Ileal Pouch-anal Anastomosis in Primary Sclerosing Cholangitis-inflammatory Bowel Disease (PSC-IBD)

Long-term Pouch and Liver Transplant Outcomes

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Objective: To compare the effect of liver transplantation (LT) on ileal pouch-anal anastomosis (IPAA) outcomes in patients with primary sclerosing cholangitis and inflammatory bowel disease (PSC-IBD).

Background: Patients with PSC-IBD may require both IPAA for colitis and LT for PSC.

Methods: Patients with PSC-IBD from out institutional pouch registry (1985–2022) were divided according to LT status and timing of LT (before and after IPAA) and their outcomes analyzed.

Results: A total of 160 patients were included: 112 (70%) nontransplanted at last follow-up; 48 (30%) transplanted, of which 23 (14%) before IPAA and 25 (16%) after. Nontransplanted patients at IPAA had more laparoscopic procedures [37 (46%) vs 8 (18%), $P = 0.002$] and less blood loss (median 250 vs 400 mL, $P = 0.006$). Morbidity and mortality at 90 days were similar. Chronic pouchitis was higher in transplanted compared with nontransplanted patients [32 (67%) vs 51 (45.5%), $P = 0.03$], but nontransplanted patients had a higher rate of chronic antibiotic refractory pouchitis. Overall survival was similar, but nontransplanted patients had more PSC-related deaths (12.5% vs 2%, $P = 0.002$). Pouch survival at 10 years was 90% for nontransplanted patients and 100% for transplanted patients (log-rank $P = 0.052$). Timing of LT had no impact on chronic pouchitis, pouch failure, or overall survival. PSC recurrence was 6% at 10 years. For transplanted patients, graft survival was similar regardless of IPAA timing.

Conclusions: In patients with PSC-IBD and IPAA, LT is linked to an increased pouchitis rate but does not affect overall and pouch survival. Timing of LT does not influence short-term and long-term pouch outcomes.

Keywords: ileal pouch-anal anastomosis, inflammatory bowel disease, liver transplantation, pouch survival, primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a rare disease of the biliary system which causes progressive inflammation and fibrosis.[1] The progressive damage to the intrahepatic and extrahepatic bile ducts may ultimately lead to cirrhosis.[2] There is no medical treatment with PSC, thus liver transplantation (LT) is an option in case of end-stage liver disease or other PSC-related complications. After LT, however, PSC recurrence occurs in 20% to 25% of cases and may require retransplantation.[3]

Patients with PSC have a concomitant diagnosis of inflammatory bowel disease (IBD) in 60% to 80% of cases.[4] PSC-IBD is a distinct disease phenotype which seems to be associated with more aggressive features of both PSC and IBD.[5] The 2 disease processes are both characterized by inflammation and deranged immune response, thus may influence one another from an anastomotic/mechanistic standpoint and due to treatment consequences.

Treatment of IBD usually involves medical therapy with biologics, steroids, and immunomodulators. Biologics, especially tumor necrosis factor-α inhibitors, may also be used for treatment of PSC,[6] while IBD treatment and immunosuppression may have overlapping or synergic effects in patients who received a LT. In case of failure of medical therapy, patients with ulcerative colitis and Crohn disease (CD) colitis generally require total proctocolectomy.[7] This can be performed as a restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) to maintain intestinal continuity. IPAA in patients who had a previous LT may be technically difficult due to adhesions and altered anatomy, and immunosuppression may affect surgical outcomes, and a previous LT may increase the risk of pouchitis.[8,9] There is some concern that IPAA after LT may adversely affect graft survival.[10]

In contrast, patients who undergo LT for PSC-IBD appear to have a higher risk of PSC recurrence compared with PSC alone[11,12]; this seems to be associated both with extent, duration and severity of IBD, and to surgical treatment, with colectomy potentially having a protective effect.[13]

The aim of our study was to compare the outcomes of patients with PSC-IBD and IPAA with or without a LT, and whether the timing of LT had an effect on IPAA outcomes or vice versa.

METHODS

Study Design and Study Population

This study was approved by our institutional review board and conducted according to the Declaration of Helsinki and good clinical practices.

We performed a retrospective review of our prospectively collected pouch registry to identify patients who had undergone

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restorative proctocolectomy with IPAA for PSC-IBD at our center between 1985 and 2022. Patients were divided into 3 groups: IPAA alone (patients who have not received LT at last follow-up), LT before IPAA, and LT after IPAA. For short-term IPAA outcomes, patients were divided in transplanted (=LT before IPAA) versus nontransplanted at IPAA (=IPAA alone+LT after IPAA). For long-term outcomes, patients were divided in transplanted (=LT before IPAA+LT after IPAA) versus nontransplanted at last follow-up (=IPAA alone). Our primary outcome was pouch survival in transplanted versus nontransplanted patients at last follow-up.

