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ORIGINAL PAPER

# Recurrence of primary sclerosing cholangitis after liver transplantation – The Hungarian experience

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**Abstract:** *Introduction:* Recurrence of primary sclerosing cholangitis (rPSC) after liver transplantation (OLT) significantly affects longterm graft survival. We aimed to evaluate the incidence of rPSC and clinical data of these patients in Hungary. *Patients and Methods:* We retrospectively analyzed data of 511 whole liver transplantations from 1995 to 2011. During the study period, 49 OLTs were performed in 43 adult patients with end-stage PSC (10%). *Results:* Out of 49 OLT, 24 cases were excluded, rPSC was diagnosed in six patients (12%). Patients with rPSC had significantly higher mortality (p = 0.009) and graft loss (p = 0.009) in comparison to patients without recurrent disease. Younger recipient age, higher donor BMI was observed in the rPSC group. One patient was diagnosed with *de novo* IBD, the remaining five patients had worsening IBD activity in the posttransplant period. PreOLT colectomy was performed in 21% of the control and none of the rPSC group. PostOLT colectomy was performed in two rPSC patients due to severe therapy resistant colitis. *Conclusions:* Recurrent PSC significantly affects long-term mortality and graft loss. Younger age at OLT, higher donor BMI and severe active IBD may be associated with PSC recurrence. PreOLT total colectomy might have protective effect against rPSC.

Keywords: disease recurrence, inflammatory bowel disease, liver transplantation, primary sclerosing cholangitis

## Introduction

Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease of unknown etiology affecting the intra- and/or extrahepatic bile ducts. Liver transplantation (OLT) is the only effective therapy for PSC patients with end-stage liver disease [1]. As a result of increasing number of patients transplanted for PSC, recurrent PSC (rPSC) has become an important condition negatively affecting graft survival [2]. The prevalence of rPSC is about 20% (5.7–59%), depending on diagnostic procedures and lengths of follow-up [2]. The diagnosis of recurrent PSC is difficult because non-anastomotic biliary stricturing is an aspecific reaction for many insults affecting the new graft [3]. To date, donor and recipient demography [4, 5], use of extended criteria donor (ECD) [6], associated active inflammatory bowel disease (IBD) [4, 6], acute rejection (ARE) [2] have been proposed to be risk factors for rPSC. In our previous study, we have reported worsening IBD activity after OLT in PSC patients [7]. In this study, we evaluated the incidence of rPSC and clinical data of PSC patients that may contribute to disease recurrence in the Hungarian liver transplant population.

## Patients and Methods

We retrospectively analyzed data of 511 whole liver transplantations from 1995 to 2011. During the study period, 49 OLTs were performed in 43 adult patients with end-stage PSC (10%). Recurrent PSC was diagnosed by the diagnostic criteria of Graziadei et al. [3]. Out of 49 OLTs, 24 cases were excluded due to hepatic artery thrombosis/stenosis (N = 8), biliary anastomotic stricture (N = 5), non-anastomotic biliary stricture within 90 days after OLT (N = 1), established ductopenic rejection (N = 3) and lacking follow-up interval mainly due to early death (N = 7). Based on radiological, histological and clinical features, six patients had recurrent PSC (rPSC) (24%), the remaining 19 patients were considered as controls (no-rPSC, 76%). We used Mayo score (Disease Activity Index) to assess the severity of ulcerative colitis (UC) before and after OLT [7].

#### Statistical analysis

We used SPSS statistics. Differences were accepted to be significant if p < 0.05.

