Sutter Health CPMC

POST TRANSPLANT OUTCOMES IN PSC

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INDICATION FOR LT IN PSC

- Decompensated cirrhosis
- Cholangiocarcinoma (CCA): hilar, < 3cm, per neoadjuvant Mayo Clinic protocol
- Recurrent bacterial cholangitis

TRANSPLANT FOR PSC IN THE US

- 5% of all adult transplant recipients in the US each year have PSC as the primary etiology of liver disease necessitating a liver transplant.

- ~14% of transplant recipients with PSC receive a living donor liver transplant (LDLT), compared to 3.5–4% of transplant recipients with other forms of chronic liver disease

Clin Liver Dis. 2016 Feb; 20(1): 191–203.

TREND IN LT FOR PSC

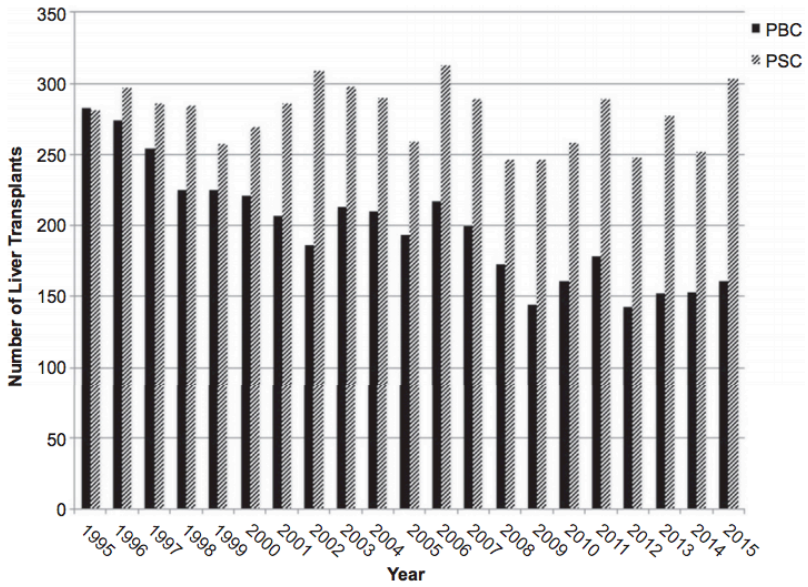

Fig. 1. Number of adult liver transplants performed each year in the United States for PBC and PSC from 1995 to 2015. (*Data from* United Network for Organ Sharing. Available at: https://www.unos.org/. Accessed July 20, 2016.)

LT for PSC has been fairly stable with an average of 292 LT per year

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POST LT OUTCOMES

Table 1
Patient survival after liver transplant for primary sclerosing cholangitis and primary biliary cholangitis

				1 y (%)		3 y (%)		5 y (%)		10 y (%)	
Indication	**Registry**	**Year**	**Cohort Size**	**Patient**	**Graft**	**Patient**	**Graft**	**Patient**	**Graft**	**Patient**	**Graft**
PSC	Mayo Clinic, United States[42]	1985–1996	150	93.7	83.4	92.2 (2-y)	83.4 (2-y)	86.4	79.0	69.8	60.5
	Birmingham, United Kingdom[19]	1986–2006	230	80	75	—	—	68	60	57	50
	UNOS[11]	1994–2009	3854	93.4	86.5	89.7	81.4	87.4	78.0	83.2	71.5
	ELTR[12]	1999–2009	2170	90	83	—	—	82	72	—	—
	UNOS (DDLT)[13]	2002–2006	100	93.0	87.0	87.5	79.7	85.5	79.2	—	—
	UNOS (LDLT)[13]	2002–2006	100	97.2	89.6	95.4	87.1	95.4	87.1	—	—
PBC	UNOS[11]	1994–2009	3052	90.2	85.0	86.7	80.5	84.4	78.1	79.0	71.9
	ELTR[12]	1999–2009	1929	90	85	—	—	83	78	—	—
	UNOS (DDLT)[13]	2002–2006	100	89.6	85.2	87.0	82.5	85.1	80.7	—	—
	UNOS (LDLT)[13]	2002–2006	100	92.8	85.6	90.1	80.9	86.4	77.4	—	—

Abbreviation: ELTR, European Liver Transplant Registry.

LT for PSC is highly successful, with 5-year patient survival rates in the United States exceeding 85%

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POST LT OUTCOMES

- PSC have post-transplant graft and patient survival that is not different than other transplant recipients

- However, when considering only recipients of a living donor allograft in the US from 2002–2013, patients with PSC transplanted at an 'experienced' center (defined as having performed >15 living donor liver transplants) had superior post-transplant graft and patient survival even after adjusting for other factors

Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999–2008. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2010;10(4 Pt 2):1003–1019. [PubMed]
Goldberg DS, French B, Abt PL, Olthoff K, Shaked A. Superior survival using living donors and donor-recipient matching using a novel living donor risk index. Hepatology. 2014;60(5):1717–1726.

