Irish Journal of Medical Science (1971 -) (2024) 193:1253–1256
https://doi.org/10.1007/s11845-023-03586-1

ORIGINAL ARTICLE

Recurrent sclerosing cholangitis post-transplant: increased recurrence rates following re-transplantation

Julia Sopena Falco[1] · **Julie Steen**[1] · **P Aiden McCormick**[1,2]

Received: 19 July 2023 / Accepted: 28 November 2023 / Published online: 5 December 2023

Abstract

Sclerosing cholangitis recurs in some patients following liver transplantation. These high-risk patients may provide clues to the pathogenesis of this disease.

Aims In this single-center study, from a high prevalence area, we investigated the incidence of recurrent sclerosing cholangitis following liver transplantation and re-transplantation.

Methods A retrospective cohort study of all patients with primary sclerosing cholangitis transplanted in the Irish National Liver Transplant program between 1993 and 2019.

Results Recurrent sclerosing cholangitis occurred in 23/112 patients (20.7%). Overall patient survival was similar in the recurrence and non-recurrence groups. Nine patients were re-transplanted for recurrent disease. Patients with recurrence were significantly younger (42.7 + − 2.5 years vs. 49.3 + − 1.3 $p < 0.05$), and colectomy post-transplant was performed more frequently in the recurrence group (6/21 vs. 9/81 $p < 0.05$). Further recurrence after re-transplantation was identified in 6/9 patients and was identified a shorter time after transplant than the first recurrence (median 41.5 months; range 26–53 vs. median 65.5; range 38: $p < 0.05$).

Discussion/conclusion Recurrent PSC following liver transplantation is common, particularly in younger patients. It occurs earlier and is more frequent following a second transplant.

Keywords Cirrhosis · Inflammatory bowel disease · Liver transplantation · Primary sclerosing cholangitis

Primary sclerosing cholangitis is a common indication for liver transplant in Northern Europe and North America but is relatively uncommon elsewhere [1–3]. The disease may recur in the new liver graft in between 8 and 27% of patients and may require re-transplantation [4, 5]. Recurrent sclerosing cholangitis has been reported to result in reduced graft and patient survival. The pathophysiology is incompletely understood, and there is currently no medical therapy proven to alter the natural history of this disease [6]. There are a number of unusual aspects of sclerosing cholangitis. In contrast to most presumed auto-immune diseases, it affects more males than females. The majority of patients also have inflammatory bowel disease, most commonly ulcerative colitis. There is also a marked geographical distribution with the disease most common in Northwest Europe, North America, Australia, and New Zealand. Despite extensive efforts and a number of associations a definite genetic basis for the disease has not been identified [7]. It is not clear why sclerosing cholangitis recurs in some patients following liver transplantation, but not in others. It is possible that investigating these high-risk patients may provide clues to the pathogenesis. In this single-center study, from a high prevalence area, we looked at our cohort of patients with recurrent sclerosing cholangitis following liver transplantation.

Methods

This study was performed in the Irish National Liver Transplant Unit, located at St. Vincent's University Hospital in Dublin. The unit is an adult-only program which commenced in 1993, and it is the only liver transplant unit in the Republic of Ireland. Patients transplanted with a diagnosis of

✉ P Aiden McCormick
a.mccormick@ucd.ie

[1] Liver Unit, St. Vincent's University Hospital, Elm Park, Donnybrook, Dublin 4 DO4 T6F4, Ireland

[2] University College Dublin (UCD), Dublin, Ireland

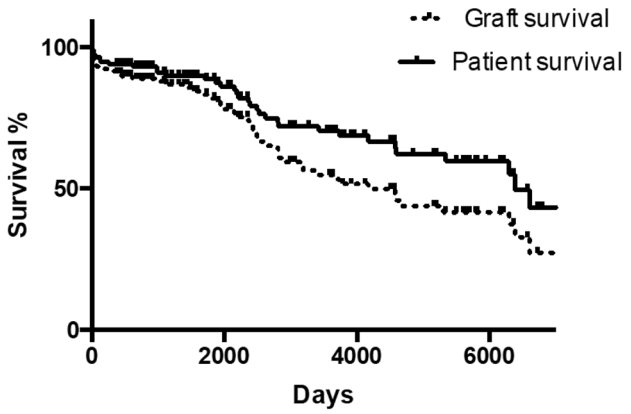

Fig. 1 Patient and graft survival for 119 patients transplanted for primary sclerosing cholangitis