## Results

Using strict inclusion and exclusion criteria, a total of 25 PSC patients were included in this study, 16 males and 9 females. The mean age at OLT was 34.7 years  $(\pm 11)$ , the mean MELD score was 14.2  $(\pm 5)$ . 76% (N = 19) had associated IBD preOLT. De novo IBD was diagnosed in two patients. The median duration of IBD before OLT was 112 months  $(\pm 100)$ . Clinical data of rPSC and no-rPSC patients are shown in Table I. The mean MELD score (rPSC 15 ± 5 vs. nPSC 11 ± 4.4, p = NS, cold ischemic time (CIT) (rPSC 440 ± 121 vs. nPSC 482  $\pm$  102, p = NS), warm ischemic time (WIT) (rPSC 57  $\pm$  15 vs. nPSC 51  $\pm$  13.5, p = NS), recipient gender (male recipient rPSC 50% vs. nPSC 68%, p = NS), type of perfusion (UW-Viaspan or HTK Custodiol) (HTK rPSC 50% vs. nPSC 53%, p = NS), type of OLT (piggyback or crossclamp) (crossclamp rPSC 85%, vs. nPSC 82%, p = NS), type of biliary reconstruction (duct-to-duct or hepaticojejunostomy) (hepaticojejunostomy rPSC 33% vs. nPSC 32%, p = NS), immunosuppression therapy (tacrolimus or cyclosporin) (tacrolimus rPSC 68% vs. nPSC 74%, p = NS), incidence of CMV mismatch (rPSC 17% vs. nPSC 21%, p = NS) were similar in the two groups. Patients with evidence of rPSC had significantly higher mortality and graft loss (Table I). In the rPSC group, none of the patients had colectomy prior to OLT, but two colectomies were indicated due to severe therapy-resistant colitis after OLT. On the contrary, there were four colectomies in the control group during the preOLT setting. We observed worsening activity of associated IBD in all patients with recurrent PSC.

## Discussion

Recurrent PSC has become an important condition after OLT [2]. The pathomechanism of both PSC and rPSC is unknown, therefore, no effective medical treatment is available to date [8]. Evaluating rPSC is a challenge due to differential diagnostic difficulties and limited number of patients. The incidence of rPSC was 12% in our cohort, which is similar to other reported results [5, 9].

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	rPSC, $N = 6$	No-rPSC, $N = 19$	p						
Donor age (years)	$39 \pm 14$	$35.5 \pm 11$	NS						
Donor BMI (kg/m <sup>2</sup> )	$24.8 \pm 2$	22.3 ± 2	NS						
Recipient age (years)	$27.7 \pm 7$	$37 \pm 12$	NS						
Retransplantation	2 (33%)	0 (0%)	0.009						
Patiend death	2 (33%)	0 (0%)	0.009						
Acute cellular rejection (ARE)	4 (67%)	8 (42%)	NS						
PreOLT IBD	5 (83%)	14 (73%)	NS						
Duration of IBD before OLT (years)	$3.9 \pm 6$	$11.5 \pm 8$	NS						
Time of colectomy									
PreOLT	0 (0%)	4 (21%)							
PostOLT	2 (33%)	2 (10%)	NS						
No colectomy	4 (67%)	13 (68%)							
Severity of IBD after OLT compared to preOLT*									
Worsened	5/5 (100%)	5/10 (50%)							
Improved	0/5 (0%)	1/10 (10%)	NS						
No change	0/5 (0%)	4/10 (40%)							

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\* De novo IBD was diagnosed in one patients in each group

Recently, it has clearly shown that rPSC has a major impact on graft survival [1]. In this study, both graft loss and mortality were negatively affected by rPSC. Conflicting results have been reported regarding risk factors for rPSC; however, almost none of these had been confirmed by others [2]. In this study, we analyzed the clinical data of patients with or without rPSC, and we found that rPSC patients were approximately 10 years younger than those without rPSC. Higher donor BMI in the rPSC group may be in accordance with the findings of Alabraba et al., who reported poor liver graft quality as a significant risk factor for rPSC [6]. ARE seems to be associated with recurrent PSC, but it is not clear whether rPSC is a consequence of biliary injury caused by ARE, or a common pathological immunoregulatory process is responsible for ARE and rPSC [2]. High rate of ARE (67%) was observed among rPSC patients in this study; however, it was not significant when compared with the control group (42%). The strongest association with recurrent PSC seems to be the presence of active IBD in the colon [2]. First reported by Vera et al., colectomy, before or during OLT, can prevent PSC recurrence in PSC/IBD [4]. Abberant homing of T cells and shared lymphocyte pool between the gut and the liver can explain this strong association [10]. In this study, none of the patients who developed rPSC underwent preOLT colectomy, postOLT colectomy was performed in two patients due to severe therapy resistant colitis, who developed rPSC later. On the contrary, there were four colectomies in the control group during the preOLT setting. All patients with rPSC suffered severe IBD after OLT. In conclusion, total colectomy prior to OLT or early after liver transplantation seems to have a protective effect for PSC, and also a life-threatening intervention. Recurrent PSC significantly affects long-term mortality and graft loss. Younger age at OLT, higher donor BMI and severe active IBD may be associated with PSC recurrence.

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