MINI REVIEW

Liver transplantation in PBC and PSC: Indications and disease recurrence

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Summary  Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent major indications for liver transplantation (LT). Despite the steady increase in the incidence and prevalence of PBC, the number of liver transplants for PBC has fallen in recent years, whereas the number of transplants for PSC has remained stable. Indications for LT for PBC and PSC are no different from those of other causes of chronic liver disease, apart from some disease-specific indications. PBC and PSC have more favourable outcomes after LT, compared to viral hepatitis and alcohol-associated liver disease. Numerous studies have clearly demonstrated that PBC and PSC recur after LT. The diagnosis of recurrent disease should be made on agreed criteria. The impact of recurrent disease on survival is unclear. Study of recurrent PBC and PSC may provide a better understanding of the mechanisms of these diseases in the native liver.

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Introduction

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent major indications for liver transplantation (LT) in western countries [1]. As early mortality after LT has fallen, attention has become focused on long-term outcomes, with recurrent disease emerging as a significant cause of late graft dysfunction and graft failure [2].

Here we review the available data on transplant activity, survival, current indications and characteristics of recurrent disease after LT for PBC and PSC.

Transplant activity

Cholestatic liver disease is becoming an increasingly uncommon indication for LT [3]. Data from United Network for Organ Sharing (UNOS) show that among 2931 cadaveric liver transplants in 1991, 18% (n = 530) were for cholestatic liver disease, compared with 10% (n = 472) of 4579 in 2000 and 7.8% (n = 475) of 6069 in 2008.

For PBC, the UNOS database shows that, between 1995 and 2006 [4], the absolute number of LT increased by mean 249 per year whereas the absolute number of LT performed for PBC decreased steadily by a mean of 5.4 cases per year. This contrasts with the steady increase in the reported incidence and prevalence of PBC [5]. The same trend has been observed in Europe where, of 34,811 liver transplants performed between 1988 and 2006, 3828 (11%) were performed for PBC, a five-fold reduction compared with the early days of LT [6]. Reasons for this decline in the number of trans-

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Liver transplantation in PBC and PSC

Figure 1  A comparison of the absolute number of liver transplantations among patients with PBC and PSC graphed by year. Only primary graft recipients were included. Trend lines are denoted by the thin black lines [4].

plants for PBC are not clear but may relate to a changing pattern of disease, increased rates of diagnosis, more effective treatment or other causes [4,7]. For PSC, about 250 LT are done annually, representing 5% of all LT [3]. Between 1995 and 2006, the number of transplants for PSC in North America remained stable. In Europe, 1731 patients with PSC underwent LT between 1988 and 2001, representing 8% of all liver transplant [1]. In some areas, such as the Scandinavian countries, which have a relatively low prevalence of hepatitis C and alcoholic liver disease (ALD), PSC is the leading indication for LT [8,9]. The annual number of PSC patients receiving a first liver allograft in the Nordic countries increased considerably during the 1990s [10]. According to the Nordic Liver Transplant Registry (NLTR), of the 278 patients transplanted in 2009, approximately 16% (n = 44) had PSC. The reasons for this partly are an expansion of the criteria for selection and partly earlier listing of some PSC patients [9] (Fig. 1).

Survival after Liver Transplantation

Cholestatic liver diseases have more favourable outcomes after LT as compared to viral hepatitis and alcoholic-associated liver disease [11]. An analysis of the ELTR in 2003 of 2959 patients with PBC showed a 1-, 5-, and 10-year patient and graft survival of 83, 77 and 69% and 79, 71 and 64%, respectively. The 1-, 5-, and 10-year patient and graft survival in 1731 patients with PSC was 83, 75% and 66% and 78, 65 and 54%, respectively [1].

