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ORIGINAL ARTICLE

Waitlist mortality and post-transplant survival in patients with cholestatic liver disease – Impact of changes in allocation policy

Katharina Staufer[1], Danijel Kivaranovic[2], Susanne Rasoul-Rockenschaub[1], Thomas Soliman[1], Michael Trauner[3] & Gabriela Berlakovich[1]

[1]Department of Surgery, Division of Transplantation, Medical University of Vienna, [2]Department of Statistics and Operations Research, University of Vienna, Vienna, and [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Austria

Abstract

Background: This study investigated the impact of Model of end-stage liver disease (MELD)-score introduction (MELDi) on waitlist mortality and post-liver transplant (LT) survival in primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).

Methods: LT candidates with PSC or PBC listed between January 1983 and March 2016 were included and followed until December 2016. After MELDi in 2004, PBC patients were listed according to labMELD, PSC patients according to the highest MELD during active cholangitis (chMELD).

Results: In total, 100 PBC and 76 PSC patients were included. Waitlist mortality in PBC was significantly higher than in PSC (16% vs. 5.3%, p = 0.031), whereas PSC patients were significantly more often withdrawn from the waitlist due to improved condition (3.0% vs. 13.2%, p = 0.017). Competing risks analysis identified MELDi (HR = 4.12) and PBC (HR = 2.95) as significant predictors of waitlist mortality. Yet, overall 10 y-patient survival increased after MELDi by 18.8% leading to a 1 y-, 5 y-, and 10 y-patient survival of 98.2%, 70.6% and 70.6% in PBC, and 83.3%, 83.3%, and 80.6% in PSC, respectively.

Conclusions: PSC patients showed significantly lower waitlist mortality irrespective of MELDi, whereas in PBC waitlist mortality further increased after MELDi. Utility of MELD and chMELD did not impair post LT outcome.

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Correspondence

Katharina Staufer, Department of Surgery, Division of Transplantation, Medical University of Vienna, Währinger Gürtel 18-20, A-1090, Vienna, Austria. E-mail: Katharina.Staufer@meduniwien.ac.at

Introduction

Liver transplantation (LT) is the treatment of choice in patients with end-stage cholestatic liver disease. Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) account for approximately 10% of all LT indications in the Unites States (US) and Europe,[1,2] whereas in the Scandinavian countries it even represents the leading cause for LT.[3] Both PBC and PSC, in general, show an excellent outcome after LT reaching 10 year (y) -survival rates of 79.0% and 83.2%, respectively, excelling most other indications.[1] Furthermore, in contrast to other liver diseases, PSC patients seem to be at lower risk of death on the waiting list.[4–6] This, among other reasons, might be attributed to country- and area-specific exception rules that have been established for PSC, resulting in exceptional Model of end stage liver disease (MELD) points within the United Network for Organ Sharing (UNOS), as well as some countries of the Eurotransplant area. This policy has led to some controversion on the preference of PSC patients in the background of a limited donor pool.

Since allocation systems for cholestatic liver diseases in the US, Asia, Scandinavia and the Eurotransplant area are not harmonized,[7,8] data on waitlist mortality and outcome may be biased and hard to compare, and stratification models for patients at risk for death on the waitlist have been claimed.[7] In Vienna, a modified MELD score is used (*ch*MELD, worst lab*MELD* during active *ch*olangitis) for allocation purposes of PSC patients.

However, waitlist mortality and long-term patient survival might have changed since the introduction of MELD score leading to a patient-oriented, sickest-first-policy. Studies showed that patients generally had a lower risk of death or removal from

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the waitlist after MELD introduction independently of LT indication,[9] yet, post LT patient survival rates substantially declined in some countries after its introduction.[10–12] In contrast, a recent UNOS analysis including only patients after MELD introduction demonstrated a significantly higher overall waitlist mortality for PBC patients compared to PSC patients of 21.6% vs. 12.7%,[13] but does not report on post LT outcome.

The present study analyzed waitlist mortality of patients listed for LT due to PSC (based on *ch*MELD score) and PBC (based on MELD score) as well as short- and long-term post-transplant survival prior to and after MELD introduction in Vienna.

