

Review

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# Autoimmune liver diseases, hepatocellular carcinoma, and recurrence of autoimmunity post-liver transplantation

Sarah Wang, Victor Dong, Aldo J. Montano-Loza, Andrew L. Mason

Division of Gastroenterology and Liver Unit, University of Alberta, Edmonton T6G 2X8, Canada.

**Correspondence to:** Prof. Andrew L. Mason, Division of Gastroenterology, 7-142 KGR, University of Alberta, 116 St & 85 Ave, Edmonton T6G 2E1, Canada. E-mail: andrew.mason@ualberta.ca

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## Abstract

Liver transplantation for the autoimmune liver diseases (AILD), which includes autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), is indicated in the setting of decompensated cirrhosis, liver failure, and hepatocellular carcinoma (HCC). The risk of HCC is thought to be low in AILD, though data on the risk factors and predictors of HCC are limited in this population. Recurrence of AILD can occur in over half of the patients, complicating the post-transplant course. The pathogenesis of recurrent AILD involves a complex interaction of genetic and environmental influences, as well as a variety of clinical risk factors. Graft and patient survival are negatively impacted by recurrent AILD and the optimal approach to the treatment of AILD recurrence is the subject of ongoing research. This review will address the current literature on the risk of HCC in AILD, as well as the development and management of recurrent AILD post-liver transplantation.

**Keywords:** Recurrence, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hepatocellular carcinoma

## INTRODUCTION

Autoimmune liver diseases (AILD) that include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), are a common indication for liver transplantation



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worldwide<sup>[1,2]</sup>. The need for liver transplantation (LT) in AILD is similar to liver diseases of other etiologies. This includes complications of decompensated cirrhosis and liver failure, as well as hepatocellular carcinoma (HCC)<sup>[1,3,4]</sup>. Over the years, the proportion of patients requiring LT has remained stable for AIH and PSC<sup>[1]</sup>. Despite the rising prevalence of PBC, transplantation rates have decreased over the past decades due to the widespread use of ursodeoxycholic acid (UDCA)<sup>[5,6]</sup>. In general, outcomes post-LT are favorable for patients with AIH, PBC, and PSC, with 5-year survival rates of approximately 70%-80%<sup>[1,2]</sup>.

The post-LT course of AILD may be complicated by recurrence of the disease. Recurrence rates of AILD have been reported anywhere from 10% to over 50% of patient<sup>[2,7]</sup>. Determining the optimal approach to studying recurrent AILD post-LT can be challenging, as studies often contain differences in diagnostic criteria, liver biopsy protocols, and follow-up times. While initial studies failed to find differences in outcomes for those with and without disease recurrence, more recent data suggest that recurrence of AILD post-LT impacts adversely on graft and overall survival<sup>[2]</sup>. Hence, AILD recurrence post-LT signifies a clinically important phenomenon that requires prompt identification and treatment.

As HCC is one of the possible LT indications in AILD, it is feasible that disease recurrence may serve as an ongoing risk factor for HCC recurrence, adding to the complexity of post-LT management. Currently, the development of HCC in AILD is thought mainly to occur in the setting of cirrhosis<sup>[8-10]</sup>. Data on the recurrence of HCC post-LT and its corresponding risk factors are lacking in patients with underlying AILD but presumably relate to the presence of extrahepatic HCC before LT.

This review will address the risk factors for HCC in AILD, and the current understanding of the pathogenesis, risk factors, and management strategies for recurrence of AILD post-LT.

## **AUTOIMMUNE LIVER DISEASES AND THE RISK OF HEPATOCELLULAR CARCINOMA**

Hepatocellular carcinoma is the sixth most common malignancy worldwide and the third most common cause of cancer-related death<sup>[11,12]</sup>. The majority of HCC develops in the setting of cirrhosis or liver inflammation<sup>[11]</sup>. The incidence of HCC is believed to vary depending on the underlying cause of liver disease. In one meta-analysis examining the development of HCC in various etiologies of cirrhosis, chronic hepatitis B (HBV), hepatitis C (HCV), and alcohol-related liver disease (ALD) were found to have the highest risk for HCC compared to other causes, including AILDs<sup>[9]</sup>. A single center study in Toronto, Canada found similar results, with incidence per 1000 person years of 26.2, 21.8, and 18.4 for HBV, HCV, and ALD cirrhosis, respectively<sup>[13]</sup>. Furthermore, in keeping with the changing landscape of cirrhosis etiology, a recent study identified nonalcoholic fatty liver disease as the fastest growing cause for HCC development among patients listed for liver transplant in the United States<sup>[9,13,14]</sup>.