primary sclerosing cholangitis between the commencement of the program in 1993 and the end of 2019 were identified from the liver transplant list. The original individual clinical notes were reviewed by two hepatologists independently. Patients with a diagnosis of cholangiocarcinoma were excluded. Follow-up was till the end of 2022. Diagnosis of recurrent sclerosing cholangitis was established on the basis of the criteria suggested by the Mayo Clinic [8]. These include the presence of characteristic non-anastomotic biliary strictures or compatible histologic abnormalities. Patients with cholangiocarcinoma were excluded as radiotherapy, and chemotherapy can cause damage mimicking recurrent PSC. Patients who died within 1 year of transplantation were also excluded as there would be insufficient time for recurrent sclerosing cholangitis to become manifest. The study was approved by the research ethics committee at St. Vincent's University Hospital. Data was graphed and analyzed using GraphPad Prism software (GraphPad Software Inc., San Diego, CA, USA). Significance of differences was analyzed using the Mann–Whitney test, log-rank test, or Chi^2 test (Fisher's exact test) and the paired Mann–Whitney test as appropriate. Unless otherwise stated, data are expressed as the mean ± standard error of the mean (s.e.m.)

Results

Between 1993 and the end of 2019, 1032 liver transplants were performed. One hundred and thirty-nine patients had a diagnosis of primary sclerosing cholangitis. The graft and survival data for 119 PSC patients without cholangiocarcinoma are shown in Fig. 1. Five and 10-year patient and graft survivals were 88.9%/70.5% and 84.5%/54.9% respectively. There were a total of 21 patients who required re-transplantation. Five re-transplants were early (< 12 months for primary non-function or hepatic artery thrombosis). For consideration of recurrent primary sclerosing cholangitis, patients who died within 1 year of transplant were excluded as there would be insufficient time for recurrent sclerosing cholangitis to manifest. Twenty patients with cholangiocarcinoma and 7 who died within 1 year of transplantation were excluded. Results on 112 patients were analyzed.

Recurrent sclerosing cholangitis was diagnosed in 23/112 patients (20.7%) (Table 1). Overall patient survival was similar in the recurrence and non-recurrence groups (Fig. 2). There were 10 late re-transplants in the recurrent PSC group and 7 in the non-recurrence group (10/23 vs. 7/89 $p < 0.01$). The re-transplants in the recurrent PSC group were all for recurrent disease, whereas in the non-recurrence group, 3 were for chronic rejection, 3 for hepatic artery thrombosis, and 1 for undefined immunological liver disease. Patients with recurrent disease were significantly younger ($42.7 + -2.5$ years vs. $49.3 + -1.3$ $p < 0.05$). Inflammatory bowel disease was present in 85/112 patients (76%), 20/23 in the recurrence group vs. 65/89 in the non-recurrence group ($p =$ n.s.). One patient re-transplanted for recurrent PSC did not have a diagnosis of inflammatory bowel disease. Ten patients had colectomy pre-transplant, 2 in the recurrent PSC group, and 8 in the non-recurrence group (2/23 vs. 8/89 $p =$ n.s.). Colectomy post-transplant was performed in 6/21 patients in the recurrence group and 9/81 in the group without recurrent disease ($p < 0.05$). In this study, there was no significant relationship between episodes of acute cellular rejection or immunosuppressive medications used and

Table 1 Patients with and without recurrent sclerosing cholangitis following first liver transplant

