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REVIEW

Recurrence of autoimmune liver diseases after liver transplantation

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Abstract

Liver transplantation (LT) is the most effective treatment modality for end stage liver disease caused by many etiologies including autoimmune processes. That said, the need for transplantation for autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC), but not for primary sclerosing cholangitis (PSC), has decreased over the years due to the availability of effective medical treatment. Autoimmune liver diseases have superior transplant outcomes than those of other etiologies. While AIH and PBC can recur after LT, recurrence is of limited clinical significance in most, but not all cases. Recurrent PSC, however, often progresses over years to a stage requiring re-transplantation. The exact incidence and the predisposing factors of disease recurrence remain debated. Better understanding of the pathogenesis and the risk factors of recurrent autoimmune liver diseases is required to develop preventive measures. In this review, we discuss the current knowledge of incidence, diagnosis, risk factors, clinical course, and treatment of recurrent autoimmune liver disease (AIH, PBC, PSC) following LT.

Key words: Recurrent autoimmune hepatitis; Recurrent primary biliary cirrhosis; Recurrent primary sclerosing cholangitis; Liver transplantation; Immunosuppression; Risk factors; Outcomes; Autoimmune liver diseases

Core tip: There is compelling evidence that autoimmune liver disease recur after liver transplantation, with incidence rates ranging from 10% to 50%. Recurrent autoimmune hepatitis and primary biliary cirrhosis do rarely impair patient and graft survival, but may require changing the immunosuppressive regimen, using corticosteroids or adding ursodeoxycholic acid, respectively. In a proportion of patients, recurrent primary sclerosing cholangitis progresses over years to a stage requiring re-transplantation.

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INTRODUCTION

Liver transplantation (LT) remains the most effective treatment for patients with end stages of autoimmune liver diseases [autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)]. Overall, autoimmune liver diseases account for approximately one quarter of LT performed in Europe and the United States[1], with a 5-year post-LT survival rate of around 85%[2]. Despite these excellent outcomes, autoimmune liver diseases recur not infrequently in the allograft. The exact rates of recurrence are somewhat obscured by inconsistency in diagnostic approach and criteria employed. Since recurrent autoimmune liver disease may be asymptomatic and, at least early on, occur in the absence of biochemical or clinical abnormalities, centers that use protocol biopsies will report greater rates of recurrence. In addition, it has been reported that AIH in the graft can occur *de novo*, *i.e.*, after LT for non-autoimmune liver disorders[2,3].

In this review, we discuss the incidence, risk factors and newer developments in the understanding of the diagnosis, clinical course, and treatment of recurrent autoimmune liver diseases after LT. *De novo* autoimmune liver disease in the graft after LT is beyond the scope of this review.

SEARCH STRATEGY

This review is based on a systematic literature search in PubMed, supplemented by the authors' own clinical experience. Specifically, the following search terms were used: "liver transplantation", "recurrence", "autoimmune liver diseases", "AIH", "primary sclerosing cholangitis", "primary biliary cirrhosis" and "incidence". We also searched manually for articles of interest referenced in publications identified in the PubMed search.

PSC

PSC is a chronic progressive inflammatory disease affecting the extra- and/or intra-hepatic bile ducts that often progresses with biliary stricturing and fibrosis within a decade from diagnosis to cirrhosis, recurrent cholangitis and/or cholangiocarcinoma (CCA). PSC is the fourth leading diagnosis for LT in the United States[4]. Approximately 4% to 5% of adult LT in the western world are performed for PSC[5].

PSC is believed to be an autoimmune disease associated with certain immunologic factors including certain subtypes of human leukocyte antigens (HLA)[6] and the presence of antineutrophil cytoplasmic antibodies[7]. There is a strong association of PSC with inflammatory bowel disease of the colon (IBD; see below). In colonic IBD, gut bacteria and endotoxins may translocate across a chronically inflamed and more permeable colonic mucosa into the portal circulation. This may subsequently lead to activation of Kupffer cells and the release of pro-inflammatory cytokines mediating biliary tree inflammation[8-10]. Activated intestinal lymphocytes, which are released into the enterohepatic circulation and may persist as memory cells, may also be involved in generating hepatic inflammation[11]. Increased hepatic expression of adhesion molecules (vascular adhesion protein-1 and mucosal addressin cell adhesion molecule) in PSC contribute to recruitment of immune cells into the tissue[12,13]. It has been hypothesized that persistence of such aberrant homing of lymphocytes from the intestine into the liver may contribute to disease recurrence in the graft[13].