According to a recent meta-analysis, the incidence of HCC in AIH is 3.06 per 1000 person-years<sup>[15]</sup> [Table 1]. Cirrhosis is the predominant risk factor for the development of HCC, with an incidence rate of 10.07 per 1000 person-years in patients with AIH cirrhosis. Other risk factors associated are older age, increased frequency of relapses, concurrent alcohol consumption, and a trend for male sex<sup>[15-20]</sup>. Asian populations are also observed to have an increased incidence of HCC, suggesting an influence of genetic and environmental factors<sup>[15]</sup>.

The risk of HCC in PBC appears to be higher than that of AIH<sup>[9,13]</sup>. According to a recent meta-analysis, the incidence of HCC in PBC is about 4.17 per 1000 person-years. Cirrhosis is a major risk factor, with an incidence rate of 15.7 per 1000 person-years. Male sex is also associated with an increased risk of HCC development in PBC, with an incidence of 9.82 per 1000 person-year<sup>[21]</sup>. The Global PBC group reported

**Table 1. Incidence and risk factors for HCC in autoimmune liver disease**

	<b>Incidence</b>	<b>Risk factors</b>
AIH	3.06 per 1000 person years (10.07 per 1000 patient years in AIH cirrhosis) <sup>[15]</sup>	Cirrhosis <sup>[15,16,18]</sup> Older age <sup>[15,34,35]</sup> Increased number of relapses <sup>[15,17,35]</sup> Alcohol <sup>[15,34]</sup> Ethnicity <sup>[15,34]</sup>
PBC	4.17 per 1000 patient-years (15.7 per 1000 patient-years in PBC cirrhosis) <sup>[21]</sup>	Cirrhosis, advanced biochemical or histologic disease <sup>[21,22,24,25]</sup> Male <sup>[22,24,26,27]</sup> Older Age <sup>[26,27]</sup> Thrombocytopenia <sup>[22]</sup> Low albumin <sup>[22]</sup> Incomplete response to treatment <sup>[22]</sup> Hepatic Decompensation <sup>[22]</sup> Alcohol <sup>[26]</sup>
PSC	Unknown (7.2 per 1000 patient-years in PSC cirrhosis in one study) <sup>[13]</sup>	Unknown

that the risk factors for HCC include advanced disease, thrombocytopenia, hepatic decompensation, and non-response to UDCA<sup>[22]</sup>. In addition, older age, low albumin, and alcohol use are associated with increased risk of HCC in PBC<sup>[23-27]</sup>.

The incidence of HCC in PSC is less well established. While PSC has a well-recognized risk of hepatobiliary malignancies, with cholangiocarcinoma developing in 13% of patients, the incidence of HCC in PSC is believed to be low<sup>[8,28]</sup>. In a retrospective study from Germany including 509 patients who were studied for 292 person-years, HCC was not observed in any patients, even though 109 patients had cirrhosis<sup>[29]</sup>. In contrast, a Canadian study assessing PSC patients with cirrhosis found that the incidence of HCC was 7.2 per 1000 patient-years<sup>[13]</sup>. Differences in these observations may be related to the severity of liver disease in the population or local factors such as variance in the transplantation rates, which can serve as a competing risk.

Currently, the American Association for the Study of Liver Diseases (AASLD) recommends screening for HCC once the annual risk exceeds 1.5%, based on studies of cost-effectiveness<sup>[30-32]</sup>. As different studies are subject to heterogeneity, clinical tools have been developed to better predict the risk of HCC in various disease entities. One of these tools is the Toronto HCC Risk Index (THRI) that relies on age, etiology, gender, and platelet count to calculate a score. THRI was validated to predict HCC risk in a variety of liver diseases, including AIH, PBC, and PSC<sup>[13]</sup>. However, further research will be required to determine whether clinical risk statistical tools can change screening practices in patients with relatively low risk for HCC, as observed in AILD.

Predictors of HCC recurrence post LT are most attributable to tumour-related factors pre-LT, such as size, number, and alpha-feto-protein level<sup>[33]</sup>. However, specific risk factors for recurrent HCC in AILD are unknown. Immunosuppression is thought to play a role in the pathophysiology of HCC recurrence post-LT, where more potent immunosuppression may prevent the early detection of residual HCC cells, and sirolimus is thought to have anti-proliferative activity<sup>[33-35]</sup>. In AILD, where the use of immunosuppression may influence the risk of recurrent AILD, there are no data to indicate which immunosuppression regimens may limit HCC recurrence.

## AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic inflammatory liver disease characterized by elevated aminotransferases, immunoglobulin G (IgG), specific autoantibodies, and interface hepatitis on histology<sup>[36]</sup>. The annual incidence of AIH varies from 0.67 to 2.0 per 100,000 depending on the geographical region and ethnic background<sup>[37-39]</sup>. As with most autoimmune diseases, AIH has a female preponderance. Type I AIH comprises 80% of all cases and is defined by the presence of anti-nuclear antibodies, anti-actin, or both. Type 2 AIH is more commonly present in children and is associated with Type 1 liver-kidney microsomal antibodies (anti-LKM) and/or antibodies against liver cytosol antigen Type 1 (anti-LC1)<sup>[40]</sup>. The first-line treatment of AIH consists of corticosteroids and azathioprine, where a biochemical response may be achieved in approximately 80% of patients<sup>[1]</sup>.

### AIH and liver transplantation

AIH accounts for approximately 4%-6% of LT in the United States and 3% in Europe<sup>[41]</sup>. Approximately 10%-20% of patients with AIH will require LT in their lifetime<sup>[42]</sup>. The indication for LT in AIH is similar to other liver diseases and includes acute liver failure, complications of end-stage liver disease, and HCC meeting standardized criteria.

Unlike PSC or PBC, AIH may present as acute liver failure not responding to medical therapy. Furthermore, an increased risk of LT is associated with a lack of early response to corticosteroids<sup>[43]</sup>. A higher rate of non-response to corticosteroids is associated with a younger age at diagnosis, an acute presentation, higher bilirubin, a Model for End Stage Liver Disease (MELD) score greater than 12 at diagnosis, and the presence of HLA DRB1\*03<sup>[44]</sup>. For patients presenting with jaundice, failure of the MELD score to improve after 7 days is another predictor of corticosteroid treatment failure<sup>[45]</sup>. Accordingly, early triage of non-response to treatment is important to identify with acute AIH for patients who may progress to acute liver failure and require an urgent LT workup. One recent retrospective study reported that patients with acute AIH presenting with an elevated International Normalized Ratio (INR) and bilirubin at 2 weeks was predictive of a need for LT within 12 months<sup>[46]</sup>. In patients with acute liver failure secondary to AIH, LT remains the optimal treatment, even though up to a third of patients may respond to corticosteroids initially<sup>[4,47]</sup>.

Outcomes in AIH post-LT are favorable, with 5- and 10-year survival rates at 90% and 75%, respectively; and graft survival rates are 84% and 72% at 1 and 5 years, respectively<sup>[48]</sup>. However, some reports suggest that patients who undergo transplantation for AIH are at increased risk of acute and chronic rejection<sup>[49,50]</sup>. The interaction between auto- and alloimmunity remains poorly understood and the impact on long-term outcomes warrants further investigation.

### Incidence and diagnosis of AIH recurrence

Recurrent AIH (rAIH) is reported in the range of 36%-68% after 5 years<sup>[51]</sup> [Table 2]. Variable frequencies are observed owing to the differences in diagnostic criteria, small sample sizes, the performance of per-protocol or event-driven biopsies, and length of follow up. The average time to recurrence is 4.6 years, with rAIH diagnosed typically more than 12 months post-LT<sup>[52,53]</sup>. Recurrence rates also tend to increase with time<sup>[2,54]</sup>.

The diagnosis of rAIH is challenging due to the lack of specific biomarkers and validated scoring systems in the post-LT population. Recurrent AIH is currently identified using the same criteria for AIH in patients without LT. This is based on a combination of elevated aminotransferases, IgG, the persistence of autoantibodies, consistent histological findings, exclusion of alternative diagnosis such as viral infection or

**Table 2. Incidence, diagnosis, risk factors, and management of recurrent autoimmune liver diseases post-liver transplantation**

	<b>Incidence</b>	<b>Diagnosis</b>	<b>Risk factors</b>	<b>Management</b>
rAIH	36%-68% <sup>[51]</sup>	Elevated transaminases/ IgGs/auto-antibodies, histologic features of portal inflammation with mononuclear cells, interface hepatitis, central perivenulitis, and focal necrosis, exclusion of alternative diagnosis such as viral infection or rejection, response to steroids <sup>[54,55-55,57,58]</sup>	Concomitant autoimmune disease <sup>[66]</sup> High AST/ALT, and IgG <sup>[66]</sup> Severe inflammatory activity on histology <sup>[66,67]</sup> HLA DRB1*03 <sup>[53,68]</sup>	Corticosteroid and/or azathioprine, or MMF <sup>[51]</sup>
rPBC	21 to 43% <sup>[91]</sup>	Liver enzyme elevation, histology showing granulomatous destruction of interlobular duct <sup>[96,97]</sup>	Extremes of age <sup>[100,114]</sup> Biochemical cholestasis within the first 12 months <sup>[100]</sup>  Immunosuppression: Cyclosporine use decreased risk as compared to tacrolimus <sup>[110-112,107,110]</sup> Genetic predisposition <sup>[108]</sup> Increased donor age, warm and cold ischemic time <sup>[109,112,114]</sup>	Preventative use of UDCA, and in combination with cyclosporine, post LT reduced the risk of rPBC <sup>[115]</sup>
rPSC	20% to 25% <sup>[2]</sup>	Diagnosis of PSC prior to LT and cholangiography showing non-anastomotic intrahepatic and/or extrahepatic bile duct strictures with irregularities and beading occurring more than 90 days post-LT Or Liver biopsy demonstrating fibrous cholangitis and/or fibro-obliterative lesions <sup>[127]</sup>	Inflammatory bowel disease <sup>[128-130]</sup> Acute cellular rejection <sup>[131,132,134,135]</sup> Donor-recipient CMV mismatch <sup>[133]</sup> Poor graft quality <sup>[133]</sup> Pre-transplant MELD > 24 <sup>[133,135]</sup> Cholangiocarcinoma <sup>[134,135]</sup> Higher donor age <sup>[134]</sup>	No proven therapies Symptomatic management

