Heterogeneity of Outcomes Following Liver Transplantation for Primary Sclerosing Cholangitis: Age Matters

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Once considered a relentlessly progressive disease, primary sclerosing cholangitis (PSC) has been increasingly recognized as heterogeneous, including more indolent variants such as small duct PSC [1]. In the absence of effective medical therapy, however, liver transplantation (LT) remains an important consideration once complications of advanced cholestatic cirrhosis supervene. Furthermore, in at least some PSC patients, even with a complicating cholangiocarcinoma, LT may be feasible [2]. In the accompanying article [3], the authors identified 8272 adults with PSC without a diagnosis of cholangiocarcinoma listed for LT using the United Network for Organ Sharing (UNOS) database over the period 2004–2015. Dividing the patients into three age groups, 18–39, 40–59, and >60 years, they explored age-related differences in presentation, waiting list status, and post-LT outcomes. Younger patients had a greater likelihood of having concomitant inflammatory bowel disease (IBD) and being African–American and male. A secondary diagnosis of autoimmune hepatitis was also more frequent in younger patients, most likely reflecting its frequent overlap with PSC in children and in adolescents. The authors also inferred that cholestasis was more pronounced in younger patients, based on bilirubin levels, whereas renal dysfunction, hepatic synthetic impairment, and complications of portal hypertension predominated in older patients. Waitlist

and post-LT mortality were higher in patients older than 60 years, possibly reflecting the presence of serious comorbidities in this age group. In contrast, graft survival was longest in middle-aged patients. Graft failure due to disease recurrence or chronic rejection was commonly reported in young and middle-aged patients. As the authors note, distinguishing these etiologies of graft failure can be challenging. Younger and middle-aged patients were more likely to undergo retransplantation for graft failure. Although deaths due to malignancy occurred at similar rates in the three age groups, cholangiocarcinoma was much less frequently reported in the older patients.

Several inferences can be drawn from the authors' astute analysis of this database. They confirm numerous earlier observations, including that in younger patients there were stronger associations with being male, African–American, having IBD, and having more profound cholestasis [4]. Superior graft outcomes in middle-aged patients may reflect a more robust immune response in younger patients leading to chronic rejection or other patient-related factors such as noncompliance. The greater likelihood of death from cholangiocarcinoma in the younger groups may reflect not only the difficulty of its detection in general [5], but also perhaps even more so in younger PSC patients with a greater predominance of cholestatic disease. In addition to disease-related phenomena, other observations from this database may reflect the difficulty of managing PSC in LT recipients. For instance, retransplantation for graft failure occurred in 55.7, 34.2, and 10.9% of the young, middle-aged, and older patients with graft failure, suggesting a reluctance to commit resources to older recipients. Nevertheless, the key message that this analysis confirms is that PSC is heterogeneous. This distinction has implications not only in managing individual patients, but also can inform the design of clinical trials once disease-

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modifying interventions are developed to specifically target variants of this heterogeneous disorder.

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