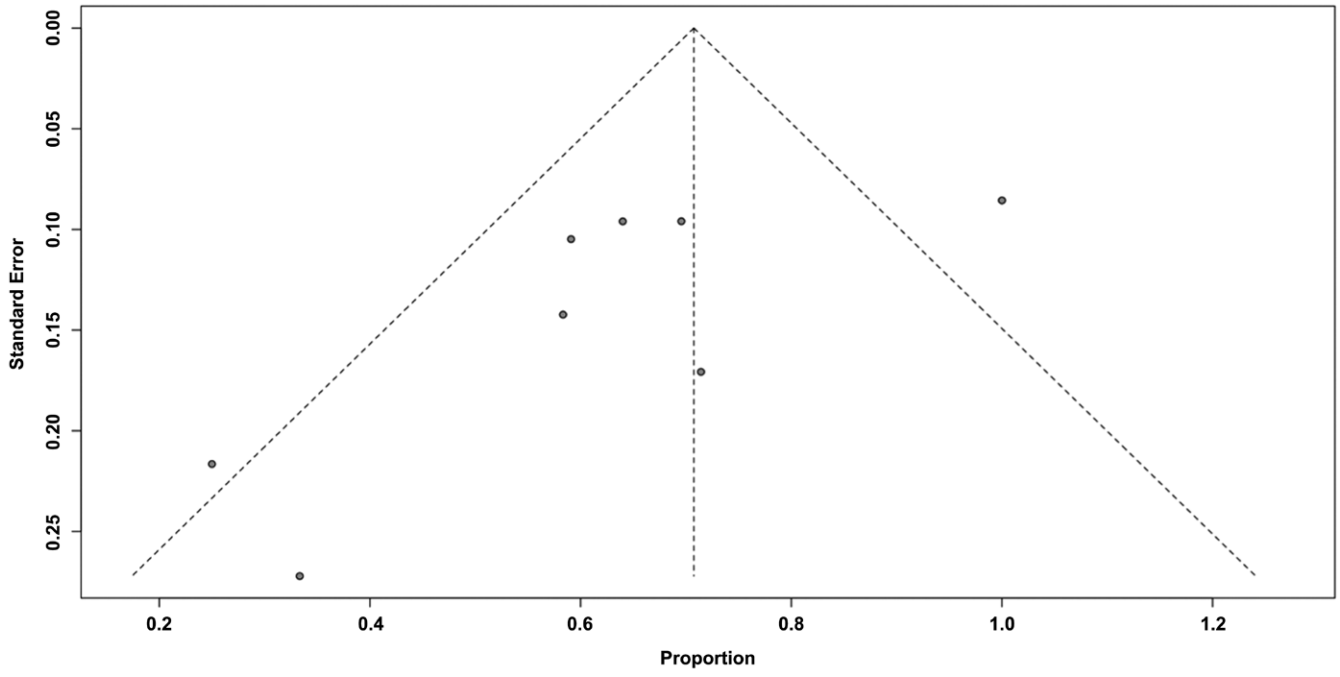

Figure 5. Funnel plot of included studies displaying publication bias.

In line with this, our study showed that in the subgroup of patients who had IPAA *before* OLT, the pooled risk of pouchitis was significantly *higher (83%)* than the group with OLT *followed by* IPAA (59%). This may suggest an inherent benefit to correcting the advanced liver disease prior to definitive surgery for patients with IBD. Although data is mixed, a prior study from Mayo Clinic showed that there is high prevalence of pouchitis in patients who had OLT *after* IPAA and that OLT did not alter the course of the pouchitis.[22] In addition, there is published literature suggesting that performing OLT after IPAA may induce a higher risk for developing pouchitis, such as the study by Maspero et al.,[23] which demonstrated that OLT in patients with PSC-UC who underwent IPAA was associated with increased pouchitis rate but not pouch failure. Combined with our study's data, this may suggest a potential protective role in performing OLT prior to IPAA, especially given the high prevalence of pouchitis in the PSC population.

One proposed mechanism explaining why OLT prior to IPAA may be protective against pouchitis is the theory that posttransplant immunosuppression might decrease the risk of developing a new onset of pouchitis.[9] This would be in line with the current understanding of immune dysregulation which has been shown to respond well to immunosuppressants including biologics such as infliximab and vedolizumab.[24] Additional support can be obtained by the fact that pouchitis has been shown to respond to topical tacrolimus, which is a calcineurin inhibitor commonly used in patients with OLT.[25]

The role of liver cirrhosis in the development of pouchitis is unclear, and there is a scarcity of literature investigating this relationship. Although it is well established that cirrhosis contributes to an alteration of the fecal microbiome, which had been previously implicated as a contributing factor in the development of hepatic encephalopathy, infection, and other comorbidities in patients with cirrhosis. Since OLT should reverse some of these changes, it may explain the reduced incidence of pouchitis seen in the study. The change in the luminal secondary bile acids seen in advanced liver disease should also be theoretically corrected with OLT. This may also explain the reduced incidence of pouchitis for those who underwent OLT before undergoing IPAA.[20] Another simpler explanation may be that patients with OLT tend to have more infectious complications and may be exposed to more antibiotic regimens, which may, in turn, explain the reduced incidence of pouchitis in this subset of patients.[26]