ALT: Alanine aminotransferase; AST: aspartate transaminase; CMV: cytomegalovirus; MELD: model for end stage liver disease; MMF: mycophenolate mofetil; UDCA: ursodeoxycholic acid.

rejection, and response to steroids<sup>[54,55]</sup>. The presence of autoantibodies is in itself not a marker of rAIH, as many patients continue to have persistence of antibodies post-LT<sup>[56]</sup>. Histological findings typically consist of portal inflammation with mononuclear cells, particularly plasma cells, interface hepatitis, central perivenulitis, and focal necrosis<sup>[55,57,58]</sup>. One study reported that histologic findings of rAIH can occur before the onset of biochemical abnormalities if protocolized liver biopsies are performed<sup>[59]</sup>.

### Pathogenesis and risk factors for AIH recurrence

The pathogenesis for AIH recurrence is unknown largely because the etiology of AIH is poorly understood. Some have proposed that recipient memory T-cells recognize auto-antigenic peptides on mismatched HLA donor grafts<sup>[3]</sup>, while others have questioned whether this process occurs in the setting of potent immunosuppression post-LT<sup>[60]</sup>. One explanation is that suppression of regulatory T cells occurs under the influence of immunosuppression, causing immune dysregulation<sup>[61]</sup>. However, alternative hypotheses have been proposed in studies showing an increased risk of rAIH with corticosteroid withdrawal and the association of long-term steroid with a lower incidence of rAIH<sup>[62-65]</sup>. Despite continued corticosteroid use, it is still notable that patients with rAIH and “normal” liver tests may still progress to cirrhosis. The type and strength of immunosuppression may play a role, but current data on the effect of specific

pharmacologic agents and disease recurrence are lacking.

The severity of inflammatory activity pre-transplant is correlated with an increased risk of rAIH. For example, we found that concomitant autoimmune disease, high aspartate transaminase/alanine transaminase, and IgG are associated with an increased risk of recurrence post-LT<sup>[66]</sup>. Histological evidence of severe inflammatory activity in the native liver is also associated with an elevated risk of rAIH<sup>[66,67]</sup>. Others have reported that the known risk factor HLA DRB1\*03 is more commonly found in patients with recurrence<sup>[53,68]</sup>. This led to the conclusion that donor-recipient mismatch may affect recurrence or graft survival, but the evidence is inconsistent. A few reports have demonstrated mismatch of HLA status increased graft survival in AIH<sup>[69,70]</sup>, while other studies have not<sup>[63,71]</sup>. The role of HLA remains a mystery in the development of rAIH and a better understanding of the process in the non-transplant setting would help in understanding the pathogenesis of disease recurrence.