Variables

Variables collected for each patients included: demographics [sex, IBD diagnosis, age at IBD diagnosis, age at IPAA), variables at IPAA (previous LT, body mass index, presence of portal hypertension, previous transjugular intrahepatic portosystemic shunt, Model of End-Stage Liver Disease (MELD) score, indication for colectomy, pouch design, type of anastomosis, approach (open vs laparoscopic), length of surgery, blood loss, complications, ileostomy closure], long-term outcomes (mortality, cause of death, cancer development, presence of cirrhosis, biologics use, pouchitis, redo IPAA, pouch failure). In the case of LT, the following variables were also recorded: age at LT, MELD score, indication for LT, donor type [donation after brain death; donation after cardiac death (DCD); living donor LT], technique of biliary anastomosis, complications after LT, immunosuppression, acute rejection, PSC recurrence, hepatic artery thrombosis, non–PSC-related biliary complications, chronic rejection, retransplantation.

Major complications were defined as Clavien-Dindo grade >2.[14] Pouchitis was defined as the concomitant presence of symptoms (stool frequency, urgency, incontinence, nighttime seepage, crampy abdominal pain) and endoscopic findings suggestive of chronic pouch inflammation (inflamed mucosa with or without a mucosal ridge, poorly distensible pouch, inflammatory polyps). Pouch failure was defined as the need for permanent ileostomy (end, loop, or continent) with or without pouch excision. Pouch survival was defined as the interval between IPAA and permanent ileostomy, censored at the last follow-up. Cirrhosis was defined as findings at liver biopsy, imaging, or transient elastography consistent with cirrhosis. Acute rejection was defined as biopsy-proven rejection (rejection activity index >4).[15] Overall survival (OS) after IPAA was defined as the interval between IPAA and date of death, censored at last follow-up. PSC recurrence was defined as evidence of radiological and/or cholangiographic features of PSC after LT. PSC-related mortality were defined as death due to complications of PSC, including end-stage liver disease and biliary complications, and excluding cancer-related deaths, which were analyzed separately.

Statistical Analysis

Differences between the groups were assessed using the Fisher exact test for categorical variables and the Student *t* test for continuous variables. All analyses were performed comparing 2 groups, thus a post hoc test was not necessary. Differences in pouch survival, OS, PSC recurrence, cancer development, and retransplantation were evaluated with the Kaplan-Meier method and compared using the log-rank test. Median follow-up was calculated with the inverse Kaplan-Meier method. A subgroup analysis comparing patients who underwent LT before versus after IPAA was also conducted with analogous methodology. Additional subgroup analyses were performed to (1) compare outcomes between patients who underwent IPAA before and after 2005 and (2) compare the rate of pouchitis in patients aged ≤ 40 versus >40 years. All analyses were 2-sided, and a significance level of 0.05 was used for all analyses. All analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp.).

RESULTS

Over a 37-year period, of 4805 patients who underwent IPAA for IBD at our center, 160 (3.3%) had a diagnosis of PSC-IBD. Of those, 23 (14%) had undergone LT before IPAA, 25 (16%) had not been transplanted at IPAA but underwent LT after IPAA, and 112 (70%) had not been transplanted at the last follow-up (Fig. 1). During the same time period, 1259 patients with a diagnosis of PSC-IBD had a total proctocolectomy with end ileostomy without a pouch. Of those, 32 (2.5%) had a LT either before or after the colectomy.

Characteristics at IPAA and Short-term Outcomes

As illustrated in Table 1, characteristics at IPAA and short-term outcomes were evaluated by dividing the cohort according to their LT status at IPAA: not-transplanted at IPAA (n = 137, 86%), versus transplanted (n = 23, 14%). At IPAA, 8 (6%) nontransplanted and 1 (4%) transplanted patients were on biologics. Immunosuppressive regimens for transplanted patients at IPAA included tacrolimus in 20 (87%) cases, mycophenolate mofetil in 4 (17%) cases, cyclosporine in 1 (4%) case, and everolimus in 1 (4%) case. Transplanted compared with nontransplanted patients were older at IBD diagnosis (median 34 vs 24 years, $P=0.005$) and at IPAA (median 48 vs 38 years, $P=0.003$), had higher MELD at IPAA (median 10 vs 6, $P<0.0001$). Transplanted patients had more 3-stage IPAAs (59%, vs 31% in nontransplanted patients, $P=0.03$). Fewer IPAAs were performed laparoscopically in transplanted patients (13% vs 41% in nontransplanted, $P=0.02$), operative time was not different between the groups, and their blood loss was higher (median 400 vs 250 mL in nontransplanted, $P=0.001$). Postoperative 90-day morbidity, major complications, and mortality did not differ between the groups. In the nontransplanted group, 1 (1%) patient never achieved ileostomy closure due to anastomotic leak.