In 2010, Kashyap reported a retrospective analysis of the UNOS database for patients transplanted between February 2002 and October 2006 for AIH, PSC, and PBC [12]. For PBC, the 1-, 3-, and 5-year patient survival among living donor (LD) and deceased donor (DD) was 92.8%, 90.1% and 86.4% and 89.6%, 87% and 85.1%, respectively. The 1-, 3-, and 5-year graft survival among LDs and DDs were 85.6%, 80.9% and 77.4% and 85.2%, 82.5%, and 80.7%, respectively. For PSC, the 1-, 3-, and 5-year patient survival among LDs and DDs for PSCs was 97.2, 95.4 and 95.4% and 93, 87.5 and 87.5%, respectively. The 1-, 3-, and 5-year graft survival among LD and DD for PSC was 89.6, 87.1% and 87.1% and 87, 79.7 and 79.2%, respectively (Table 1).

Table 1  Patient survival after liver transplantation for PBC and PSC.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Registry</th>
<th>1 year (%)</th>
<th>3 year (%)</th>
<th>5 year (%)</th>
<th>10 year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBC</td>
<td>UNOS (LD)</td>
<td>92.8</td>
<td>90.1</td>
<td>86.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UNOS (DD)</td>
<td>89.6</td>
<td>87</td>
<td>85.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NLTR</td>
<td>93.7</td>
<td></td>
<td>88.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ELTR</td>
<td>83</td>
<td></td>
<td>77</td>
<td>69</td>
</tr>
<tr>
<td>PSC</td>
<td>UNOS (LD)</td>
<td>97.2</td>
<td>95.4</td>
<td>95.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UNOS (DD)</td>
<td>93</td>
<td>87.5</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NLTR</td>
<td>94</td>
<td></td>
<td>83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ELTR</td>
<td>83</td>
<td></td>
<td>75</td>
<td>66</td>
</tr>
</tbody>
</table>


Indication and timing of Liver Transplantation

Primary biliary cirrhosis

Indications for LT for PBC are not different from those of other etiologies: an unacceptable quality of life because of liver disease or an anticipated survival of 1 year or less. In 1999, Christensen showed that the optimal time for transplantation in PBC (defined as the point when the probability of survival after transplantation is greater than the probability of survival without transplantation) is when the serum bilirubin is around 10 mg/dl (170 mmol/l) [13]. Referral to a LT unit should be considered when the bilirubin reaches 6 mg/dL (103 mmol/L), the Mayo risk score is ≥ 7.8, and the MELD score is > 12 [14]. Severe, treatment-resistant pruritus or severe hepatic encephalopathy may also merit consideration for transplantation [15]. Fatigue is one of the principal factors contributing to the functional impairment in the quality of life but is not associated with the histological stage of disease [16–19]. The pathophysiology remains poorly understood, although there are several hypothesized mechanisms including structural cerebral abnormalities, autonomic nervous system dysfunction, cytokines and adipokines, progesterone metabolites, psychological elements, and variable degrees of peripheral muscle mitochondrial dysfunction [19–24]. Treatable causes of fatigue such as depression,
anemia, thyroid disease, celiac disease, Addison’s disease, and the unwanted effects of drugs such as sleeping tablets and antihistamines, must be excluded. Björnsson [23] analysed the impact of fatigue on prognosis in PBC and found that high levels of fatigue at baseline were a predictor of risk of liver-related mortality and need for transplantation. Similar findings were reported by Jones [26], who showed that, over 9 years of follow-up, survival was significantly lower in PBC patients with higher fatigue scores. Several drugs have been evaluated but only modafinil and methotrexate have shown some favorable effects on reducing fatigue [23—33]. Chronic fatigue itself is not an indication for transplantation as available evidence suggests that it may not improved by this procedure [34].

The origin of pruritus in chronic cholestasis is not yet fully understood [35]. Recently, novel itch-specific neuronal pathways, itch mediators and their relevant receptors have been identified [35]. Cholestyramine is widely used as first-line treatment, although the evidence to support this is limited. Rifampicin at a daily dose up to 600 mg is effective in about one third [36,37] although may be hepatotoxic. Other possible therapies include glucocorticoids, sertraline, and opiate antagonists [38]. Plasmapheresis MARS or external biliary drainage may be successful. LT remains the last resort for intractable pruritus [6].

