ORIGINAL ARTICLE

Current policy for allocation of donor livers in the Netherlands advantages primary sclerosing cholangitis patients on the liver transplantation waiting list—a retrospective study

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SUMMARY

Studies from the USA and Nordic countries indicate primary sclerosing cholangitis (PSC) patients have low mortality on the liver transplantation (LTx) waiting list. However, this may vary among geographical areas. Therefore, we compared waiting list mortality and post-transplant survival between laboratory model for end-stage liver disease (LM) and MELD exception (ME)-prioritized PSC and non-PSC candidates in a nationwide study in the Netherlands. A retrospective analysis of patients waitlisted from 2006 to 2013 was conducted. A total of 852 candidates (146 PSC) were waitlisted of whom 609 (71.5%) underwent LTx and 159 (18.7%) died before transplantation. None of the ME PSC patients died, and they had a higher probability of LTx than LM PSC [HR obtained by considering ME as a time-dependent covariate (HR^{ME} 9.86; 95% CI 6.14–15.85)] and ME non-PSC patients (HR^{ME} 4.60; 95% CI 3.78–5.61). After liver transplantation, PSC patients alive at 3 years of follow-up had a higher probability of relisting than non-PSC patients (HR 7.94; 95% CI 1.98–31.85) but a significantly lower mortality (HR 0.51; 95% CI 0.27–0.95). In conclusion, current LTx prioritization advantages PSC patients on the LTx waiting list. Receiving ME points is strongly associated with timely LTx.

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic, slowly progressive cholestatic liver disease characterized by intra- and extrahepatic biliary strictures which may lead to (decompensated) liver cirrhosis [1,2]. The only curative treatment for end-stage PSC is liver transplantation (LTx) with an excellent survival of approximately 80% at 5 years [3–5].

Since December 2006, prioritization for liver donation in the Netherlands is performed using the model for end-stage liver disease (MELD) score, which aims to transplant patients at highest short-term mortality risk based on objective parameters [6,7]. However, allocation of donor livers using the MELD score may be less applicable for PSC patients with other complications than decompensated cirrhosis [8,9], such as recurrent episodes of cholangitis or hepatobiliary malignancies [8–12]. These complications are not associated with progressive worsening of liver function and may hinder laboratory MELD (LM) score prioritization on the LTx waiting list. To counter this problem, PSC patients frequently receive MELD exception (ME) points to prioritize their position on the waiting list and allow equal access to liver donation [13,14].

Recent data from the USA, however, reported that MELD score-prioritized PSC patients were less likely to die or be removed from the LTx waiting list due to clinical deterioration [15,16], irrespective of ME points. These findings question the appropriateness of the current ME point system in prioritization for liver donation. Consequently, in the USA, an effort to change the exception point system has been initiated [17,18]. However, data from European countries on waiting list mortality in PSC patients after introduction of MELD are lacking. Furthermore, analyses in different cohorts are required as waiting list dynamics may vary among geographical areas, for instance because of differences in prevalence of PSC, indications for LTx, deceased organ donation rate and frequency of living donor liver transplantation. This study aimed to compare waiting list mortality as well as post-transplant outcomes between PSC and non-PSC patients by current waiting list policy in the Netherlands. In addition, we aimed to determine the influence of ME points on waiting list survival.

Patients and methods

Population and study design

All patients aged ≥18 years listed for liver transplantation in the period from the introduction of MELD score prioritization in the Netherlands on 16 December 2006 through 31 December 2013 were included. Patients were identified from the Dutch Organ Transplant Registry (NTS). Patients listed for retransplantation, acute liver failure (high urgency status on liver transplantation waiting list) or combined liver and kidney transplantation were excluded.

Data collection

The following clinical and laboratory data were obtained from the NTS: date of birth, sex, indications for LTx, date of listing, biochemistry at listing [bilirubin, creatinine and international normalized ratio (INR)], date and reason of delisting and post-transplant survival. Data were recorded until November 2016. Additional data on reason of waiting list removal and cause of death were collected from the medical records from the three liver transplant centres in the Netherlands: The University Medical Centres in Rotterdam, Groningen and Leiden. Data from the Eurotransplant database were collected to evaluate whether MELD exception (ME) points were awarded during listing. Criteria for awarding exception points are standardized in the Eurotransplant manual [19,20]. In case of standard exceptions (SEs), recipients must fulfil country and disease-specific criteria, whereas nonstandard exceptions (NSEs) have to be approved by a national audit group. The criteria for awarding standard exception points in most countries are as follows: (i) at least two spontaneously occurring septic episodes within 6 months (not due to interventions, not treatable by interventions); (ii) splenomegaly >12 cm; (iii) body mass index reduction >10% within 12 months. At least two of these criteria have to be met to award SE points to PSC patients [19]. However, in the Netherlands, standard exceptions for PSC are not applied. Rather, PSC patients only receive nonstandard exception points in case of recurrent infections [cholangitis/biliary sepsis, at least two episodes within 6 months (not due to interventions, not treatable by interventions) with hospitalization]. These NSEs are strictly enforced. The corresponding centre submits the request to the audit group which comprises auditors from all Dutch liver transplant centres who then vote on the request.

This study was conducted in accordance with the protocol and the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Research Board of the corresponding centre and, at each participating centre, in accordance with local regulations.

