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FORUM

# PSC recurrence post liver transplantation: retransplantation justified or not?

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This Forum discusses the paper by Visseren et al: Recurrence of primary sclerosing cholangitis after liver transplantation – analysing the European Liver Transplant Registry and beyond. Transpl Int. 2021:34; 1455.

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Postliver transplant (LT), primary disease recurrence is a major cause of graft failure and long-term patient mortality [1]. For decades, hepatitis C virus (HCV) recurrence was the number one cause of graft loss [2]; however, with the development of potent anti-viral therapy, HCV transplant recipients no longer experience graft loss and death. In contrast, recurrence of autoimmune disease—particularly Primary Sclerosing Cholangitis (PSC)—remains a valid concern for the liver transplant community. This is despite an excellent short-term outcome post LT, with a survival rate above 90% within the first year after transplant [3]. PSC disease recurrence is reported to be around 15–25% after 10 years post-transplantation [4,5]. Similar rates of recurrent PSC (rPSC) have also been reported in pediatric recipients with a median onset of 36 months post LT [6]. Although pathophysiology of rPSC remains unknown, multiple possible risk factors, including donor, recipient, and transplant-related risk factors have been reported to potentially participate in disease recurrence. These include recipient-specific risk factors including younger age, presence of tissue IgG4, HLA DRB1 subtype, active colitis, and ileao-anal anastomosis as well as presence of DSA and CMV mismatch [4,7].

Confirmation of the diagnosis of rPSC can be challenging, particularly in the post-transplant setting, where nonanastomotic strictures are fairly common and not always because of rPSC. Currently, the best diagnotic tools for rPSC are utilization of criteria such as the one proposed by Graziadei *et al.* [3] after exclusion of other causes of secondary sclerosing cholangitis. Confidence in the diagnosis of rPSC is necessary to ensure monitoring for progression to advanced disease, early detection of signs of graft loss, and timely discussion for retransplantation.

When graft failure occurs, liver retransplantation may be the only alternative to death. However, retransplantation is generally controversial, because of significantly lower patient and graft survival rates compared with primary transplantation. This is because of myriad surgical challenges, septic complications, and multiorgan failure [8]. Given the scarcity of donor organs for patients on the wait list, coupled with poorer outcomes with retransplantation, there arise significant ethical challenges to retransplantation.

Negative impact of rPSC on graft survival and higher need for retransplantation were previously reported by several multicenter studies [3,4,7,9]. However, little is known on the impact of rPSC on long-term patient survival. Using the European Liver Transplant Registry (ELTR) data, the study by Visseren *et al.* [10] reports a negative impact on patient survival with a HR of 2.31 among patients with rPSC independent of other transplant related co-variates. Another important finding of this study is the timing of rPSC, with a worse survival outcome when recurrence occurred within the first 5 years post LT as opposed to a later diagnosis of recurrence. Furthermore, the rate of rPSC on subsequent liver grafts (≥2) of 16% after a median of 5 years, still demonstrated similar survival when compared with patients without rPSC, but retransplanted for other causes.

While this is the largest multicenter study on rPSC post-transplant, it should be noted that granular patient data, such as imaging and biopsy, were only available from a third of all the transplant centere included in the ELTR. This raises questions around potential selection bias leading to the unexpected finding that in patients with rPSC, 10-year graft survival was worse after first transplant than second transplant (61% vs. 77%). Nevertheless, upon examination of graft and patient survival in patients with and without rPSC, 5-




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year graft survival for second graft was noted to be 77% vs. 79%, with no difference in patient survival.

The dilemma raised by the current report and other studies on rPSC is the overall high rate of retransplantation (13%) for patients with rPSC in the current era of organ shortage. Every year, about 25–30% of patients listed for liver transplantation die on the wait list. In the absence of knowledge in the pathophysiology of rPSC and lack of preventive therapy, the ethical principle of fair and equitable distribution of organs based on long-term outcomes is on the front line when considering listing patients for retransplantation. This study, albeit retrospective analysis of registry with limitations as discussed above, appears to support the idea that (1) patients with rPSC postliver transplant have reduced graft and patient survival; and (2) patients who undergo a second liver transplant for rPSC do no worse than patients who undergo a second liver transplant for other causes, with similar graft and patient survival. Thus, based on a pure needs and outcomes standpoint, it seems reasonable to continue offering retransplant to patients with rPSC until further prospective studies demonstrate otherwise.

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## Conflicts of interest

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