Primary sclerosing cholangitis

LT for those with PSC is indicated with liver failure with complications similar to those for end-stage liver disease caused by other aetiologies. Timing of transplantation is difficult to predict because of the variability of the course of the disease, the risk of development of malignant disorders in the liver/biliary tract, recurrent bacterial infections in the biliary tract and the impact of inflammatory bowel disease (IBD).

Several prognostic models for PSC patients have been published [39—41]. The Mayo score, including age, bilirubin, serum AST and albumin, and history of variceal bleeding as prognostic parameters, provides more valid survival information than the Child-Pugh Classification [40]. However, the AASLD guidelines 2010 advised against the use of prognostic models for predicting clinical outcomes in an individual patient as no consensus exists regarding the optimal model [42]. Therefore, the decision to list a PSC patient for LT should include clinical signs and symptoms, biochemical parameters, the risk of hepatobiliary malignancy, and in some patients the status of the concomitant IBD. Other indications for patients with PSC include intractable pruritus, recurrent bacterial cholangitis and, only very rarely, cholangiocarcinoma (CCA).

Pruritus, as in PBC, can be severe and disabling. In these patients, worsening of pruritus, along with rising levels of serum bilirubin, should prompt evaluation in order to exclude the presence of a dominant stricture (DS). If a DS is present endoscopic treatment may alleviate the symptoms, otherwise the management of pruritus should be similar to that of patients with PBC [42]. DSs occur in up to 50% of PSC patients and may lead to biliary obstruction and severe cholestasis [43—45], resulting in bacterial colonization and secondary cholangitis. Some patients respond to therapeutic drainage of the obstruction plus antibiotics, but sometimes patients with recurrent bacterial cholangitis may require prophylactic long-term antibiotics. Rarely, recurrent cholangitis can be so severe as to become the primary indication for OLT [46].

PSC patients are at high risk of CCA development. This is often detected late, when it is no longer resectable [47,48]. No effective screening strategy has been validated to date. Medical management with stenting, radiation therapy, or conventional chemotherapy and surgery are largely ineffective and the outcome is generally poor, with a median survival of <1 year [49,50]. LT has been tried, for both resectable and unresectable tumors [51], but the dismal outcomes, with survival rates of 22%—77% at 1 year and 0%—39% at 3 years [52—55] mean that, for most centres, CCA is a contra-indication. However, innovative approaches using a combination of neoadjuvant chemotherapy, irradiation and transplantation hold some promise for a highly selected subgroup [56—59]. In 2006, the Mayo Clinic reported satisfactory results in highly selected patients transplanted for CCA: LT was performed as part of a neoadjuvant chemo-irradiation protocol and when pretransplant staging laparotomy demonstrates no evidence of metastatic disease in regional lymph nodes or elsewhere [60]. However, this approach is currently limited to a few centers and has not been well replicated elsewhere. These good results may be in part explained by strictly patient selection; furthermore, approximately half of these patients did not have pathologic confirmation of disease prior to administration of neoadjuvant therapy. The Mayo Clinic data also show better survival for patients with CCA arising in PSC than for patients with de novo CCA, probably due to the earlier detection.

In 2009, the MELD Exception Study Group [61] stated that the available data justify priority for PSC patients with unresectable CCA with no evidence of metastatic disease in regional lymph nodes or elsewhere, enrolled in clinical trials. In the United States, an appealed MELD score may be granted via a regional review board appeal process to help prioritize these patients.

IBD is present in up to 90% of those with PSC [45,62,63]. There is no correlation between bowel activity and stage of liver disease [64]. IBD in the setting of PSC differs from IBD in the absence of PSC in several features in that there is a greater chance of an extensive colitis, rectal sparing, backwash ileitis, a mild or quiescent disease course, increased risk of colorectal neoplasia, increased risk of pouchitis in patients with ileal pouch anal anastomosis, and increased risk of peristomal varices in patients with ileostomy [42,65].