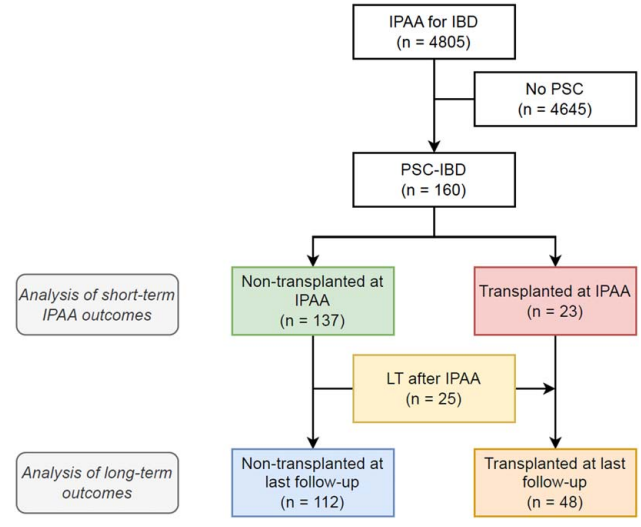


FIGURE 1. Flowchart of patients included in the study and in each analysis.

TABLE 1. Characteristics at IPAA and Short-term Outcomes

	All (N = 160)	Not transplanted at IPAA (n = 137)	Transplanted before IPAA (n = 23)	*P*
Female	50 (31)	45 (33)	5 (22)	0.288
Age at IBD diagnosis (y)	25 (18–33)	24 (18–32)	34 (25–46)	0.005
Age at IPAA (y)	39 (31–48)	38 (29–46)	48 (39–54)	0.003
Diagnosis				0.403
Ulcerative colitis	156 (98)	133 (97)	23 (100)	
CD	4 (2)	4 (3)	0	
BMI at IPAA (kg/m^2)	24.6 (22–28)	24.6 (22–28)	24.9 (23–26.5)	0.777
Portal hypertension at IPAA	30 (19)	28 (20)	2 (9)	0.093
TIPS before IPAA	5 (4)	4 (3)	1 (4)	0.845
MELD >6 at IPAA	50 (51)	34 (42)	16 (94)	<0.001
MELD at IPAA	7 (6–9)	6 (6–8)	10 (9–13)	<0.0001
Indication for TAC				0.804
Refractory	84 (52)	70 (50)	14 (60)	
Emergency	1 (0.5)	1 (0.5)	0	
Dysplasia	73 (47)	64 (48)	9 (40)	
Other	2 (0.5)	2 (1.5)	0	
Stages				1
Two-stage	97 (61)	83 (61)	14 (61)	
Modified 2-stage	6 (4)	5 (4)	1 (4)	
Three-stage	57 (36)	49 (36)	8 (35)	
Pouch design				0.474
J pouch	147 (92)	125 (91)	22 (96)	
S pouch	13 (8)	12 (9)	1 (4)	
Stapled anastomosis	130 (82)	110 (81)	20 (87)	0.485
Laparoscopic	46 (29)	43 (41)	3 (13)	0.022
Converted	4/46	4/43	0	0.580
Duration of surgery (min)	240 (178–297)	235 (169–291)	264 (193–317)	0.215
EBL (mL)	250 (100–400)	250 (100–400)	400 (190–850)	0.001
Any complication after IPAA	67 (43)	55 (41)	12 (52)	0.333
Major complication after IPAA	26 (16)	22 (16)	4 (17)	0.873
Median CCI after IPAA	20.9 (20.9–33)	25 (20.9–33)	20.9 (18–24)	0.3325
Type of complication				
Anastomotic leak	9 (6)	8 (6)	1 (4)	0.774
Pelvic abscess	14 (9)	13 (9.5)	1 (4)	0.419
Fistula	3 (2)	3 (2)	0	0.474
Bleeding	12 (7.5)	11 (8)	1 (4)	0.535
Infection	16 (10)	15 (11)	1 (4)	0.329
Respiratory complication	1 (1)	1 (1)	0	0.681
Cardiovascular complication	2 (1)	2 (1.5)	0	0.560
Thromboembolism	2 (1)	2 (1.5)	0	0.560
UTI	1 (1)	1 (1)	0	0.681
Ileus	12 (7.5)	9 (7)	3 (13)	0.275
SBO	1 (1)	1 (1)	0	0.681
High ostomy output	9 (6)	6 (4)	3 (13)	0.095
Other	17 (11)	13 (9.5)	4 (17)	
90-d IPAA mortality	3 (1)	3 (2)	0	0.469
Stoma never closed	1 (0.6)	1 (1)	0	0.549

Data are n (%) or median (interquartile range).

BMI indicates body mass index; CCI, Comprehensive Complication Index; EBL, estimated blood loss; SBO, small bowel obstruction; TAC, total abdominal colectomy; TIPS, transjugular intrahepatic portosystemic shunt; UTI, urinary tract infection.

Long-term Outcomes

To evaluate long-term outcomes, patients were divided according to their transplant status at last follow-up: nontransplanted (IPAA alone) versus transplanted (LT before IPAA +LT after IPAA) (Table 2).