PSC develops in approximately 5% of patients with IBD. Conversely, up to 85% of patients with PSC ultimately develop IBD[14]. Prospective studies in children with PSC and IBD suggest that the progression of the liver disease is independent of the severity of IBD[15,16]. Studies in adult populations have yielded conflicting results regarding potential interaction between disease severity of IBD and PSC both, pre- and post-LT. Marelli *et al*[17] reported that PSC patients needing LT have often a relative benign clinical course of ulcerative colitis (UC). Similarly, Navaneethan *et al*[18] reported that UC tends to remain in remission or to improve after LT. On the contrary, Moncrief *et al*[19] found that the activity of IBD, both clinically and histologically, increases after LT.

Patents with PSC are at increased risk of developing hepatobiliary (CCA/gallbladder carcinoma) and colorectal neoplasias[20,21]. Since there is no effective medical therapy available for PSC, LT is the sole potentially curative therapeutic option for advanced disease. LT for PSC is associated with an excellent long term survival of more than 80% and 70% at 5 and 10 years, respectively[22,23]. Post LT, the disease recurs in about 20% (5%-50%) with a median time from LT to diagnosis of recurrence usually ranging from 3 to 5 years, depending on the type and timing of diagnostic procedures employed during follow-up[24-27].

DIAGNOSIS OF RECURRENT PSC

Diagnosing recurrent PSC is often challenging due to difficulty in distinguishing it from other conditions potentially leading to non-anastomotic biliary strictures. This includes ischemia related biliary insults associated with ischemia/reperfusion injury, hepatic artery thrombosis and/or chronic ductopenic rejection, bacterial or fungal cholangitis, and ABO incompatibility between the donor and the recipient[1,28,29]. The diagnosis largely relies on radiological demonstration of diffuse, non-anastomotic biliary strictures in a patient transplanted for PSC, provided any other of the aforementioned etiologies for diffuse, non-anastomotic biliary stricturing has been excluded. The diagnosis may be further supported by

Table 1 Mayo clinic criteria for recurrent primary sclerosing cholangitis after liver transplantation[12]

Inclusion criteria
Confirmed diagnosis of PSC before LT
Cholangiography showing non-anastomotic intra- and/or extra-hepatic biliary strictures with beading and irregularities of bile ducts at least 90 d after LT and/or
Histopathological findings of fibrous cholangitis and/or fibro-obliterative lesions
Exclusion criteria
Hepatic artery thrombosis or stenosis
Chronic ductopenic rejection
Anastomotic and non-anastomotic strictures before day 90 after LT
ABO incompatible LT

LT: Liver transplantation; PSC: Primary sclerosing cholangitis.

liver biopsy, but established fibro-obliterative bile duct lesion or periductal concentric fibrosis are seen in only a minority of patients with PSC recurrence[30]. Most commonly used criteria for the diagnosis of recurrent PSC after LT are the so called Mayo clinic criteria originally proposed by Graziadei *et al*[23] (Table 1). These criteria are conservative and, as mentioned above, require to rule out all aforementioned other causes for non-anastomotic biliary strictures in the graft.

RISK FACTORS FOR PSC RECURRENCE

Numerous risk factors for the PSC recurrence have been proposed including the following: Certain HLA associations with recipient or donor (HLA-DRB1*08, HLA DR52)[31,32]; male recipient[33], as with PSC in general, and a recipient-donor gender mismatch[29]; recipient age - albeit inconsistently (older or younger)[32,34]; an intact colon in the recipient prior to transplantation[33], and the presence of UC after LT[35]; use of extended donor criteria grafts[26]; acute cellular rejection (ACR)[32], steroid-resistant ACR[32,36] or use of OKT3[4]; maintenance of steroid therapy for UC for more than 3 mo[35]; the presence of CCA prior to LT[25]; and cytomegalovirus infection in the recipient[32,37]. A high rate of recurrence has been reported in recipients of grafts from first-degree living related donors, with PSC recurrence being observed in two relatively small single center series from Japan in 55% and 59% of recipients, respectively[38,39]. Standard immunosuppressive agents either cyclosporine or tacrolimus did not seem to affect PSC recurrence, neither did post-transplant (prophylactic) use of ursodeoxycholic acid (UDCA)[4,26].