The course of IBD after LT seems to be uncertain, and the impact of immunosuppressive therapy and other risk factors associated with these conditions remain controversial. Several studies have demonstrated increased exacerbations of IBD despite postransplant immunosuppressive maintenance therapy [66—70], while others have shown an unchanged or improved course [71—73]. Comparison of studies is difficult as the methods used for assessment of IBD disease activity and the immunosuppression regimen after LT vary.

PSC transplant recipients with concomitant IBD are more likely to develop colon cancer, with a cumulative risk of 14% at 5 years and 17% at 10 years after LT [74,75]. Therefore, routine surveillance colonoscopy is recommended. UDCA may be associated with a reduced risk of colon cancer,
Table 2  Recurrent rate of PBC after liver transplantation.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Cohort size</th>
<th>Recurrence rate (%)</th>
<th>Median time to recurrence (months)</th>
<th>Risk factors for recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuberger et al. [94] 1982–2002 485</td>
<td>23</td>
<td>62 (with Tac) 123 (with CyA)</td>
<td>Tac-based immunosuppression (OR = 2.73) Younger age; cold ischemic time</td>
<td></td>
</tr>
<tr>
<td>Abu-Elmagd et al. [88] 1982–1996 421</td>
<td>11</td>
<td>66</td>
<td>Tac-based immunosuppression (P = 0.001)</td>
<td></td>
</tr>
<tr>
<td>Charatcharoenwitthaya et al. [87] 1985–2002 164</td>
<td>34</td>
<td>42</td>
<td>Tac-based immunosuppression (P = 0.11) HLA recipient B48 (P = 0.01)</td>
<td></td>
</tr>
<tr>
<td>Sanchez et al. [89] 1985–1999 169</td>
<td>10.9</td>
<td>58 (CyA ± Aza, Pred) 60 (CyA ± MMF, Pred) 24 (Tac ± MMF, Pred)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Manousou et al. [110] 1988–2008 138</td>
<td>26</td>
<td>74 (with Aza) 31 (if never on Aza)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Jacob et al. [93] 1989–2006 115</td>
<td>14</td>
<td>61</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

Data from centers with a minimum of 100 patients transplanted for PBC. Tac: Tacrolimus; CyA: Ciclosporin; Aza: Azathioprine; MMF: Mycophenolate Mofetil; Pred: prednisolone; ND: not determined.

Although neither has been proven to be effective in this situation. For recipients who develop a refractory disease and/or colorectal dysplasia or carcinoma, proctocolectomy with ileal pouch anal anastomosis may be the treatment of choice but there is a higher risk of pouchitis and neoplasia [76–80].

Concomitant severe IBD in patients with advanced PSC requiring LT represent an important challenge. Colectomy prior to LT may lead to severe hepatic decompensation, rendering the patient unavailable for LT or at least increasing the risk of the transplantation. In some centers, simultaneous LT and colectomy is preferred in these patients [74,81].

Recurrence of disease after transplantation

Primary biliary cirrhosis

Recurrent PBC (rPBC) was first reported in 1982 [82], and despite initial controversy, is now widely accepted in both cadaveric and LD grafts [83–85]. The reported prevalence rates range from 0 to 35% [86–93], and this wide variability may be due different approaches by transplant units to the use of protocol biopsies and to the variable adherence to histological criteria used in different centers. Data from our center in the period 1982–2002, when protocol biopsies were routinely used (until 1997), show a rate of rPBC of 23% [86]. The reported incidence rate is 21–37% and 43% at 10 and 15 years, respectively [86,94,95]. The median time to rPBC ranges between 3 and 5.5 years [88,89,91,95].

Many patients with rPBC have normal or clinically insignificant elevations of liver function tests at time of diagnosis [88,89,96–98]; serum AMA is not a marker for recurrence [97,99]. The gold standard for the diagnosis of rPBC is the histological finding of granulomatous cholangitis [90–92,94,97–99] or florid duct lesion, which are present in approximately 60% of initial diagnostic liver biopsy [88]. However, less specific inflammatory features, such as dense lymphoplasmacytic or plasma cell infiltrates within the portal tracts, may correlate with subsequent disease recurrence [92,97,100,101]. Also, it is important differentiate between recurrent disease and other causes of bile-duct damage in the allograft, such as acute or chronic allograft rejection, ischemia, infection, or drug damage, though frequently it may be difficult or indeed impossible.