After a median follow-up of 10 (interquartile range: 4–20) years, 44 deaths occurred, 30 in the nontransplanted and 14 in the transplanted group. OS after IPAA was 86% at 5 years and 79% at 10 years. For nontransplanted patients, OS was 82% at 5 years and 71% at 10 years, while for transplanted patients it was 95% at 5 years and 92.5% at 10 years (log-rank $P = 0.14$) (Fig. 2). PSC-related deaths were higher in the nontransplanted group (12.5% vs 2%, $P = 0.002$). Fifteen (13%) patients in the nontransplanted group were listed for LT, of which 11 died, while 4 are still on the waitlist. Cancer developed in 14 (9%) cases: 3 (3%) cases in the nontransplanted group and 11 (23%) cases in the transplanted group (log-rank $P = 0.01$). The type of cancer for nontransplanted patients was cholangiocarcinoma in 2 cases, and gallbladder adenocarcinoma in 1 case. For transplanted patients, cancer types were cholangiocarcinoma in 4 cases, posttransplant lymphoproliferative disorders in 4 cases, prostate cancer in 2 cases, and unknown primary in 1 case.

Occurrence of pouchitis was higher in the transplanted group (67% vs 45.5% in nontransplanted, $P = 0.03$), and more patients in the transplanted group required chronic antibiotic therapy for pouchitis (54% vs 35% in nontransplanted). When performing a subgroup analysis of patients aged ≤ 40 versus > 40 years, the pouchitis rate remained higher in the transplanted

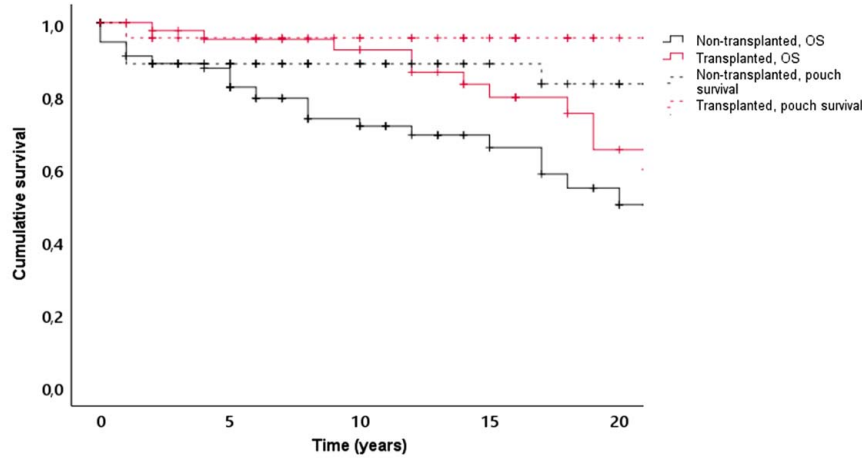
TABLE 2. Long-term Outcomes

	All (N = 160)	Not transplanted at last follow-up (n = 112)	Transplanted at last follow-up (n = 48)	*P*
Median follow-up post-IPAA (y)	10 (4–20)	7 (3–17)	16 (7–23)	0.003†
Deaths	44 (27.5)	30 (27)	14 (29)	0.137†
Cause of death				0.002
Cancer-related	6 (4)	3 (3)	3 (3)	
IBD-related	2 (1)	2 (2)	0	
PSC-related	15 (9)	14 (12.5)	1 (2)	
LT-related	5 (3)	—	5 (10)	
Other	10 (6)	5 (5)	5 (10)	
Unknown	6 (4)	6 (5)	0	
Cancer development	14 (9)	3 (3)	11 (23)	0.013†
Cholangiocarcinoma	6 (4)	2 (2)	4 (8)	
Cirrhosis*	37 (23)	30 (29)	7 (16)	0.074
Biologics use after IPAA	7 (4)	6 (5)	1 (2)	0.319
Anti-TNF	3 (2)	3 (3)	0	
Anti-integrin	4 (2.5)	3 (3)	1 (2)	
Anti-IL	3 (2)	3 (3)	0	
Pouchitis	83 (52)	51 (45.5)	32 (67)	0.034
Antibiotic responsive	32/83 (39)	15/51 (29)	17/32 (53)	0.029
Chronic antibiotic dependent	29/83 (35)	18/51 (35)	11/32 (35)	
Chronic antibiotic resistant	22/83 (26)	18/51 (35)	4/32 (12)	
Treatment of pouchitis				
Antibiotics	65 (41)	39 (35)	26 (54)	0.022
Steroids	8 (5)	4 (4)	4 (8)	0.205
Biologics	3 (2)	2 (2)	1 (2)	0.899
Other	10 (6)	3 (3)	7 (15)	
Redo pouch	5 (3)	4 (4)	1 (2)	
Pouch failure	9 (6)	8 (7)	1 (2)	0.052†

Data are n (%) or median (interquartile range).
*Presence of cirrhosis at last follow-up (post-transplant for transplanted patients).
†Log-rank *P*-value.
IL indicates interleukin; PTLD, posttransplant lymphoproliferative disorder; TNF, tumor necrosis factor.

group in the younger cohort (74% vs 47% in nontransplanted, $P = 0.026$), while in the older cohort, the rate was comparable (62.5% vs 54% in nontransplanted, $P = 0.487$).

