INVITED COMMENTARY

Prognosis of primary sclerosing cholangitis – time to look at the population as a whole, not only from the center's or waiting list perspective

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Equitable and fair allocation of liver grafts remains a challenge in transplantation of organs from deceased donors. Both the prognosis with and without transplantation should be reliably assessed when deciding which patient should be preferred during the allocation process. In this issue of the journal, Goet *et al.* present their analysis of the current policy regarding allocation of donor livers for patients with primary sclerosing cholangitis (PSC) in the Netherlands (NL) who were entered unto the Eurotransplant (ET) waiting list during a 7-year period from December 2006 through December 2013. A total of 852 patients including 146 patients with PSC were registered on the waiting list. After a median follow-up of 214 days, the majority of these underwent liver transplantation (n = 609, 71.5%), whereas 159 (18.7%) died or were delisted because they were too sick for a transplant, 60 (7.0%) were delisted for unspecified reasons, while 25 (2.9%) remained on the waiting list, before a graft became available.

In the ET area, liver allocation is MELD-based, with the option of granting exception points to patients with specified disease categories such as HCC or PSC under defined conditions (standard exception – SE) similar to UNOS allocation. Of note, in the study by Goet *et al.*, none of the MELD exception point (ME) patients died on the waiting list, and PSC with ME patients had a higher probability of receiving a graft than purely MELD (labMELD) PSC patients (which is not surprising) but also a higher probability of receiving a graft compared to ME-non-PSC patients. Patients with PSC experienced significantly lower mortality post-transplant. However, when looking at patients alive 3 years after the transplant, patients with PSC had an almost eightfold increased risk of being listed again for a retransplant compared to patients with non-PSC [1].

The authors rightly point out that the current allocation policy of ET gives patients with PSC an advantage over other candidates on the waiting list when exception points (ME) are being granted. While not questioning the validity of the current system, altogether they provide data that may help to shape future policies of ET.

Regardless of the underlying disease, when it comes to make decisions about prioritization on the waiting list, the natural course of disease has to be determined.

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This is particularly difficult in PSC. PSC is a debilitating cholestatic disease, often associated with inflammatory bowel disease (IBD) which ultimately leads to cirrhosis of the liver. Predominant causes of death are sepsis due to ascending cholangitis and the development of cholangiocarcinoma (CC), including intrahepatic CC, perihilar CC, and extrahepatic CC as well as gallbladder cancer (GBCa). The course is highly variable depending on factors that are not reflected in the current allocation algorithms. Current guidelines of the American College of Gastroenterology (ACG) recommend liver transplantation for patients with PSC in case of decompensated cirrhosis, and these patients should be referred when their MELD score is greater than 14 [2]. A progression to cirrhosis with progressive liver failure is not the real challenge for allocation, and this is reflected by the laboratory-based MELD score. It is rather those patients who have a relatively stable liver function who may be at risk for cholangiosepsis and development of CC.

At UNOS, the latest change in allocation policy was adopted in 2015 [3]: exception points for patients with PSC may be granted if the patient has been in the ICU at least twice over the last 3 months with need for vasopressor therapy and has been shown to have developed cirrhosis PLUS one of two criteria: either a biliary stricture unresponsive to treatment or has been diagnosed with highly resistant infectious organisms (VRE, ESBL,CRE, MDR acinetobacter) [4]. This reflects both the urgent need for transplantation in case of recurrent biliary sepsis and the risk of CC as there is a growing body of evidence that dominant strictures unresponsive to treatment may be a sign of or predispose to CC [5].

Nevertheless, there still is a lack of precise diagnostic algorithms when trying to detect early CC. Tumor markers such as CA19-9 are nonspecific in cholestatic liver disease. Brush cytology of the biliary tree may show signs of dysplasia, but in those patients with dysplasia and no other signs of CC, the time interval of progression to overt CC is not predictable [6]. On the other hand, patients in whom CC was detected within a surveillance protocol had a better 5-year survival with 68% compared to 20% when CC presented in a cohort without surveillance, irrespective of eventual liver transplantation [7].

As with most cancers, age of the patient does play a role, as was pointed out recently by the group of Rupp *et al.* When analyzing their cohort of 215 patients with PSC, they compared those with an age older than 50 years (32/215, 14.9%) with the rest of the cohort to find out that these had a reduced transplantation-free survival (10.5 years vs. 20.8 years) with the leading causes of death being liver failure and CC [8].

With regard to impending liver failure and the need for transplant, the natural history of PSC varies considerably. Boonstra *et al.* [9] could show some years ago in a population-based cohort of 599 patients in NL that included also patients from three Dutch transplant centers that the median (transplant-free) survival after diagnosis was 21.3 years in the entire cohort compared to 13.2 years in the cohort seen at transplant centers. Thus, if viewed from a transplant center's or waiting list perspective alone, there is a risk of bias, be it referral bias or time-lead bias, as exemplified in a recent study from Hannover, Germany [10].

Population-based studies may better reflect prognostic parameters than waiting list cohorts or transplanted cohorts that are analyzed retrospectively. One such study, again from the Netherlands, was published last year. Based on a population of 692 patients with PSC in NL, it proposed a model based on PSC subtype, age at diagnosis, albumin, AST, alkaline phosphatase (AP), and bilirubin. After a median follow-up of more than 9 years (110 months) in these 692 patients, PSC-related death occurred in 10% of patients while 18% underwent liver transplantation. In the validation cohort of 264 patients with a median follow-up of 103 months, PSC-related death occurred in 14% while 7% underwent liver transplantation [11]. The largest study to date analyzing the prognosis of patients with PSC was published last year. In collecting and analyzing the data of 7121 patients from 37 centers in 17 countries, Weismüller *et al.* could demonstrate a risk stratification for the primary endpoint of death or liver transplantation. While older age has a negative impact, female sex and Crohn's disease (as opposed to ulcerative colitis) were associated with improved prognosis as was the small-duct variant of PSC. One important observation was made regarding the secondary endpoint: development of hepatobiliary (HB) malignancy (predominantly CC). The incidence rate of HB malignancy increased with age, with a low incidence of 1.2 per 100 patient years in those younger than 20 years to 21.0 per 100 patients years in those over the age of 60 years. Of importance also was the observation that over one-third of HB malignancies were diagnosed within the first year following the diagnosis of PSC [12].

What does this mean for future allocation policies? We should look at the natural course of disease in population-based studies rather than from a center or waiting list perspective. Recent data, including those

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presented in the timely article of Goet *et al.* in this issue of the journal, may lead to further refinements in allocation policies. Whatever changes are decided, we have to bear in mind that on the background of organ scarcity, favoring one particular group of patients will put other patients on a disadvantage [13].

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