Risk factors for rPBC remain poorly understood. The impact of donor and recipient age remain controversial. Recently, Charatcharoenwitthaya [87] suggested a relationship between older recipient age at LT and a higher rate of rPBC, in contrast with previous findings [86,88]. In a series from our unit [86], we failed to identify such an effect.

The relationship between rPBC and warm and cold ischemic time has been suggested but with conflicting results [86,88].

Tacrolimus-based immunosuppression correlates with an increased risk of rPBC in patients undergoing deceased [86,87,94,95,101,102] and LD LT [103], with a reduced time to recurrence [94], compared with ciclosporin. In a series from our unit, tacrolimus as initial immunosuppression was associated with recurrence on multivariate analysis (HR
Table 3  Recurrent rate of PSC after Liver Transplantation.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Cohort size</th>
<th>Recurrence rate</th>
<th>Median time to recurrence (months)</th>
<th>Risk factors for recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graziadei et al. [120] 1985—1996 150</td>
<td>20% 8.3% (with both histological and cholangiographic features)</td>
<td>14 (with cholangiographic criteria) 46 (with histologic criteria)</td>
<td>Associated IBD ($P = \text{n.s.}$)</td>
<td></td>
</tr>
<tr>
<td>Vera et al. [81] 1986—2000 152</td>
<td>37% (16% based on histology and 21% based on radiology)</td>
<td>36</td>
<td>Male sex (RR 1.2); intact colon before LT (RR 8.7)</td>
<td></td>
</tr>
<tr>
<td>Campsen et al. [121] 1988—2006 130</td>
<td>17%</td>
<td>ND</td>
<td>CCA prior to OLT (RR 3.77)</td>
<td></td>
</tr>
<tr>
<td>Alabraba et al. [122] 1986—2006 230</td>
<td>23.5%</td>
<td>4.6</td>
<td>Time to colectomy ($P = 0.028$) Type of colectomy ($P = 0.024$) EDC graft ($P = 0.046$)</td>
<td></td>
</tr>
</tbody>
</table>

Data from centers with a minimum of 100 patients transplanted for PSC. IBD: Inflammatory bowel disease; EDC: Extended donor criteria.

2.3); the median time to recurrence was 10.2 years for patients taking cyclosporine compared with 5.1 years for those taking tacrolimus [94]. There is not a clear explanation for these findings, but they could be related to the beneficial effect that cyclosporine has shown to have in patients with PBC [104—108]. Different conclusions were reached by Gautam [109] in a meta-analysis published in 2006, evaluating 16 studies and 1241 patients that suggested no difference between ciclosporin and tacrolimus in terms of recurrence. Similar finding were recently reported by Manousou [110] who found that neither ciclosporin nor tacrolimus alone had any impact on rPBC, but ciclosporin in combination with azathioprine resulted in the lowest rates of rPBC. However, apart from the difference in terms of recurrence rate, there is no impact on survival with different immunosuppressive drugs [87,95]. No other studies have found a clear correlation between rPBC and azathioprine [89—91,94,111], corticosteroids [86,89,90,112] and mycophenolate mofetil [89].

There is increasing evidence for a genetic predisposition for PBC, but the effect of HLA matching on disease recurrence after transplant remains controversial. In 2007, Morioka [113] suggested that a lower number of HLA mismatches between donor and recipient was an independent risk factor for disease recurrence following LDLT. A relationship between HLA-mismatching, particularly DR-locus mismatch, and rPBC was reported with DDLT too [114,115]. In contrast, many other studies failed to observe significant degrees of mismatching between recipient and donor HLA profiles in DDLT [87—89,91,110] and LDLT [116] (Table 2).