### Management and outcomes of AIH recurrence

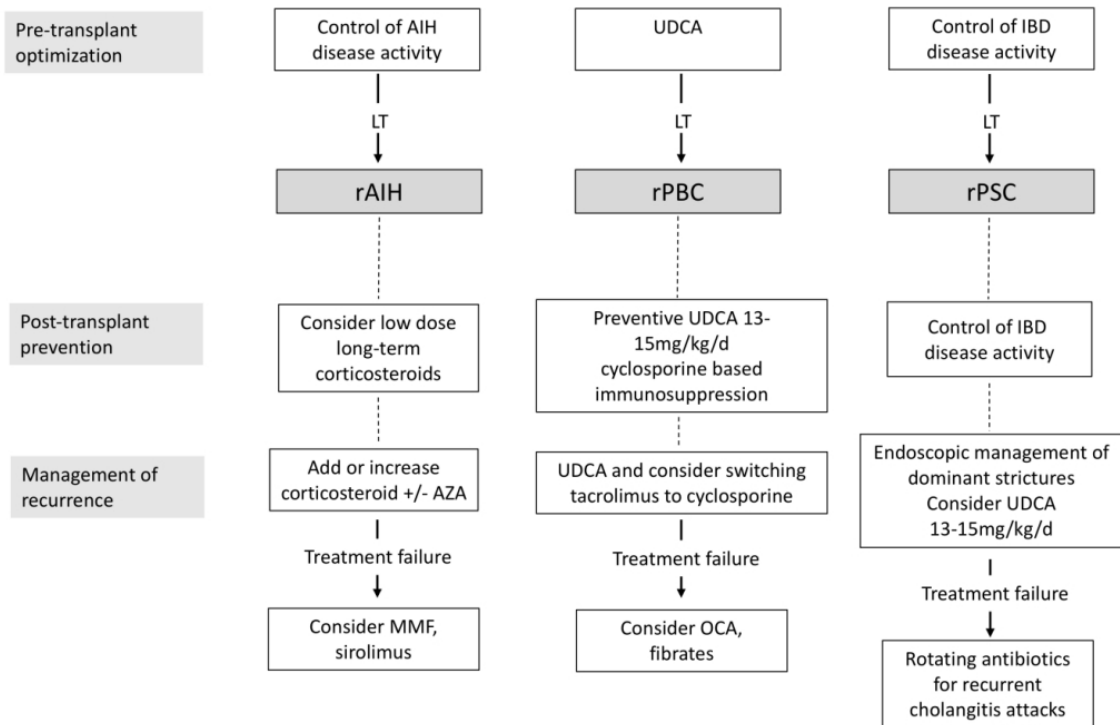
Graft failure occurs in 13% to 50% of patients with rAIH<sup>[56,63]</sup>. Compared to other liver diseases, rAIH is associated with a higher risk of graft loss and an increased risk of death from liver failure<sup>[72,73]</sup>. Re-transplantation is performed for pediatric and young adult patients with progressive liver failure from rAIH<sup>[2]</sup>. Treatment of AIH recurrence depends on the clinical presentation and severity of the disease. In most cases, optimizing immunosuppression with corticosteroid and/or azathioprine can induce and maintain disease remission [Figure 1]<sup>[51]</sup>. In treatment failure, other immunosuppressive agents, such as mycophenolate mofetil (MMF), or sirolimus are found to have some benefit in rAIH management<sup>[54,74]</sup>. The role of preventative corticosteroid use is controversial because a meta-analysis failed to demonstrate a benefit of continuous steroids on graft survival, rejection rates, rAIH, and patient survival<sup>[51]</sup>. Accordingly, the current AASLD guidelines suggest discontinuing corticosteroids post LT and monitoring for rAIH<sup>[51]</sup>.

### PRIMARY BILIARY CHOLANGITIS

Primary biliary cholangitis (PBC) is a cholestatic autoimmune liver disease characterized by chronic, destructive non-suppurative granulomatous cholangitis of the small and medium-sized intrahepatic bile ducts<sup>[75]</sup>. The disease is rare, with an incidence reported to be approximately 0.7 to 49 per million per year, and predominantly affects women, with a 10:1 female preponderance<sup>[5,76]</sup>. PBC is distinguished serologically by the presence of anti-mitochondrial antibodies (AMA) reactive to pyruvate dehydrogenase complex (PDC)-E2 that is found in over 80% of patients with PBC<sup>[76]</sup>. Notably, PDC-E2 is aberrantly expressed on the surface of cholangiocytes and this is thought to lead to the loss of tolerance to self with the expression of AMA<sup>[77]</sup>.

The pathogenesis of PBC is complex and it is thought that an environmental agent(s) may trigger disease in a genetically susceptible host<sup>[78]</sup>. Genomic studies have implicated variants in HLA class II and the interleukin 12 pathway in the development of PBC<sup>[78,79]</sup>. Potential triggers theorized to induce an autoimmune response in PBC include xenobiotics, drugs, bacteria, and viruses<sup>[80]</sup>. Of these agents, only the human betaretrovirus has been shown to trigger the PBC phenotype of increased PDC-E2 expression in cholangiocytes<sup>[81]</sup>. The role of autoimmunity in the development of PBC is questionable because the loss of tolerance to mitochondrial proteins has not been experimentally shown to trigger cholangitis, and immunosuppression does not provide benefit for preventing the disease progression<sup>[80]</sup>.

The first-line management of PBC is UDCA, which has been shown to improve liver transplant-free survival<sup>[82]</sup>. For those not achieving adequate response to UDCA, the second line therapy includes the addition of obeticholic acid and bezafibrate, which may also serve to manage pruritus as well<sup>[83-86]</sup>.