During follow-up, 5 (3%) patients required a redo IPAA procedure: 4 (4%) nontransplanted patients (due to anastomotic leak in 2 cases, tip of J leak in 1 case, and pouch-vaginal fistula in



N. at risk					
Overall survival					
Non-transplanted	112	66	35	19	11
Transplanted	48	39	31	22	12
Pouch survival					
Non-transplanted	112	60	31	17	10
Transplanted	48	39	31	22	11

FIGURE 2. Kaplan-Meier curve of OS and pouch survival in transplanted versus nontransplanted patients.

TABLE 3. LT Before IPAA Versus After IPAA—Demographics and Short-term Outcomes

	LT before IPAA (N = 23)	LT after IPAA (N = 25)	*P*
Interval IPAA—LT (y)	8 (4–14)	6 (3.5–8)	
Age at IBD diagnosis (y)	34 (25–46)	23 (17–26)	0.002
Age at IPAA (y)	48 (39–54)	35 (29–44)	< 0.001
Age at LT (y)	38 (29.5–48)	46 (38–50)	0.034
MELD at LT	20 (16–21.5)	24 (14–25)	0.492
Indication for LT			0.056
End-stage liver disease	20 (87)	19 (76)	
Biliary complications	2 (9)	0	
Bile duct neoplasia	0	6 (24)	
Autoimmune hepatitis	1 (4)	0	
Donor type			0.011
DBD	19 (83)	15 (60)	
DCD	0	1 (4)	
Living donor	0	8 (32)	
Unknown	4 (17)	1 (4)	
Technique of biliary anastomosis			0.160
Duct-to-duct	3 (13)	5 (20)	
Hepatojejunostomy	6 (26)	17 (68)	
Other	3 (13)	1 (4)	
Unknown	11 (48)	2 (8)	
Complications after LT	10 (44)	15 (60)	0.239
Major	8 (35)	8 (32)	0.490
Immunosuppression			
Steroids	20 (87)	24 (96)	0.257
Tacrolimus	23 (100)	24 (96)	0.332
Cyclosporine	0	1 (4)	0.332
Mycophenolate mofetil	6 (26)	12 (48)	0.117
Everolimus/sirolimus	1 (4)	1 (4)	0.952
Other	0	3 (12)	0.086
Acute rejection	5 (22)	4 (16)	0.707

Data are n (%) or median (interquartile range).

DBD indicates donation after brain death; DCD, donation after cardiac death; LT, liver transplantation; IPAA, ileal pouch-anal anastomosis; MELD, Model of End-Stage Liver Disease.

1 case) and 1 (1%) transplanted patient (due to twisted pouch syndrome).

Pouch failure, including the patient who never had their ileostomy reversed, occurred in 9 (6%) cases: 8 (7%) in nontransplanted patients and 1 (2%) in transplanted patients. Pouch failure in the nontransplanted group occurred due to refractory pouchitis in 5 cases, pelvic sepsis in 2 cases (including the patient who never had their stoma closed), and CD of the pouch in 1 case. Pouch failure in the transplanted patient occurred due to chronic partial small bowel obstruction. Pouch survival at 10 years after IPAA was 94%: 90% for nontransplanted and 100% for transplanted patients (log-rank $P = 0.052$).

Outcomes Before and After 2005

Outcomes of patients who underwent IPAA before 2005 and from 2005 onwards were evaluated. Post-IPAA OS was higher from 2005 onwards for the overall cohort (5-year survival 94%, vs 80% before 2005, log-rank $P = 0.015$). Pouch survival was comparable (5-year pouch survival 95% in both groups, $P = 0.81$).

LT Before Versus After IPAA

Table 3 shows demographics and short-term LT outcomes for patients who underwent LT before IPAA versus after. Patients who underwent LT before IPAA were older at IBD diagnosis and IPAA, and younger at LT compared with patients who underwent LT after IPAA. The most common indication for LT was end-stage liver disease in both groups, but patients who underwent LT after IPAA had more bile duct neoplasia as indications for LT (24% vs 0 in the LT before IPAA group, $P = 0.06$) (Fig. 3). Patients who underwent LT after IPAA received more grafts from living donors (32% vs 0 in the LT before IPAA group, $P = 0.01$). Morbidity, major complications, and acute rejection rates were similar between the 2 groups. There was no 90-day mortality.

Long-term outcomes are shown in Table 4. The rate of pouchitis and pouch survival were similar between the groups, with pouch survival at 10 years being 100% for both groups.

PSC recurrence occurred in 7 (15%) patients (6 in the LT before IPAA group, 1 in the LT after IPAA group) after a median of 11.5 years. Of them, 3 experienced graft loss requiring retransplantation (2 in the LT before IPAA group, and the patient in the LT after IPAA group). The PSC recurrence rate at 10 years after LT was 6%, with no differences between timing of IPAA.