	Recurrent sclerosing cholangitis ($n = 23$)	No-recurrence ($n = 89$)	p value
Age at first transplant (m ± s.e.m.)	42.7 ± 2.5	49.3 ± 1.3	$p < 0.01$
Sex (M/F)	19/4	64/25	n.s.
Inflammatory bowel disease	20/23	65/89	n.s.
Colectomy pre-transplant	2/23	8/89	n.s.
Colectomy post-transplant	6/21	9/81	$p < 0.05$
Pouch surgery pre/post-transplant	1/1	5/3	n.s.
Mortality	5/23	23/89	n.s.
Late re-transplant (> 1 year post-transplant)	10/23	7/89	$p < 0.01$

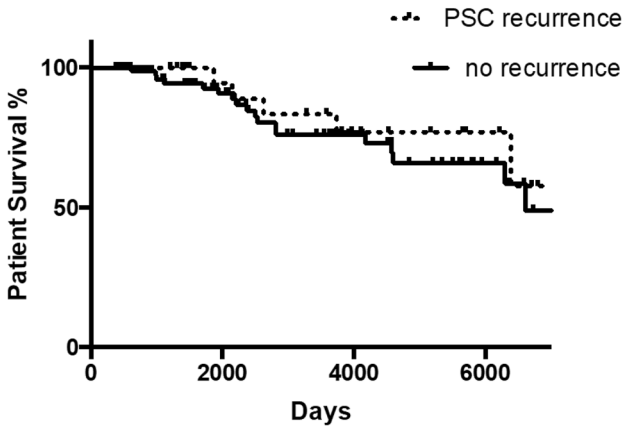

Fig. 2 Patient survival for 112 patients with and without recurrence of sclerosing cholangitis. Patients who died within 1 year of initial liver transplant were excluded

the risk of recurrent disease. Of the 10 patients with recurrent disease, 1 died shortly after re-transplantation. Disease recurrence was subsequently identified in 6, and suspected in another, with 1 patient requiring one re-transplant and 2 requiring two further re-transplants for recurrent disease. All 6 patients with disease recurrence in the graft were male. Recurrent disease was identified sooner after re-transplant than after the first transplant in the 6 affected patients (median 41.5; range 26–53 months vs. median 65.5; range 38–86 months: $p < 0.05$).

Discussion

In this study, recurrent sclerosing cholangitis following liver transplant occurred in 20.7% of patients following liver transplant. This figure is similar to that reported by a recent large study including centers from the Netherlands, Canada, and the USA [9]. Further recurrence occurred in 6/9 (67%) after re-transplantation for recurrent sclerosing with 2 patients requiring a third transplant. Despite a total of 14 re-transplants for recurrence, overall patient survival was similar to patients without recurrent disease. Patients with recurrence were younger at the time of the first transplant. This was also noted in a large Scandinavian multicentre study [10]. Patients with recurrent disease were also younger in a large international study including 131 patients with recurrent PSC, 42.1 vs. 47.1 years, although this was not statistically significant on multivariate analysis [9]. In our study, the majority of patients transplanted for recurrence had a further recurrence at a shorter interval compared to the first transplant. This is similar to the previous experience reported with chronic rejection, where patients transplanted for chronic rejection had frequent and earlier recurrences [11]. Patients with recurrent sclerosing cholangitis were more likely to require colectomy post-transplant, suggesting increased severity of inflammatory bowel activity in these patients.

A large number of studies have looked at factors associated with recurrent sclerosing cholangitis [4, 5, 10]. These factors include inflammatory bowel disease, cholangiocarcinoma, donor age, MELD score, and multiple episodes of acute cellular rejection. Evidence of increased inflammatory bowel activity is a consistent feature in many reports. Colectomy prior to liver transplant has been associated with a reduced risk, although this is controversial [12]. Interestingly, it has been reported that colectomy and ileostomy reduce risk compared to colectomy and pouch-anal anastomosis [13]. This difference could be related to on-going inflammation in the ileo-anal pouch [13]. It has been suggested that changes in the gut microbiota may be associated with primary sclerosing cholangitis and recurrent sclerosing cholangitis following liver transplant [14]. A recent multicentre study identified inflammation as a significant risk factor for recurrence [9]. Inflammatory conditions identified included recurrent cholangitis as an indication for transplant, acute cellular rejection, or active inflammatory bowel disease post-transplant. In our study, the fact that patients with recurrent sclerosing cholangitis required colectomy more frequently would support the hypothesis that inflammatory bowel disease post-transplant is important. The major limitation of this study is that it is from a single center. The strengths are that it is the only liver transplant program in Ireland and thus captures the vast majority of cases of primary sclerosing cholangitis needing liver transplant in this defined population. Follow-up was complete, with no patients lost to follow-up.