**Figure 1.** Prevention and treatment of AIHD recurrence post LT. AZA: Azathioprine; IBD: inflammatory bowel disease; MMF: mycophenolate mofetil; OCA: obeticholic acid; UDCA: ursodeoxycholic acid.

### PBC and liver transplantation

Overall, liver transplantation for PBC has decreased by 20% in the US from 1996 to 2006, despite an increasing prevalence of PBC and this is attributable to improved disease management with UDCA<sup>[87,88]</sup>. Several risk scores incorporating improvement in alkaline phosphatase and bilirubin on UDCA therapy have been validated to predict LT-free survival<sup>[89]</sup>. The indication for LT in PBC is similar to other liver diseases and also includes those with intractable severe pruritus as the sole indication for LT<sup>[90,91]</sup>. Although the severity of fatigue may be extreme in PBC, it is not a standalone indication for LT especially because the symptom may not necessarily improve post-LT<sup>[92,93]</sup>. Rarely, non-cirrhotic patients who suffer from complications of presinusoidal portal hypertension may require LT<sup>[94]</sup>.

Outcomes after LT for PBC are excellent. Patient survival at 1 and 5 years ranges from 83%-93% and 77%-86% and graft survival at 1 and 5 years ranges from 79%-88% and 71% to 84%<sup>[48,95]</sup>.

### Incidence and diagnosis of PBC recurrence

The incidence of recurrent PBC (rPBC) is approximately 21%-37% at 10 years and 43% at 15 years<sup>[91]</sup>. The median time to recurrence is between 3 to 5.5 years<sup>[96]</sup>. As observed with rAIH, the difference in reported recurrence rates is related to the variable histologic criteria, use of protocol biopsies, and length of follow up between centers. The diagnosis of rPBC is typically based on histology, where granulomatous destruction of the interlobular duct is a pathognomonic finding. Less specific but more sensitive histological features include moderate lymphocytic cholangitis and dense lymphoplasmacytic infiltrate<sup>[96,97]</sup>. Liver enzymes may be normal or minimally elevated even in the presence of histologic abnormalities<sup>[97,98]</sup>. Serum AMA does not appear to correlate with PBC recurrence<sup>[98,99]</sup>.

### **Pathogenesis and risk factors for PBC recurrence**

The pathogenesis of rPBC is poorly understood. The development of cholestatic liver tests in the first year following LT signals the subsequent development of rPBC<sup>[100]</sup>. We have argued that this is more in keeping with an infectious disease process as autoimmunity would be an unlikely cause of pathology early on when immunosuppression levels are highest. Recurrent disease also occurs with evidence of the PBC phenotype of PDC-E2 expression in the allograft. One report documented close to 70% of patients with serum AMA and aberrant expression of PDC-E2 in cholangiocytes, whereas less than 30% of patients had histological evidence of rPBC<sup>[101]</sup>. Another pathological process that signals the subsequent occurrence of rPBC is epithelial mesenchymal transition in cholangiocytes that predates discernable histological changes of rPBC<sup>[102]</sup>. This developmental pathway may be driven by Wnt transcription factors, which have been identified in PBC liver in microarray studies<sup>[103]</sup>. A commonality in the development of Wnt signaling and PDC-E2 expression in cholangiocytes is betaretrovirus infection, but this has not been directly implicated in rPBC<sup>[81]</sup>.

The role of HLA in the development of rPBC is debatable. One Japanese study involving living donor transplant recipients showed that HLA matching is associated with increased risk of rPBC<sup>[104]</sup> but this was not confirmed in other studies<sup>[105]</sup>. Similarly, studies including deceased donors reported conflicting results concerning the role of HLA as well<sup>[71,96,106,107]</sup>. A study from the United Kingdom reported that the risk of rPBC differed based on varying single nucleotide polymorphisms at the IL12A locus. The highest risk of rPBC was associated with rs62270414 genotype AG or GG, and the lowest risk was observed in those with the rs62270414 genotype AA<sup>[108]</sup>. In this study, the use of cyclosporine versus tacrolimus was found to be protective<sup>[108]</sup>.