Alabraba *et al*[27] observed in a large cohort (n = 230) that PSC recurred less frequently (P = 0.028) in patients who had undergone colectomy before or at the time of LT compared to patients with an intact colon post-LT. This seems to indicate that a residual (inflamed) colon is linked to PSC recurrence in the graft in a proportion of patients. Regardless of whether this association is related to an immune mechanism or a toxic effect[4,40], it underscores the importance of adequate control of colonic IBD post LT.

Several of the aforementioned associations, however, seem spurious such as the contradictory observations on recipient age. Others seem questionable, in particular, those linking PSC recurrence to risk factors for graft ischemia and to rejection (ACR, steroid resistant ACR, OKT3 use). These events predispose to ischemic type and/or alloimmune type non-anastomotic biliary stricturing, respectively, which casts doubt on the correct diagnosis of recurrent PSC in these cases. In addition, all reported associations are derived from retrospective analyses of relatively small single center series with all their inherent limitations. Before accepting them and drawing firm conclusions, they would need to be confirmed, ideally in a prospective manner, in independent patient cohorts.

MANAGEMENT OF RECURRENT PSC

There is no treatment of proven efficacy for recurrent PSC after LT. Prophylaxis and/or treatment with UDCA is practiced in many centers because it improves the liver biochemical profile, but whether its use affects outcomes remains uncertain[41,42]. In fact, the latter seems rather questionable, given the fact that UDCA does not benefit outcomes of PSC in the non-transplant setting[41]. That said, UDCA lowers the risk of developing colon dysplasia leading to colon adenomas and carcinomas in patients with UC and PSC; its use may be justified for that reason in this patient population also post LT[43]. In the absence of any effective medical prophylaxis/therapy of PSC recurrence post LT, symptomatic treatment of biliary strictures and their complications, such as cholangitis or choledocholithiasis, remains the only option. As in the non-transplant setting, dominant strictures may be managed temporarily by percutaneous or endoscopic means, but many patients with PSC recurrence post LT will eventually have to be considered for re-transplantation.

CLINICAL IMPACT OF RECURRENT PSC

Short and mid-term patient and graft survival do not appear to be impaired by PSC recurrence. However, it is now well recognized that PSC recurrence can affect graft outcome and may increase the need for re-transplantation and perhaps also impairs patient survival with longer patient follow-up[27,41,44]. Thus, the need for re-transplantation for graft failure secondary to recurrent disease is relevantly higher in PSC (12.4%) than in PBC (1%-5%)[45].

PBC

PBC is an immune mediated chronic cholestatic liver disease predominantly affecting middle aged women. It is characterized by circulating anti-mitochondrial antibodies (AMA) and progressive immune-mediated destruction of mid-sized intrahepatic bile ducts (intra-

Table 2 Diagnostic criteria for recurrent primary biliary cirrhosis after liver transplantation[49]

Confirmed diagnosis of PBC in the explant histology
Characteristic histologic features[1]
Lymphoplasmacytic portal infiltrate
Lymphoid aggregates
Epithelioid granulomas
Evidence of bile duct injury
Persistence of AMA or AMA-M2
Exclusion of other causes of graft dysfunction
Acute and chronic rejection
Graft *vs* host disease
Bile flow impairment or cholangitis
Vascular complications
Viral hepatitis
Drug induced hepatitis

[1]Definite recurrent PBC: 3 of 4 portal tract lesions are observed; Probable recurrent PBC: 2 of 4 portal tract lesions are observed. PBC: Primary biliary cirrhosis; AMA: Anti-mitochondrial antibodies.

lobular bile ductules). Over a decade or more, the persistent immune attack leads to bile duct paucity, fibrosis, and, ultimately, cirrhosis with its associated morbidity and mortality[46]. LT is the sole effective treatment option for end-stage PBC.