This study showed that recurrent sclerosing cholangitis is common, particularly in patients transplanted at a younger age. Patients with recurrence required colectomy, post-transplant, more frequently than those without, suggesting increased inflammatory bowel activity in this cohort. Patients requiring re-transplantation have a high likelihood of further recurrence. There is currently no treatment to prevent recurrence. The links between inflammatory bowel activity, colectomy, and recurrence may indicate that approaches targeting inflammatory bowel disease may be fruitful, particularly for patients requiring re-transplantation for recurrent disease.

Data Availability The data contains personal information and thus cannot be made available under GDPR regulations.

Declarations

Ethical approval The study was approved by the research ethics committee at St. Vincent's University Hospital (Ref No: RCR23010).

Competing interests The authors declare no competing interests.

References

1. Emek E, Serin A, Sahin T et al (2019) Experience in liver transplantation due to primary sclerosing cholangitis: a single center experience. Transplant Proc 51(7):2439–2441
2. Jadaun SS, Mehtani R, Hasnain A et al (2023) Good outcomes of living donor liver transplant in primary sclerosing cholangitis: an experience from North India. Hepatol Int 17(2):499–506
3. Carbone M, Kodra Y, Rocchetti A et al (2020) Primary sclerosing cholangitis: burden of disease and mortality using data from the National Rare Diseases Registry in Italy. Int J Environ Res Public Health 17(9):3095
4. Visseren T, Erler NS, Polak WG et al (2021) Recurrence of primary sclerosing cholangitis after liver transplantation - analysing the European Liver Transplant Registry and beyond. Transpl Int 34(8):1455–1467
5. Hildebrand T, Pannicke N, Dechene A et al (2016) Biliary strictures and recurrence after liver transplantation for primary sclerosing cholangitis: A retrospective multicenter analysis. Liver Transpl 22(1):42–52
6. Lazaridis KN, LaRusso NF (2016) Primary sclerosing cholangitis. N Engl J Med 375(12):1161–1170
7. Ellinghaus D (2022) How genetic risk contributes to autoimmune liver disease. Semin Immunopathol 44(4):397–410
8. Graziadei IW, Wiesner RH, Batts KP et al (1999) Recurrence of primary sclerosing cholangitis following liver transplantation. Hepatology 29(4):1050–1056
9. Visseren T, Erler NS, Heimbach JK et al (2022) Inflammatory conditions play a role in recurrence of PSC after liver transplantation: an international multicentre study. JHEP Rep 4(12):100599
10. Lindstrom L, Jorgensen KK, Boberg KM et al (2018) Risk factors and prognosis for recurrent primary sclerosing cholangitis after liver transplantation: a Nordic Multicentre Study. Scand J Gastroenterol 53(3):297–304
11. Wiesner RH, Ludwig J, van Hoek B, Krom RA (1991) Current concepts in cell-mediated hepatic allograft rejection leading to ductopenia and liver failure. Hepatology 14(4 Pt 1):721–729
12. Buchholz BM, Lykoudis PM, Ravikumar R et al (2018) Role of colectomy in preventing recurrent primary sclerosing cholangitis in liver transplant recipients. World J Gastroenterol 24(28):3171–3180
13. Trivedi PJ, Reece J, Laing RW et al (2018) The impact of ileal pouch-anal anastomosis on graft survival following liver transplantation for primary sclerosing cholangitis. Aliment Pharmacol Ther 48(3):322–332
14. Hole MJ, Jorgensen KK, Holm K et al (2023) A shared mucosal gut microbiota signature in primary sclerosing cholangitis before and after liver transplantation. Hepatology 77(3):715–728