Methods

All patients with cholestatic liver disease, such as PBC and PSC, listed for LT between January 1983 and March 2016 were included in the study and followed until December 2016. Data on waitlist mortality, removal from waitlist and its causes, patient survival after transplantation, graft survival, causes of death, need for re-transplantation, concomitant or de novo development of cholangiocarcinoma, occurrence of de novo malignancies after LT, presence of inflammatory bowel disease (IBD), and recurrence of liver disease was collected by retrospective chart review.

Of note, in Vienna patients with PSC are listed according to the worst lab*MELD* during active recurrent *ch*olangitis (chMELD), while patients with PBC are listed for LT based on their current labMELD. Furthermore, time on the waitlist is considered in all patients by adding one point per month waiting time to the MELD score.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki (1964, including current revisions) and GCP Guidelines after approval of the ethics committee of the Medical University of Vienna. Written informed consent was waived according to the ethics committee.

Statistical considerations

Quantitative variables were compared by Mann–Whitney *U*-tests and expressed as median with interquartile range (IQR). Qualitative variables were described using absolute and relative frequencies and compared by Chi-Square- or Fisher's exact tests, as appropriate. Waitlist mortality defined as time on the waiting list in months, until death or removal from the waiting list was assessed in all patients. In order to identify risk factors of waitlist mortality a multivariate competing risks regression analysis (Fine Gray model) was performed accounting for liver disease entity, age, sex, and MELD introduction. Waitlist mortality or delisting due to poor condition was considered as the outcome of interest, LT was modeled as competing risk and all other outcomes were censored at the date of delisting. Post-transplant patient and graft survival (event defined as either re-transplantation or death) was estimated using the Kaplan–Meier method. Log–Rank tests were used to compare survival curves. To account for a possible bias due to changing allocation systems in Vienna in 2004, a further comparative analysis for patients listed within the preMELD era was performed by calculation of the labMELD/chMELD as a measure of disease severity in all patients. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM Statistics SPSS 24.0 (IBM Corp., Armonk, NY) and R 3.3.1.

Results

Characteristics of patients listed for liver transplantation

In total, 176 patients were included in the study, 100 patients with PBC (87.0% female; median age: 54.1 y, IQR: 48.2–61.8) and 76 patients with PSC (44.7% female; median age: 46.1 y, IQR: 35.3–52.2). Patient characteristics at time of listing for LT are presented in Table 1. Of note, CCA was neither found prior to listing for LT, nor was it considered an indication for LT in any of the patients.

Waitlist mortality and reasons for delisting

Reasons for removal from the waiting list are displayed in Table 2a. All over waitlist mortality was 11.4% (20/176). Waitlist

Table 1 Patient characteristics at time of listing for liver transplantation

	All patients N = 176	PBC N = 100	PSC N = 76	p-value
Age at listing (y) median (IQR)	50.9 (44.0; 59.0)	54.1 (48.2; 61.8)	46.1 (35.3; 52.2)	<0.001
Sex; % female (n)	68.8 (121)	87.0 (87)	44.7 (34)	<0.001
Blood group, % (n)				
A	43.2 (76)	44.0 (44)	42.1 (32)	0.757
B	11.4 (20)	9.0 (9)	14.5 (11)	0.267
AB	6.3 (11)	3.0 (3)	10.5 (8)	0.059
0	38.6 (68)	43.0 (43)	32.9 (25)	0.156
Missing	0.6 (1)	1.0 (1)	0.0 (0)	n.d.
HCC, % (n)	5.1 (9)	7.0 (7)	2.6 (2)	0.303
Harmful alcohol consumption, % (n)	4.0 (7)	3.0 (3)	5.3 (4)	0.467
AIH-overlap, % (n)	8.5 (15)	7.0 (7)	10.5 (8)	0.407
CPS, % (n)				
A	9.7 (17)	8.0 (8)	11.8 (9)	0.307
B	43.8 (77)	43.0 (43)	44.7 (34)	0.492
C	33.0 (58)	38.0 (38)	26.3 (20)	0.171
Missing	13.6 (24)	11.0 (11)	17.1 (13)	n.d.

PBC … primary biliary cholangitis, PSC … primary sclerosing cholangitis, y … year, IQR … interquartile range, HCC … hepatocellular carcinoma, AIH … autoimmune hepatitis, CPS … Child Pugh Score, nd … not done.

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