PBC is the third most common indication for LT (9%) in the European Liver Transplant Registry, after virus (hepatitis C and B) and alcohol related cirrhosis[47], and one of the top six indications for LT in the United States[2,48]. Of note, however, the number of patients transplanted and even that wait-listed for PBC has markedly decreased during more recent periods[49,50]. Moreover, PBC related deaths have decreased in both men and women over the last few decades. This decreased mortality/need for transplantation seems to be attributable to increased use of UDCA, which has been shown to slow down histological progression to cirrhosis and to improve overall and transplant-free survival[51].

Fatigue (85%) and pruritus (70%) are leading symptoms of PBC patients[52,53]. Environmental factors, genetic predispositions, and molecular mimicry triggering autoimmunity have all been implicated in the pathogenesis PBC, but their relative significance and the exact patho-mechanism(s) involved remain controversial[54]. PBC is considered one of "the best" indications for LT with 1, 5, and 10-year survival rates of 86%, 80% and 72%, respectively, according to the European Liver Transplant Registry[47]. The first report of PBC recurrence after LT was published in 1982[55]. Reported disease recurrence rates range from 10% to 50%[24,56-58], during a median time of 3-5.5 years of follow-up post LT[59]. However, the exact frequency of recurrent PBC, its time course, and its effect on patient and graft survival remain ill-defined, as routine follow-up with protocol liver biopsy is not standard for PBC patients in most LT programs.

DIAGNOSIS OF RECURRENT PBC

The diagnosis of recurrent PBC can be difficult, as the diagnostic criteria used in the pre-transplant setting are obscured post LT by the following: Only a minority (12%) of patients with recurrent PBC report potentially disease-related, but typically non-specific symptoms[60]. AMA, the serologic hallmark of PBC, and elevated serum immunoglobulins M remain present beyond LT and therefore lose their diagnostic value for disease recurrence. This also implies that the (auto)immune mechanism(s) driving PBC are not affected by replacing the liver, nor by post-LT immunosuppression[2]. A cholestatic liver enzyme pattern with elevated alkaline phosphatase and gamma glutamyl transpeptidase is entirely non-specific after LT and found in many other common conditions including acute or chronic rejection, viral infections, and bile duct or hepatic vein/artery pathology, to name just a few. Even the hallmark histologic feature of PBC in the non-transplant setting, immune mediated injury of small bile ducts and bile duct paucity maybe mimicked post LT by acute and chronic rejection. Only if these typical histologic findings co-occur in the presence of biliary epitheloid granulomas the diagnosis can be regarded as histologically proven. The following criteria first described by Hubscher *et al*[61], have been widely adopted to diagnose recurrent PBC after LT (Table 2).

RISK FACTORS FOR RECURRENT PBC

A potential impact on the development of recurrent PBC of donor and recipient age, duration of cold and warm ischemia, number of HLA mismatches, and immunosuppressive regimen post LT remain controversial. Morioka *et al*[62] reported that little donor/recipient HLA mismatch was an independent risk factor for disease recurrence following living related donor LT. Two other large studies have shown an association between HLA-mismatches, especially in the DR-locus, and recurrent PBC also in deceased donor LT[63,64]. In contrast, Jacob *et al*[65] found that patients without a HLA-B mismatch were at higher risk of disease recurrence.

Several, but not all analyses (mostly retrospective, single center series) reported that, when compared with cyclosporine, tacrolimus-based immunosuppression is associated with a higher frequency and shorter time to PBC recurrence post LT[50,66,67]. However, the large meta-analysis by Gautam *et al*[24] evaluating 16 studies summarizing a total of 1241 patients, failed to confirm that tacrolimus and cyclosporine based immunosuppressive regimens are differentially associated with PBC recurrence. An appropriately sized, prospective, randomized control trial would be required to definitely resolve this issue. Such a study, however, seems unlikely to be ever conducted for various reasons not the least of which being the rarity of PBC as an indication for LT

these days.

MANAGEMENT OF RECURRENT PBC

The Mayo group was the first to report that treatment with UDCA normalizes liver enzymes in about half of the patients with PBC recurrence, but in only one fifth of untreated patients[68]. Despite that, UDCA treatment was not shown to be associated with significant changes in liver histology, patient and graft survival[63]. Whether UDCA affects the course of recurrent PBC post LT remains, therefore, somewhat unclear, although a beneficial effect might be anticipated given its well documented effects on disease progression and transplant-free survival in the non-transplant setting[69,70].