The use of other immunosuppressive agents like azathioprine and MMF and their relationship with rPBC are more difficult to interpret. In the era from the mid-1980s to the mid-1990s, azathioprine was used in conjunction with both cyclosporine and tacrolimus, so the risk attributable to azathioprine is uncertain<sup>[107,109]</sup>. As reported in most series, the type of immunosuppression appears to influence recurrent disease. In a large multicenter study of 785 LT recipients with PBC, the use of tacrolimus was a major risk factor for rPBC, whereas cyclosporine was protective<sup>[100]</sup>. This has been a recurrent finding that cyclosporine use correlates with decreased risk of rPBC and a prolonged interval to develop rPBC as compared to tacrolimus<sup>[107,110-112]</sup>. While the mechanisms that modulate outcomes with different calcineurin inhibitors remain unclear, it seems likely that the increased potency of immunosuppression overall amplifies the risk of rPBC<sup>[113]</sup>. Furthermore, we have suggested that the protective effect of cyclosporine is due to the known antiviral properties and have shown that cyclosporine inhibits betaretrovirus linked with the pathogenesis of PBC<sup>[111]</sup>.

With regard to recipient risk, a younger age of diagnosis increases the chance of developing rPBC<sup>[100]</sup>. The donor factors include increased donor age, as well as warm and cold ischemic time providing an increased incidence of rPBC<sup>[109,112,114]</sup>.

### **Management and outcomes after PBC recurrence**

As used in the pre-transplant setting, UDCA has become the first-line management for rPBC. While UDCA is associated with improved liver function tests, data on the impact on histological regression, graft function, or patient survival are limited<sup>[114]</sup>. Notably in the largest study to date, UDCA (13-15mg/kg/day) has been shown to decrease the risk graft dysfunction and death, as well as the risk of rPBC. The study also found that the use of cyclosporine had an additive effect to UDCA in reducing recurrence, graft loss, and mortality<sup>[115]</sup>. Thus, while the treatment of rPBC is not established, preventative UDCA and possibly the use of cyclosporine-based immunosuppression are useful strategies to prevent recurrence. Further studies are



required to determine if second-line therapies, such as obeticholic acid, and fibrates, are effective in the management of rPBC, especially now that it has been established that recurrence is associated with increased risk of graft loss and death<sup>[100]</sup>.

## PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) is a progressive disease of the biliary tract characterized by inflammation and scarring of intrahepatic and extrahepatic bile ducts leading to cirrhosis<sup>[116]</sup>. The prevalence in North America ranges from 1 to 16 per 100,000 people<sup>[117]</sup>. Approximately 80% of PSC patients suffer from inflammatory bowel disease (IBD), especially ulcerative colitis<sup>[118]</sup>. PSC is usually diagnosed by demonstrating large bile duct strictures by cholangiography in the absence of other causes. Liver biopsy is not required for diagnosis and may reveal the characteristic periductal concentric “onion skin” fibrosis<sup>[119]</sup>. Currently, there are no proven therapies for PSC and the role of UDCA is uncertain<sup>[116]</sup>.

PSC is an immune-mediated disease that may occur in association with a variety of other autoimmune diseases<sup>[120,121]</sup>. Genetic predisposition is linked with both HLA and non-HLA loci, some of which were also related to IBD<sup>[78,122,123]</sup>. Several environmental and infectious factors have been proposed to trigger the development of this disease<sup>[78,117]</sup>. The predominance of a skewing towards a specific intrahepatic T-cell receptor V $\beta$  subset suggests the possibility of a microbial superantigen activity in PSC patients<sup>[124]</sup>.

### PSC and liver transplantation

Transplantation is required for patients with PSC with life-threatening complications of cirrhosis or recurrent cholangitis<sup>[91]</sup>. In highly selected cases, LT is considered for selected patients with cholangiocarcinoma in conjunction with neoadjuvant chemotherapy<sup>[125]</sup>. On a prognostic level, patients with serum alkaline phosphatase levels greater than or equal to 2.4 times the upper limit of normal are at increased risk of LT<sup>[126]</sup>. The post-LT survival for PSC is excellent with 1-year, 3-year, 5-year, and 10-year post-LT survival rates of 93.4%, 89.7%, 87.4%, and 83.2%, respectively, in the United States<sup>[127]</sup>.

### Incidence and diagnosis of PSC recurrence

One of the major complications post-LT is the development of recurrent PSC (rPSC). Rates of rPSC are reported to occur in 20% to 25% of patients over 10 years<sup>[2]</sup>. The diagnosis is often challenging and exclusion of other causes of biliary strictures must be ruled out. These include hepatic artery thrombosis, anastomotic strictures, non-anastomotic strictures occurring less than 90 days post-LT, donor-recipient ABO incompatibility, and chronic ductopenic rejection<sup>[127]</sup>. Diagnostic criteria of rPSC include a diagnosis of PSC prior to LT and a cholangiographic appearance of non-anastomotic intrahepatic and/or extrahepatic bile duct strictures with irregularities and beading occurring more than 90 days post-LT<sup>[127]</sup>. Some advocate the use of a diagnostic liver biopsy demonstrating concentric fibrous cholangitis and/or fibro-obliterative lesions to make a diagnosis of rPSC although this is less well-accepted<sup>[127]</sup>.