RECURRENT PSC

- Recurrent PSC, is estimated to occur in the range of 15–35% of transplant recipients

- Wide range of the estimated risk of recurrent PSC rests in part on the challenges in diagnosing recurrent PSC, as it is considered a diagnosis of exclusion.

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RECURRENT PSC RATES

Table 3
Rates of recurrent primary sclerosing cholangitis after liver transplant

Reference	Time Period	Number of Patients	Recurrence Rate (%)	Median Time to Recurrence (Range)
Graziadei et al,[15] 1999	1985–1996	120	20 (8.3 based on both cholangiographic and histologic features)	36 mo (14–108 mo), histologic criteria; 8.6 mo (3–43 mo), cholangiographic criteria
Alabraba et al,[19] 2009	1986–2006	230	23.5	4.6 y (0.5–12.9 y)
Goss et al,[20] 1997	1984–1996	127	8.6	Not provided
Jeyarajah et al,[21] 1998	1998–1995	118	15.7	21 mo (mean)
Kugelmas et al,[22] 2003	1988–2000	71	21.1	52 mo (mean) (12–110)
Ravikumar et al,[23] 2015	1990–2010	565	14.3	Not provided
Vera et al,[24] 2002	1986–2000	152	37	36 mo (1–120)

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RECURRENT PSC

- In post LT setting, characteristic of PSC can also be seen in patients who have developed a
  - Hepatic artery stenosis/thrombosis
  - Chronic ductopenic rejection
  - Cytomegalovirus infections of the biliary tract, and/or
  - Received a transplant from a donor with an incompatible blood type or from a donation after cardiac arrest

- For these reasons, the diagnosis of recurrent PSC is one of exclusion, and requires exclusion of conditions that can mimic recurrent PSC

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RECURRENT PSC

Diagnostic criteria for recurrent primary sclerosing cholangitis following liver transplantation[23]

Inclusion criteria	Exclusion criteria
• Confirmed diagnosis of PSC prior to liver transplantation • Cholangiography (MRCP or ERCP) performed ≥90 days after transplantation demonstrating intrahepatic and/or extrahepatic biliary structuring, beading, and/or irregularity, OR • Liver biopsy demonstrating fibrous cholangitis and/or fibro-obliterative lesions, with or without biliary fibrosis or cirrhosis, and/or ductopenia	• Hepatic artery stenosis or thrombosis on radiographic imaging or angiography • Chronic ductopenic rejection on histologic evaluation of liver biopsy • Isolated extrahepatic anastomotic strictures • Donor and recipient ABO incompatibility • Non-anastomotic strictures occurring prior to day 90 post-transplantation

Zenouzi R, Weismuller TJ, Hubener P, et al. Low risk of hepatocellular carcinoma in patients with primary sclerosing cholangitis with cirrhosis. Clinical gastroenterology and hepatology. 2014;12(10):1733–1738, with permission.

RISK FOR RECURRENT PSC

Table 4
Risk factors for recurrent primary sclerosing cholangitis

HLA-DRB1*08 (in Recipient or Donor)[26]	Use of extended donor criteria grafts[19]
Absence of donor HLA-DR52[21]	Steroid-resistant ACR[26]
Recipient-donor gender mismatch[30]	Use of OKT3[22]
Male recipient[24]	Presence of UC after LT[23]
Younger recipient age[21]	Maintenance of steroid therapy for UC >3 mo[25]
Intact colon before LT[24]	Presence of cholangiocarcinoma before LT[27]
>1 episode of ACR[21]	Concurrent cytomegalovirus infection in recipient[21]
First-degree related donors (LDLT)[29]	

Abbreviations: ACR, acute cellular rejection; HLA, human leukocyte antigen.

Presence of ulcerative colitis
Acute cellular rejection (ACR)

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TREATMENT FOR RECURRENT PSC

- There is no proven medical therapy for recurrent PSC (rPSC)after LT
- Although ursodiol is used in most transplant centers and improves the liver biochemical profile, its effect on outcomes remains unclear
- Prophylactic use of UDCA may be justified in patients with coexisting UC who may benefit from UDCA by reducing the risk of colon cancer
- As in the nontransplant setting, biliary strictures may be managed by endoscopic or percutaneous methods

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Pardi DS, Loftus EV Jr, Kremers WK, et al. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. Gastroenterology 2003;124(4):889–93.

ACUTE CELLULAR REJECTION (ACR)

- Patients with PSC are commonly thought to have a higher risk of ACR compared with LT recipients with other primary liver diseases.
  - Reported rates are variable
  - Variable immunosuppressive regimens, inconsistent use of protocol biopsies, and histologic definition of ACR
- Conflicting evidence regarding concomitant IBD as risk of ACR

ACR AFTER LT IN PSC

Table 5
Incidence of rejection after liver transplant for primary sclerosing cholangitis

Reference	Year	Cohort Size	Rejection Rate (%)	Type of Rejection	Median (Range) Follow-up (mo)
Graziadei et al,[42] 1999	1985–1996	150	69	ACR	55 (10–138)
Brandsaeter et al,[26] 2005	1984–2003	49	71	ACR	77 (17–182)
Jeyarajah et al,[21] 1998	1985–1995	115	39	ACR	Minimal follow-up 12 mo
Graziadei et al,[42] 1999	1985–1996	150	8	Chronic	56 (10–138)
Jeyarajah et al,[21] 1998	1985–1995	115	39	Chronic	Not provided
Milkiewicz et al,[43] 2000	1982–1998	136	7	Chronic	Not provided

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LATE ACR

- Late acute rejection (LAR), which is more common in PBC, PSC, and autoimmune hepatitis (AIH), is associated with worse patient and graft survival.