Moreover, the preliminary results of a French multicenter study presented in 2015 at the International Liver Meeting of the European Association for the Study of the Liver suggested a beneficial effect of UDCA in preventing PBC recurrence post LT[71]. The authors reported on 90 PBC LT recipients followed for an average of 12 years, 19 of which were on UDCA since LT. Recurrence was diagnosed in 48 (53%) patients. In both, univariate and multivariate Cox models, use of UDCA was the only factor that significantly affected the risk of PBC recurrence (HR = 0.31, 95%CI: 0.11-0.85). While this may suggest a role for UDCA treatment as prophylaxis for PBC recurrence after LT, neither disease recurrence itself, nor UDCA prophylaxis did affect post-LT patent/graft survival.

That said, and given the ever increasing survival rate and life-expectancy after LT, PBC recurrence might become clinically relevant in the future. Thus, a proportion of patients may live long enough to develop clinically relevant disease in the graft. While the French study supports the use of UDCA as prophylaxis for PBC recurrence after LT, its final publication, and confirmation in independent patient cohorts, ideally with hard end-points such as patient and graft survival, are required before accepting UDCA prophylaxis as standard of care in clinical practice.

In the non-transplant setting, several novel drugs have recently been suggested to be benefit PBC patients who do not completely respond to UDCA[72]. The preliminary report of the phase Ⅲ POISE multinational trial revealed promising results in treating PBC patients with obeticholic acid, a farnesoid X receptor agonist[73]. Several small studies suggested Bezafibrate, targeting the pregnane X receptor and peroxisome proliferator-activated receptor alfa, to hold promise for PBC treatment[72]. Whether these newer therapies will in the future play a role in the management of recurrent PBC after LT remains to be seen.

CLINICAL IMPACT OF RECURRENT PBC

Even if recurring, PBC in the graft seems to hardly ever affect outcomes. Thus, overall long-term graft and patient survival was not affected in any of the published reports[45,59,65]. In the two largest reported experiences with LT for PBC, only 3 out of 485 and 2 out of 154 cases, respectively, required re-transplantation[69,74]. While recurrent PBC has also been described after a second and third LT, the proportion of graft failure due to disease recurrence seems again low after re-LT (7%-14%)[75].

AUTOIMMUNE HEPATITIS

AIH is associated with human leukocytes antigens DR3 or DR4. AIH is a relatively rare, progressive, inflammatory chronic liver disease that mainly affects women and is typically associated with circulating autoantibodies (in particular, high titers of antinuclear and anti-smooth muscle antibodies) and increased levels of serum immunoglobulin G (IgG). Its etio-pathogenesis remains ill defined, but both, genetic predisposition and triggering environmental factors are thought to play a role[76,77]. LT may be indicated in AIH for both, end-stage cirrhosis with liver failure and/or complications of portal hypertension, and severe acute flairs. The latter can present as a picture mimicking fulminant hepatic failure, but in most cases is an acute exacerbation of the pre-existing, underlying chronic disease. That said, AIH is globally one of the rarer indications for LT, likely due to a combination of low incidence rates and highly effective medical therapy (corticosteroids and other immunosuppressive regimens). Medical therapy is able to prevent disease progression and to avoid LT in almost 90% of patients. In the non-transplant setting, treatment of AIH with immunosuppressive regimens has been reported to be associated with excellent 10-year survival rates ranging from 80% to 93%[78-81]. That said, around 10% of patients will eventually require LT, in particular when medical treatment does not lead to remission within 4 years[82].

Thus, AIH accounts for only 4%-6% of LT in the United States[83] and 3% in Europe[84]. LT for end-stage AIH achieves excellent outcomes, patient survival rates at 1 and 5 years amounting to approximately 90 and 80%, respectively[85-87]. AIH recurrence in the allograft was first reported by the King's College group in 1984[88] and, subsequently, confirmed by several other reports[89,90]. Recurrence rates between 16% and 43% have been reported for patients transplanted for AIH-related cirrhosis[85,91-93]. That said, similarly to PSC and PBC, the exact frequency of recurrent AIH, its time course, and its impact on patient and graft survival remains ill defined, as routine follow-up with protocol liver biopsy is not standard for AIH patients in most LT programs.

