Editorial Commentary

Assessment of morbidity and mortality after liver transplantation for primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a progressive liver disease that causes biliary inflammation, recurrent cholangitis, and liver fibrosis (1). Although there are therapeutic options that temporarily reduce the itching and jaundice caused by PSC, there is currently no effective definitive treatment. The rate of disease progression varies among individuals, but it ultimately leads to end-stage liver disease and necessitates liver transplantation (2). In some cases, PSC can also progress to cholangiocarcinoma which is the second most common, and the most lethal, tumor of the liver (3). There are significant challenges with liver transplantation in patients with PSC including (I) technical difficulties, (II) recurrent cholangitis post-liver transplantation due to an immunosuppressive state, (III) increased risk of rejection due to the autoimmune nature of the disease, (IV) recurrence of the disease post-liver transplantation, and (V) the shortage of liver allografts which necessitates the use of extended criteria and donation after circulatory death grafts. Despite these challenges, the post-liver transplant graft and patient survival in patients with PSC is similar to non-PSC patients (2-6).

The highest incidence of PSC (1.58/100,000) is reported in Finland (7), and there is a large cohort of liver transplant patients with PSC in that country. A recent study by Vannas *et al.* (8) investigated the short-term and long-term morbidity and mortality after liver transplantation in Finnish patients with PSC using a comprehensive complication index (CCI) (9). In a cohort of 199 PSC patients who underwent liver transplantation, two study groups were defined for analysis: (I) with classical PSC symptoms (n=148) and (II) with increased risk of cholangiocarcinoma only (n=51). The authors calculated two CCI scores (I) at 1-year post-liver transplantation and (II) overall at last follow-up (median follow-up of 9 years). Study covariates included patient sex, type of biliary anastomosis, Model for End-Stage Liver Disease (MELD) score, body mass index (BMI), use of immunosuppression medication, and date of liver transplantation. The two studies groups did not differ for CCI at 1-year or overall. Patient survival was significantly lower when 1-year CCI was greater than 42. Lower survival was associated with cholangitis, infections, and hypertension. High MELD score (>20) was associated with higher 1-year and overall CCI. Both low and high BMI (<22 and >25 kg/m^2) were associated with higher 1-year and overall CCI.

This study had many limitations. First, this retrospective study spans nearly four decades, from 1984 to 2020. The data collection period included the introduction of the MELD score in 2002 (covering only 18 years of the study and the introduction of the CCI in 2013 (covering only 7 years of the study). The authors themselves stated that the

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accuracy of the data may be flawed, especially in registered complications from paper-based records from the 1980s and 1990s. Similarly, long-term follow-up for complications for those same patients 20 to 30 years post-transplant is likely limited, with high risk for error. Another important limitation is the choice of recipients in 50% of the cohort (before the introduction of the MELD score in 2002) since the decision-making for transplant was based on differing local models or on the sole discretion of the transplant surgeon. In this group of patients, 102 had a MELD score <10 (51%) and 70 patients had a MELD score between 10–20 (35%), resulting in only 14% having a MELD >20. Such low MELD scores might fail to represent the disease severity seen in the United States and throughout most of the world. Additionally, reporting overall complications over such an extended time period results in a simple time bias because patients followed for a longer period will have more complications, as they have more time to develop them.

As expected, CCI scores in patients who underwent liver transplantation before 2000 had a significantly higher overall value (62.4) compared to those patients who underwent liver transplantation after 2000 (41.8, P<0.001). This shows that the MELD score after 2002 helped a better patient selection, and how the surgeons and physicians became more adept in-patient care pre- and post-liver transplantation

In this large cohort liver transplantation study in patients with PSC, the Finnish Group demonstrated that a higher MELD score and a lower BMI were significantly associated with higher CCI (8). Although higher MELD-higher surgical complications interaction can be justified, the latter (lower BMI-higher surgical complication) could be expected differently for surgical complications in many liver transplantation studies. On the other hand, lower BMI (<22 kg/m^2) could be associated with significant nutritional issues which could explain higher surgical complications in this patient population. With the large cohort of PSC patients, the authors were able to analyze the impact of immunosuppressive drugs on the development of complications (8). As the study spans over 36 years, 60% of patients were treated with a cyclosporine-based and 38% with a tacrolimus-based immunosuppressive regimen which showed no significant difference in the CCI scores. However, the authors found that using mycophenolate mofetil (MMF) was associated with significantly lower CCI scores on the long-term follow-up. Although this finding could be explained with better control of the immune system in patients with PSC, the authors did not report what kind of complications were better in the MMF group. Moreover, the authors failed to report the trough levels of tacrolimus and cyclosporine over the years and whether those patients with higher CCI had lower or comparable trough levels compared to those with lower CCI which could increase our understanding of the assessment of complications.

Although the authors concluded that morbidity measured with a 1-year CCI score appeared to significantly affect the 1-year patient survival, in the long-term, morbidity measured with an overall CCI score appeared to be mainly increased by low-grade complications, such as infections and hypertension. However, we wonder if studies that span over 36 years could accurately assess and compare morbidity when the management of PSC gets better over decades by expert hepatologists, better and novel knowledge, such as the impact of gut microbiota (10,11), and better surgeons with improved techniques and knowledge in liver transplantation (6).

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