Uemura T, Ikegami T, Sanchez EQ, et al. Late acute rejection after liver transplantation impacts patient survival. Clin Transpl 2008;22(3):316–23

RETRANSPLANT FOR RPSC

- Long-term data indicate that rPSC significantly affects graft survival, rate of retransplant, and patient survival
- Retransplant is a viable option in patients who develop rPSC with subsequent graft loss.
- In a retrospective review of the United Network for Organ Sharing (UNOS) database, the rate of retransplant was significantly higher in patients with PSC compared with patients with primary biliary cholangitis (PBC) (12.4% vs. 8.5%) and PSC was identified as an independent predictor for retransplantation

Rowe IA, Webb K, Gunson BK, et al. The impact of disease recurrence on graft survival following liver transplantation: a single centre experience. Transpl Int 2008;21(5):459–65.
Maheshwari A, Yoo HY, Thuluvath PJ. Long-term outcome of liver transplantation in patients with PSC: a comparative analysis with PBC. Am J Gastroenterol 2004; 99(3):538–42.

INFLAMMATORY DISEASE (IBD) COURSE AFTER LT FOR PSC

- In general, one-third of patients with PSC and IBD will have worsening of IBD symptoms post-liver transplantation
- Choice of immunosuppression can impact post-transplant activity of IBD in patients with PSC.
- Specifically, combination therapy with tacrolimus and mycophenolate mofetil has been associated with worsening of IBD activity while combination cyclosporine and azathioprine was associated with fewer IBD flares after LT

Jorgensen KK, Lindstrom L, Cvancarova M, et al. Immunosuppression after liver transplantation for primary sclerosing cholangitis influences activity of inflammatory bowel disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013;11(5):517–523

Singh S, Loftus EV, Jr, Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. The American journal of gastroenterology. 2013;108(9):1417–1425.

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MANAGEMENT OF IBD AFTER LT

- Similar to pre-LT with increased risk of infection if biologics are added to standard LT immunosuppression
  - Consider Azathiopurine in moderate to severe IBD with tacrolimus
  - Severe cases—will need anti-TNF

Moncrief KJ, Savu A, Ma MM, Bain VG, Wong WW, Tandon P. The natural history of inflammatory bowel disease and primary sclerosing cholangitis after liver transplantation--a single-centre experience. Canadian journal of gastroenterology = Journal canadien de gastroenterologie. 2010;24(1):40–46. [PMC free article] [PubMed]

Singh S, Loftus EV, Jr, Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. The American journal of gastroenterology. 2013;108(9):1417–1425.

RISK OF CRC OR DYSPLASIA

- The risk of developing colorectal cancer in patients with PSC and IBD persists after liver transplantation, thus continued yearly colorectal surveillance is recommended

- In one study, the risk of cumulative incidence of dysplasia was 15% at 5 years and 21% at 8 years (comparable to pre-LT risk)

Vera A, Gunson BK, Ussatoff V, et al. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Transplantation. 2003;75(12):1983–1988.

POUCHITIS

- A total of 63 PSC/ileal-pouch anal anastomosis (IPAA) patients were studied, including 19 patients with OLT and 44 patients without OLT.
- Fifty patients (79.4%) had chronic antibiotic-refractory pouchitis (CARP).
- In both univariable and multivariable analyses (adjusting for OLT status), none of the variables studied was associated significantly with CARP ($P > .20$).
- All 7 patients (100%) with IPAA-then-OLT were diagnosed as having CARP, of whom 4 developed CARP before OLT, which persisted after OLT, and 3 had CARP after OLT.

Freeman K et. al. Impact of orthotopic liver transplant for primary sclerosing cholangitis on chronic antibiotic refractory pouchitis. Clin Gastroenterol Hepatol. 2008 Jan;6(1):62-8. Epub 2007 Dec 11.

POUCHITIS

- Of 12 patients with OLT-then-IPAA, 7 (58.3%) developed CARP.
- The frequency of CARP in OLT-then-IPAA was statistically significantly lower than that in IPAA-then-OLT (58.3% vs 100%; P = .047).
- CARP is common in patients with ulcerative colitis and PSC.
- OLT in these patients may not affect the frequency of CARP in general and appears not to alter the disease course of pre-existing CARP.
- However, in a subset of patients, OLT might reduce the risk for the development of de novo CARP

Freeman K et. al. Impact of orthotopic liver transplant for primary sclerosing cholangitis on chronic antibiotic refractory pouchitis. Clin Gastroenterol Hepatol. 2008 Jan;6(1):62-8. Epub 2007 Dec 11.

THANK YOU.