DIAGNOSIS OF RECURRENT AIH

There is no single specific biomarker to diagnose recurrent AIH after LT. The diagnosis rests on the presence of the diagnostic criteria summarized in Table 3. It is essential to rule out other etiologies causing a hepatitic

Table 3 Diagnostic criteria of recurrent autoimmune hepatitis[60,64,69]

Liver transplantation for confirmed diagnosis of autoimmune hepatitis
Elevated transaminases
Hyper-gammaglobulinemia (elevation of IgG)
Presence of autoantibodies (ANA, SMA and/or anti-LKM1)
Compatible histopathology (interface hepatitis with portal inflammation and/or lymphoplasmacytic inflammatory infiltrates)
Response to corticosteroid
Exclusion of differential diagnostic considerations (including late/atypcial, acute cellular rejection)

IgG: Immunoglobulin G; ANA: Antinuclear antibodies; SMA: Smooth muscle antibodies; LKM1: Liver/kidney microsomal antibodies type 1.

pattern of liver damage including ACR, viral infections/hepatitis, and drug induced liver injury[77,85,94]. In our experience, it can be particularly difficult to discriminate between late, often histologically somewhat atypical ACR and recurrent AIH. However, treatment of both requires increased immunosuppression and distinction between these latter two differentials may therefore be of limited consequence for immediate clinical management.

RISK FACTORS FOR RECURRENT AIH

Several risk factors including certain HLA antigen patterns have been reported to predispose to recurrent AIH post LT, but the results are conflicting and risk factors for recurrent AIH remain ill defined. A strong association of HLA DR3 or HLA DR4 was observed by some, but others failed to find an association with HLA phenotype[85,88,95-97]. Recurrent disease seems not associated with incidence rates of ACR nor with the degree of donor/recipient HLA mismatching[85]. In addition, the incidence of AIH recurrence was not different with cyclosporine *vs* tacrolimus based immunosuppression, nor associated with pre-transplant or post-transplant overall dose and duration of corticosteroid treatment[24]. Rapid weaning of steroids post LT has been suggested to be associated with higher recurrence rates and may therefore need to be exercised with caution in patients transplanted for AIH[86,87,95]. AIH that is poorly controlled prior to LT has been reported to be associated with a higher risk of recurrence post LT. Thus, Ayata *et al*[98] found that severe necro-inflammatory activity in the explant predicts AIH recurrence. In addition, coexistent autoimmune diseases, and high transaminases and IgG prior to transplant have been reported to be associated with an increased risk of AIH recurrence[97]. Collectively, however, the risk factors and their relative contribution to AIH recurrence post LT remain ill defined.

CLINICAL IMPACT AND MANAGEMENT OF RECURRENCE AIH

The majority of patients with recurrent AIH responds to intensified immunosuppressive therapy either in the form of re-introduction/addition or increasing the dose of corticosteroids and/or other immunosuppressive agents[98,99]. In treatment failure, augmenting the standard immunosuppressive regimen with a mycophenolate preparation[75], switching from one to the other calcineurin inhibitor (CNI)[98], or replacing CNI with sirolimus have all been successfully tried[100]. With this in mind, early diagnosis is key for successfully managing AIH recurrence[101], and long-term outcomes do not appear to be impaired in the vast majority of patients, fewer than 5% requiring re-LT for disease recurrence[40,102-104].

CONCLUSION

LT for end-stages of autoimmune liver diseases is associated with excellent long term patient and graft survival. While the underlying autoimmune liver disease recurs after LT in a proportion of patients, disease recurrence rarely affects graft and patients survival, with the exception of recurrent PSC. The latter not infrequently progresses over years to a stage requiring re-transplantation.

That said, the exact incidence rates, outcomes, and risk factors for the post LT recurrence of the underlying autoimmune liver disease remain somewhat ill defined due to diagnostic difficulties. Moreover, the risk/benefit ratio of protocol biopsies during long-term follow-up in this patient population remains unclear. While beyond the scope of this review, this may explain, at least in part, the absence of systematic screening (including protocol biopsies) in most programs.

In order to address these uncertainties and to elucidate potential risk factors for recurrent disease allowing to develop preventative strategies, in particular for recurrent PSC, prospective, adequately powered multicenter studies with longer follow-up is required.

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