Although there seemed to be a difference in those with OLT in terms of the timing associated with the IPAA procedure, our results showed no difference in the risk of pouchitis between the OLT and non-OLT groups who required IPAA. This is in line with Freeman et al.,[9] which examined the effect of OLT on the course of chronic pouchitis in PSC-UC patients and found that patients with OLT had a similar disease course to non-OLT patients. The authors postulated that in patients with PSC and IPAA, OLT with posttransplant immunosuppression may decrease the risk of development of new-onset chronic pouchitis, which is also supported by our findings.

The benefit of OLT prior to IPAA was lost in those who underwent IPAA first. For example, Zins et al.[22] reported a similar rate of prevalence of pouchitis in 7 patients with previous IPAA for UC who then required OLT for PSC. In another report of 4 patients with IPAA and PSC who had OLT,[27] only one patient developed chronic pouchitis requiring long-term metronidazole. This suggests that once the pouch is created, OLT and post-OLT immunosuppressant were not as helpful in deterring the rates of pouchitis and that correction of the liver disease through OLT prior to creation of the pouch seemed to have a more protective effect.

There are some considerations in patients who have IPAA after OLT. There is an increased risk of postoperative dehydration and electrolyte imbalance, which could be secondary to the significant shortening of the short bowel required in both procedures. Also, immunosuppression might affect the rate of healing in patients undergoing IPAA, which could prolong hospital stay. Furthermore, there are some technical challenges that may face surgeons who perform IPAA in patients with OLT.[28]

The strength of this study is that it is the first study to pool a large number of patients. This study has some limitations. It is difficult to assess the timeline between OLT and IPAA. In addition, the total number of patients identified is limited by the prevalence of both diseases and surgical procedures in question. While our study predominantly relies on retrospective and single-center data, we acknowledge the potential impact of varying methodological quality within the literature on our findings. Thus, considering the available evidence spectrum, caution is advised when interpreting our results. There is also variability in the time (1995–2023) at which these studies were conducted. This might be reflected in the differences in technology, surgical procedures, perioperative management, and type of immunosuppression regimens used in these studies. We also could not distinguish between the types of pouchitis, and given the high rates of antibiotic-responsive pouchitis after IPAA, the relatively lower incidence of chronic pouchitis may be overreflected. Moreover, due to limitations in available data, we were unable to assess the potential for posttransplant immunosuppressive medications to confound the observed protective effect of OLT prior to IPAA against pouchitis.

In conclusion, this study showed that performing OLT before IPAA might lower the risk of developing pouchitis. Further research is needed to determine if certain risk factors or patient characteristics might increase the risk of such a complication and if a certain grace time is needed between the 2 procedures to ensure a better outcome. Further prospective studies with larger sample sizes are warranted to reproduce this and investigate the reason behind this difference.

Acknowledgments

The abstract of this paper was presented at the Advances in Inflammatory Bowel Disease (AIBD) 2023 conference and awarded the **"Best of 2023 AIBD Surgery Abstracts."**

Author Contributions

Saqr Alsakarneh: Substantial contributions to acquisition, analysis, and interpretation of data for the work. Saqr has approved the final draft submitted. Mohamed Ahmed: Substantial contributions to the interpertation of data and drafting of the work. Mohamed has approved the final draft submitted. Fouad Jaber: Substantial contributions to the acquisition, analysis, and interpretation of data for the work. Fouad has approved the final draft submitted. Raffi

Karagozian: Revising the manuscript critically for important intellectual content. Raffi has approved the final draft submitted. Mir Zulqarnian: Substantial contributions in drafting the manuscript and revising the manuscript critically for important intellectual content. Mir has approved the final draft submitted. Fadi Francis: Revising the manuscript critically for important intellectual content. Fadi has approved the final draft submitted. Francis A. Farraye: Substantial contributions to the conception and design of the work and revising the manuscript critically for important intellectual content. Francis has approved the final draft submitted. Jana G. Hashash: The concept, design, and idea for this research were developed by Jana. Substantial contributions to the conception and design of the work; the interpretation of data for the work, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, drafting the work or revising it critically for important intellectual content. Francis has approved the final draft submitted.

Conflicts of Interest

J.G.H. holds the position of clinical associate editor for Crohn's & Colitis 360 and has been recused from reviewing or making decisions for the manuscript. F.A.F: AbbVie, Avalo Therapeutics, BMS, Braintree Labs, Fresenius Kabi, GI Reviewers, GSK, IBD Educational Group, Iterative Health, Janssen, Pharmacosmos, Pfizer, Sandoz Immunology, Sebela, Viatris. DSMB: Lilly. J.G.H: Advisory Board for BMS. Rest of authors have no conflict of interest. Disclosures: None to disclose.

Data Availability

Data is available upon a reasonable request from the corresponding author.

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