Eight (17%) patients required retransplantation: 6 (26%) patients who underwent LT before IPAA and 2 (8%) who underwent LT after IPAA (log-rank $P = 0.21$). Causes of retransplantation for the LT before IPAA groups were chronic rejection in 2 cases, and acute rejection, hepatic artery thrombosis, and recurrent PSC in 1 case each; patients in the LT after IPAA group required retransplantation due to ischemic cholangiopathy with hepatic artery thrombosis in 1 case and recurrent PSC in the other. The retransplantation rate at 10 years post-LT was 18%. Patients who underwent LT before IPAA were more prone to early retransplantation compared with those who had LT after IPAA (median 0, vs 10.5 years, $P = 0.03$).

DISCUSSION

The coexistence of PSC and IBD has implications on disease severity and treatment. In patients with PSC-IBD, the course of PSC is influenced by the potential need for colectomy; conversely, the course of IBD is influenced by the potential need for LT.

In our study on 160 patients undergoing restorative proctocolectomy with IPAA for PSC-IBD, 48 (30%) received LT either before (14%) or after (16%) IPAA. Transplanted patients had higher rates of cancer development and pouchitis, especially in younger patients, while nontransplanted patients had more PSC-related deaths (many while awaiting LT) and more pouch failures.

In our large cohort of patients undergoing IPAA for IBD, 3.3% of patients had concomitant PSC, which is consistent with the prevalence reported in the literature.[16] Patients who underwent IPAA alone and IPAA before LT were younger at IPAA and at IBD diagnosis, as can be expected due to selection bias. Unsurprisingly, patients who had undergone LT before IPAA were less likely to receive a laparoscopic IPAA and had more blood loss, likely related to worse liver disease as reflected by higher MELD scores at IPAA. However, the potentially higher technical difficulty resulting for a previous complex operation such as LT did not result in a higher rate of major morbidity or 90-day mortality. The pattern of postoperative complications was also similar between the 2 groups.

The interplay between PSC and IBD is not limited to surgical outcomes. Medical therapies for IBD may exert an effect on PSC, and vice versa. Treatment of IBD with anti–tumor necrosis factor α and anti-integrin monoclonal antibodies