### Pathogenesis and risk factors for recurrent PSC

Although many studies have examined the risk factors, it is unclear why rPSC develops post-LT. One of the main risk factors is IBD, as demonstrated with the decreased frequency of rPSC following colectomy prior to LT<sup>[128]</sup>. Others have reported that the presence of ulcerative colitis post-LT is significantly associated with the development of rPSC<sup>[129]</sup>. In those without a prior history of ulcerative colitis, the development of *de novo* colitis increases the risk considerably<sup>[130]</sup>. These studies underscore the importance of colonic disease post-LT and suggest that the management with either prophylactic colectomy or the treatment of IBD is protective against the development of rPSC.

Another significant risk factor for rPSC that has been extensively studied is the occurrence of acute cellular rejection post-LT. In a North American study, for example, 71% of patients with rPSC had prior acute rejection as compared to 22% of patients without rPSC, and 29% of patients with rPSC had steroid-resistant rejection *versus* none of the patients without rPSC<sup>[131]</sup>. A study from the Netherlands also found that acute cellular rejection increased the frequency of rPSC<sup>[132]</sup>. Some have suggested that the link of rPSC with rejection may be inflammation of the biliary epithelium that occurs in acute cellular rejection leading to damage of the bile ducts<sup>[127]</sup>. It is equally possible that the increased use of immune suppression and immune reconstitution may influence the development of rPSC.

A multitude of other risk factors have also been identified to be predictors of rPSC. Donor-recipient cytomegalovirus mismatch was found to increase risk<sup>[133]</sup>. Graft quality including increased donor age and extended donor criteria grafts were also identified as risk factors for rPSC development<sup>[133]</sup>. Furthermore, the severity of PSC pre-LT with a MELD score greater than 24 and increased INR at the time of LT both increase the risk of rPSC<sup>[133]</sup>.

More recently a meta-analysis reported that colectomy prior to LT, presence of IBD, cholangiocarcinoma, higher donor age, and single or multiple episodes of rejection, were all independent risk factors of developing rPSC<sup>[134]</sup>. A separate meta-analysis confirmed that cholangiocarcinoma, multiple episodes of rejection, MELD score, and use of MMF and cyclosporine for immunosuppression were significantly associated with increased risk of rPSC<sup>[135]</sup>.

### **Management and outcomes of recurrent PSC**

There are no proven therapies for rPSC. However, we advocate judicious use of immunosuppression as cyclosporine appears protective versus tacrolimus<sup>[135]</sup> and immune reconstitution is associated with flares in the disease process. Whereas UDCA appears to improve liver function tests, its effects on patient outcomes with rPSC are less clear<sup>[127]</sup>. Overall, symptomatic management of complications including biliary strictures, cholangitis, and pruritus, is generally the only option. The development of rPSC also significantly affects graft survival and leads to the highest risk of graft loss in patients with AILD. Retransplantation is ultimately required for 20% to 43% of patients with rPSC<sup>[133]</sup>.

### **PROSPECTUS**

Autoimmune liver diseases are a major indication for LT worldwide. In general, while outcomes for AIH, PBC, and PSC are favorable post-LT, recurrence of AILD is common, with reported rates varying based on diagnostic criteria and follow-up times. Currently, our lack of knowledge of AILD pathogenesis severely impacts our understanding of disease recurrence in the post-transplant setting, leading to limited effective treatments.

HCC can occur in the AILD, with cirrhosis as the major risk factor. Recurrence of AILD following transplantation for HCC may play a role in clinical outcomes, though studies on HCC recurrence in AILD are sparse. Nevertheless, recurrence of AILD has shown decreased graft and patient survival post-LT, prompting the need for improved management strategies.

In AIH, the role of disease activity and the use of immunosuppression to control inflammation appear to contribute significantly to the development of recurrence. Future studies focused on maintaining remission with AIH, with alternative pharmacologic options for non-responders, are required to better manage recurrence in the post-transplant population. In PBC, while the beneficial role of preventative UDCA and cyclosporine is understood, future prospective studies are needed to confirm the role of second-line

therapies on long-term outcomes. In PSC, there is a need to develop effective management strategies in both the pre-and post-LT setting.

In summary, the mechanisms that mediate recurrence of AILD post-LT are complex and a better understanding of the processes involved are required to achieve improved outcomes in patients following LT.

## DECLARATIONS

### Authors' contributions

Contributed to the search and selection of the articles, review of articles, conception and design of the manuscript, writing and revising of the manuscript draft, and review of the final version of the manuscript: Wang S, Dong V, Mason AL

Contributed to the selection of articles, revising of the draft, and review of the final version of the manuscript: Montano-Loza AJ.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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