Recurrence of disease after OLT for PBC has little impact on patient and graft survival [95,114]. However, with a longer follow-up, it may be possible detect the impact of rPBC on long-term survival [2,110]. In our series published in 2008 [2], the proportion of grafts lost to recurrent disease was 5.4% of all grafts lost in those transplanted for PBC, with a median time from recurrent disease of 7.8 years.

Because of the possible beneficial effect of ursodeoxycholic acid (UDCA) in slowing the progression of PBC pretransplant, it would be sensible to offer it to those with evidence of rPBC. However, the assessment of drug efficacy is challenging as many patients have normal or near normal liver tests at diagnosis; the current data, which are limited suggest that UDCA does not seems to influence patient and graft survival [87].

Primary sclerosing cholangitis

rPSC must be distinguished from secondary sclerosing cholangitis, which may be associated with ischemia of the biliary tree, hepatic artery thrombosis, acute or chronic rejection, ABO mismatch and infection (bacterial or viral).

Recurrence of PSC was first suggested by Lerut [117] in 1988 and was followed by other reports [118,119]. The estimated frequency of recurrence depends on both the length of follow-up, since the recurrence rate seems to increase with time, and on the follow-up protocols [81]. PSC recurrence occurs in 20%—25% of recipients of DDs, 5—10 years since transplant [120—122]. Our unit recently published an analysis of 230 recipients with a median follow-up time of 82.5 months and found a rate of rPSC of 23.5%, with a time to developing rPSC of 4.1 years [122]. With living donors, data on prevalence of recurrence, apart from some sporadic small-size report from far East [123—126], are lacking.

The diagnosis of recurrent disease can be difficult. Graziadei proposed the Mayo clinic criteria in 1999 [120] which require a confirmed diagnosis of PSC prior to LT; cholangiography showing nonanastomotic biliary strictures of the intrahepatic and/or extrahepatic biliary tree with beading and irregularity occurring more than 90 days posttransplan-
tation or liver histology revealing fibrous cholangitis and/or fibro-obliterrative lesions of large bile ducts, with or without ductopenia or biliary cirrhosis. Alternative causes of nonanastomotic biliary stricture must be excluded.

Risk factors for rPSC include active IBD with a need for corticosteroid therapy, presence of an intact colon [81,122], male sex, presence of CCA prior to LT, history of acute cellular rejection [121,127,128], and human leukocyte antigen DRB1*08 (HLA-DRB1*08) [127]. Moreover, in our series, it was found that extended donor criteria (EDC) grafts are from parental donors might increase the risk of rPSC [122]. Regarding LDLT, there are preliminary data to support that using grafts from parental donors might increase the risk of rPSC [129] (Table 3).

The impact of rPSC on graft survival is a controversial issue. Maheshwari et al. [130] in 2004 analyzed 3309 patients from the UNOS database transplanted for PSC and found a higher retransplantation rate and a lower survival, comparing with PBC recipients from the same study population, and this became apparent 7 year after transplantation. These data have been confirmed elsewhere [2,121,131], but other studies report no effect [128].

There is no established medical therapy for rPSC and there are no established preventive therapies in the non-transplant setting. The efficacy of UDCA has not yet been demonstrated but its use is associated with improvement of liver tests but whether this translates into a better clinical outcome is uncertain. However, its use may be associated with a reduced risk of colon cancer. Symptomatic treatment of pruritus and interventional cholangiographic treatment of biliary strictures should be considered when DSs are present but this is rarely present or achievable in practice.

Conclusion

PBC and PSC are major indication for LT. Numerous studies have clearly demonstrated recurrence after liver transplant but the underlying pathological mechanism are poorly understood. The diagnosis of recurrent disease should be made on agreed criteria. The impact of recurrent disease on survival is unclear. No effective treatment is available at the present for both diseases, apart from the endoscopic management of bile duct strictures in patients with rPSC.

Further studies are needed to better understand the natural history of rPBC and PSC posttransplant and to define the risk factors in order to provide insight into the mechanisms of these autoimmune diseases in the native liver.

Disclosure of interest

The authors have no conflicts of interest to disclose.

References


Liver transplantation in PBC and PSC