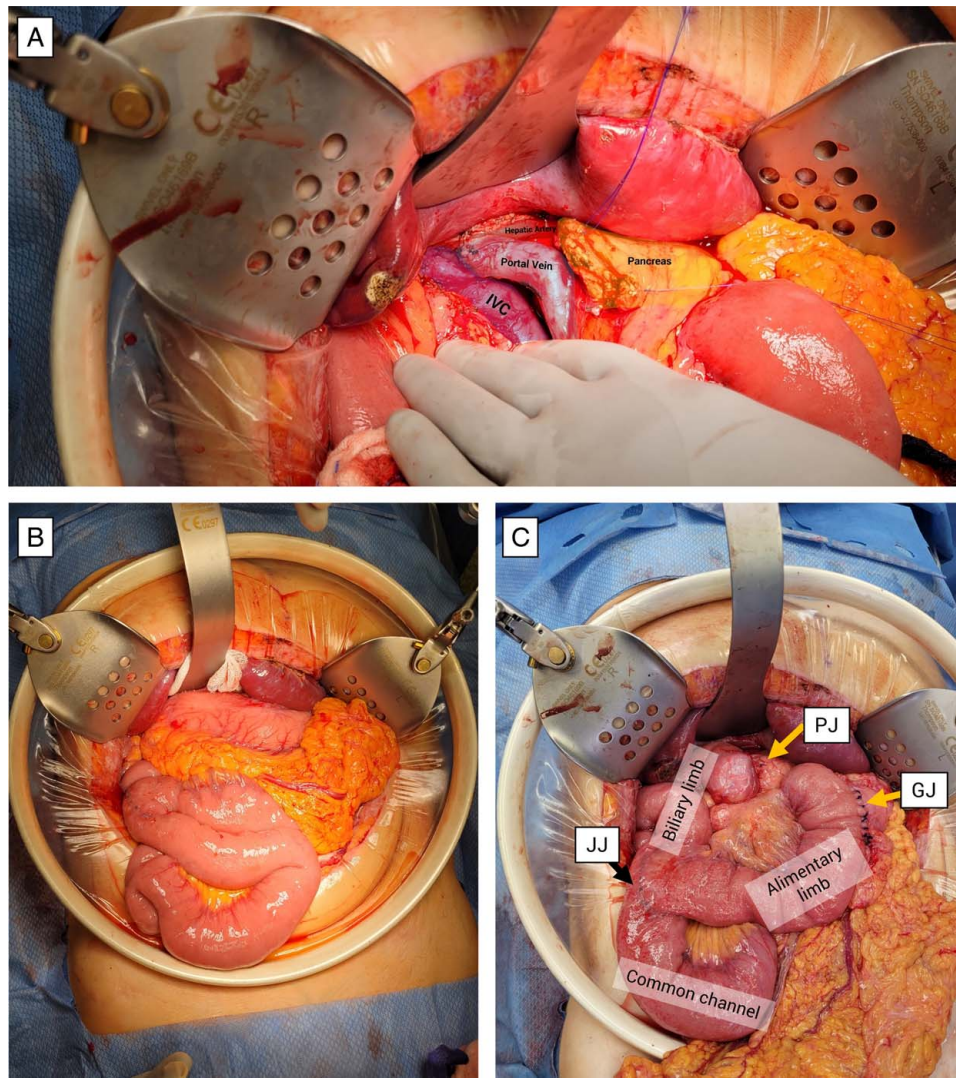


FIGURE 3. Intraoperative view before, during and after pancreatoduodenectomy in patients with previous IPAA for ulcerative colitis and living donor LT for PSC-related cirrhosis and bile duct neoplasia. A, Hepatic hilum with transected pancreatic stump. B, Initial view after laparotomy, showing the liver graft and the roux-en-Y hepaticojejunostomy. C, Final appearance after pancreatoduodenectomy with preserved hepatojejunostomy and jejunojejunostomy from living donor LT, pancreatojejunostomy performed on the hepatojejunostomy limb, and pylorus-preserving gastrojejunostomy. IVC indicates inferior vena cava.

may positively affect PSC.[17] Immunosuppression after LT has also been associated with IBD flare-ups, especially tacrolimus and cyclosporine,[18,19] while prolonged steroid use for ulcerative colitis has been associated with recurrent PSC.[20] In our series, rate of biologics use after IPAA was similar between transplanted and nontransplanted patients. Immunosuppression did not seem to have an adverse effect on IBD-related outcomes, although the difference in the rate of pouchitis and of pouchitis-related treatment may be related to immunosuppressive therapy.

The increased rate of pouchitis could also be related to the altered vascular outflow of the pouch due to the liver graft. Indeed, portal vein thrombosis is a known risk factor for pouchitis;[21] similar mechanisms may be at play in the case of LT.

In the current series, the rate of pouchitis in patients with PSC-IBD (52%) was higher than our historical rate for all patients (16%),[22] and significantly higher in patients who had undergone LT at last follow-up (67%, vs 45.5% in non-transplanted patients, $P = 0.03$). In 2008, our institution had already reported an association between LT and chronic antibiotic refractory pouchitis in a similar patient population.[8] Differently from this previous report, we found no difference in pouchitis according to the timing of LT but found an association with age. While the pouchitis rate remained stable in non-transplanted patients regardless of age, it was increased in younger patients ($\leq$40 years) in the transplanted cohort.

Barnes et al[23] recently reported a meta-analysis which show a 63% any acute pouchitis and 47% chronic pouchitis rate after IPAA in PSC-IBD patients. An increasingly popular theory regarding the etiology of pouchitis involves the microbiome, whose role is increasingly recognized in both PSC and IBD.[24] Patients with PSC-IBD appear to have a different gut microbiome compared with patients with IBD alone and may be associated

TABLE 4. LT Before IPAA Versus After IPAA—Long-term Outcomes

	LT before IPAA (N = 23)	LT after IPAA (N = 25)	*P*
Median FU from LT (y)	24 (11–28)	7 (2–14)	< 0.0001*
Median FU from IPAA (y)	12 (4–21)	18 (14–23)	0.066*
Deaths	9 (39)	5 (20)	0.149*
Cancer-related	3 (13)	0	
IBD-related	0	0	
PSC-related	1 (4)	0	
LT-related	2 (9)	3 (12)	
Other	3 (14)	2 (8)	
Any cancer development	5 (22)	6 (24)	0.236
Cholangiocarcinoma	0	4 (16)	
Post-LT cirrhosis	3 (14)	4 (17)	0.728
Pouchitis	16 (70)	16 (67)	0.831
Pouch failure	0	1 (4)	0.535*
PSC recurrence	6 (27)	1 (4)	0.503*
Interval between LT and PSC recurrence (y)	13 (8–20)	9	
Hepatic artery complications	3 (13)	2 (8)	0.532
Biliary complications	4 (18)	4 (16)	0.843
Anastomotic stricture	3 (13)	3 (12)	
Ischemic cholangiopathy	1 (4)	1 (4)	
Chronic rejection	2 (9)	0	0.123
Retransplantation	6 (26)	2 (8)	0.208*
Interval between LT and retransplantation (y)	0 (0–6.5)	10.5 (9–12)	0.026

Data are n (%) or median (interquartile range).

IL indicates interleukin; PTLD, posttransplant lymphoproliferative disorder; TNF, tumor necrosis factor.

*Log-rank *P* value.

with the increased pouchitis rate in patients with PSC-IBD. As previously mentioned, the even higher rate in patients with PSC-IBD who underwent LT may be further explained by the microbiomic disruption associated with immunosuppression.[25] Immunosuppressive agents may however also be employed as therapeutic agents for chronic antibiotic refractory pouchitis,[26] both via systemic and local administration, for example, topical tacrolimus.[27] This reflects our poor understanding of the underlying mechanisms leading to pouchitis.

After a median follow-up of 10 years, the rate of pouch failure in our cohort was 6%, which is similar to previous reports of IPAA for all IBD-related indications.[22,28] Pouch failure occurred in only 1 (2%) transplanted patients, versus 8 (7%) nontransplanted patients (log-rank $P = 0.052$): despite this trend toward significance, this result cannot be easily interpreted from a clinical standpoint and may be the result of a type I error. Interestingly, pouchitis was the cause of pouch failure in 5 out of 8 patients in the nontransplanted group, versus none in the transplanted group, despite the higher rate of pouchitis in the transplanted cohort. This seems to imply that pouchitis, while more frequent in transplanted patients, was more severe in nontransplanted patients.

Patients with PSC-IBD are at increased risk of cancer development than the general population. In particular, patients with PSC are at increased risk of cholangiocarcinoma and gallbladder carcinoma,[29] which was reflected in our series. Cancer development was higher in the LT cohort: this is both a result of immunosuppression (indeed, posttransplant lymphoproliferative disorder developed in 4, or 8%, cases) and of collinearity, as 6 (24%) patients who underwent LT after IPAA had bile duct neoplasia as the indication for LT.

While LT is the only curative treatment for PSC, with excellent long-term outcomes, it is associated with increased rates of acute and chronic rejection compared with other indications, as well as the risk of PSC recurrence which may cause graft loss and require retransplantation.[3,30] The acute rejection rate in our series was 19%, which is comparable to the literature, especially considering the length of the study period,[31] during which immunosuppressive regimens have improved.

Trivedi et al,[32] in their study on 143 LT for PSC, reported post-LT survival outcomes comparable to ours. In their study, they explored the relationship between donor type and outcomes, as the use of grafts from extended criteria donors has been linked to PSC recurrence and worse post-LT outcomes.[33] In their study, they found no differences in graft and patient survival with donation after brain death versus DCD grafts. In our series, only 1 patient received a DCD graft while, interestingly, patients who underwent LT after IPAA received more living donor grafts than patients who underwent LT before IPAA (32% vs 0%, $P = 0.01$) despite similar MELD scores at LT. This may be due to differences in the donor pool and allocation system between the United Kingdom and the United States, which make it harder for patients with PSC to receive a graft from a deceased donor,[34] thus favoring patients who either have a directed living donor or who are listed in centers who perform undirected living donor LTs.[35] In addition, 12.5% nontransplanted patients died due to PSC-related death, compared with one in the transplanted group ($P = 0.002$), and out of 15 patients who were listed and not transplanted, 11 died on the waitlist.

PSC recurrence in our cohort was 15%, slightly lower than reports of PSC recurrence in patients with PSC who did not undergo colectomy.[33] Both IBD activity/colitis and colectomy have been associated with post-LT outcomes and PSC recurrence. Increased post-LT IBD activity has been linked to higher rates of PSC recurrence, while colectomy may have a protective effect,[33,36] although reports are controversial.[10] Another study from the Birmingham group on 240 patients with PSC-IBD undergoing LT found increased graft loss after IPAA compared with colectomy with ileostomy, with no differences between the IPAA and the no colectomy groups.[10] While we cannot directly comment on the effect of IPAA on graft loss, as all patients in our study cohort underwent IPAA, our retransplantation rate of 18% at 10 years was lower than the report by Trivedi and colleagues, with recurrent PSC and rejection being the most common causes of graft failure. Interestingly, we found that patients who underwent LT before IPAA mostly experienced early graft loss and subsequent retransplantation, with 4 out of 6 cases occurring within 12 months of LT, while patients in the LT after IPAA group underwent retransplantation at 9 and 12 years after LT ($P = 0.03$).

This study has limitations. It is a single-center retrospective study from a tertiary referral center for PSC-IBD, IPAA, and LT, which limits the generalizability of our conclusions. Due to the study design, which included 2 surgical events as inclusion criteria, some patient groups are at risk of immortal time bias; specifically, patients who underwent LT before IPAA have immortal time bias between LT and IPAA (they had to be alive and undergo IPAA to be included in the study), while patients who underwent LT after IPAA had immortal time bias between IPAA and LT (they had to be alive and undergo LT to be included in that group, otherwise they would have remained in the IPAA alone group). Due to the retrospective nature of the study, some data could not be extrapolated, including IBD activity before IPAA, number of acute rejection episodes, and number of pouchitis episodes per year. Follow-up was significantly longer for patients who underwent LT before IPAA compared with all other groups, due to selection bias. The

study takes into account almost 4 decades, during which several changes have occurred in (1) medical treatment of PSC and IBD; (2) surgical technique for both IPAA and LT; (3) immunosuppressive treatment after LT; (4) graft allocation. Finally, results from this study pertain to a select group of patients who underwent either IPAA or both IPAA and LT, limiting the applicability of our results to other patients with PSC-IBD.

In conclusion, in this study on 112 nontransplanted patients versus 48 transplanted patients who underwent IPAA for PSC-IBD, LT was associated with higher rates of pouchitis, but not pouch failure. Patients who did not undergo LT were at increased risk of PSC-related death. Timing of LT related to IPAA did not affect pouchitis. Timing of IPAA related to LT did not affect PSC recurrence, rejection, or retransplantation, but patients who underwent LT before IPAA were more likely to experience early retransplantation compared with those undergoing LT after IPAA.

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