Calculations

We calculated laboratory MELD score using the formula: $0.957 \times \text{Log}_e$ (creatinine mg/dl) + $0.378 \times \text{Log}_e$ (bili mg/dl) + $1.120 \times \text{Log}_e$(INR) + 0.643. Laboratory values less than 1.0 were set to 1.0 in the calculation; maximum serum creatinine in the equation was 4.0 mg/dl; and laboratory MELD scores exceeding 40 were adjusted to 40 [19].

Statistical analysis

The primary outcome was mortality on the liver transplantation waiting list, defined as the combined endpoint of death or waiting list removal due to clinical deterioration. Removal due to clinical deterioration was considered equal to death, as a fatal outcome in patients 'too sick to transplant' is nearly always inevitable. Patients removed due to clinical improvement, refusal and addiction or mental problems as well as waiting list candidates still alive on the waiting list at the end of follow-up were censored at withdrawal from the waiting list or end of the study.

Statistical analyses were performed with IBM SPSS Statistics version 22.0 (Released 2013, IBM Corp., Armon, NY, USA) and SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). Data are presented as median and interquartile range (IQR) for continuous variables. Differences in baseline characteristics were compared using the chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. A value of $P < 0.05$ was considered to be statistically significant.

In our study, the three competing outcomes on the waiting list were LTx, death and removal for other reasons. In conventional survival analysis, patients are assumed to have only one type of event during follow-up. Consequently, these analyses yield less accurate estimates of waiting list survival: overestimation of the probability of death on the waiting list on the one hand and underestimation of the probability of LTx on the other hand [21,22]. Therefore, to determine whether there were significant differences between PSC and non-PSC patients in waiting list survival, we performed competing risk analyses. This method uses cumulative incidence curves based on survival functions per event type and permits simultaneous assessment of the different outcomes [21,22].

To determine whether there were significant differences between ME and LM candidates in waiting list survival, the impact of individual covariates on the instantaneous hazard rate of events was assessed with univariate and multivariable Cox proportional hazard models. The time until patients received ME points was modelled as a time-dependent covariate. In multivariable analyses, we used informal methods, keeping ME points and PSC versus non-PSC as a covariate in the model, as well as backward stepwise selection containing covariates with $P < 0.20$ in univariable Cox regression.

For transplanted patients, we assessed post-transplant outcomes (relisting for LTx or death) using Cox proportional hazard analyses. For the assessment of relisting for LTx, we used the landmark method [23]. In these analyses, time starts at a clinically meaningful fixed time point after an intervention or initiation of therapy. As one of the main reasons for relisting for LTx in PSC patients is recurrence with a median time to recurrence ranging from 3 to 5 years [24–28], we chose 3 years as a fixed time point, but also applied the landmark method at multiple time points between 1 and 3 years of post-transplant follow-up.

Results

Study population characteristics

During the study period, 852 candidates (146 PSC and 706 non-PSC) were listed for LTx in the Netherlands. The main indications for liver transplantation were hepatocellular carcinoma (HCC; $n = 237$), cholestatic liver disease/autoimmune hepatitis ($n = 218$), alcoholic liver disease ($n = 142$) and viral hepatitis ($n = 77$; Table S1). Two-thirds were male (68.0%); the [median (IQR)] age was 54.0 (46–61) years. PSC patients were significantly younger than non-PSC patients ($P < 0.001$; Table 1). The median laboratory MELD score at listing was not significantly different between PSC patients and non-PSC patients. Bilirubin was higher in PSC patients, while creatinine and INR levels were significantly higher in non-PSC patients ($P < 0.001$; Table 1).

MELD exception points on the liver transplantation waiting list

During the study period, ME points were granted to 22/146 (15.1%) PSC patients and to 228/706 (32.3%) non-PSC patients. In PSC patients, all ME points awarded were NSE. In the non-PSC group that received ME points, 27/228 (11.8%) patients received NSE points and 201/228 (88.2%) received SE points. Standard exceptions were mostly awarded for HCC (171 patients). Overall, PSC patients were less likely to receive ME points compared to non-PSC patient (HR

Table 1. Demographic and clinical characteristics of patients at the time of listing for liver transplantation.

Characteristics	Total cohort (n = 852)	PSC patients (n = 146)	Non-PSC patients (n = 706)	P-value
Gender, male	579 (68)	106 (73)	473 (67)	0.186
Age at listing	54.0 (46-61)	46.5 (39-54)	56.0 (49-61)	**<0.001**
Blood type				
O	392 (46)	66 (45)	326 (46)	0.828
A	314 (37)	58 (40)	314 (44)	
B	102 (12)	15 (10)	102 (14)	
AB	44 (5)	7 (5)	44 (6)	
Laboratory values at listing				
Total bilirubin (μM)	38 (16-87)	60 (27-136)	35 (16-76)	**<0.001**
Creatinine (μM)	71 (58-89)	63 (52-77)	72 (60-93)	**<0.001**
INR	1.3 (1.1-1.5)	1.2 (1.0-1.4)	1.3 (1.1-1.5)	**<0.001**
MELD score	13.0 (9.0-18.0)	13.5 (9.0-18.0)	13.0 (8.0-18.0)	0.532

INR, international normalized ratio; MELD, model for end-stage liver disease.

Data are presented as number and percentage for categorical data, or as median and interquartile range for continuous data. P-values are calculated using the chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables. *P*-values illustrated in bold reflect significant findings below the cut-off of 0.05.

0.34; (95% confidence interval [CI]): 0.22–0.53; $P < 0.001$). In sub-analyses, HCC patients had higher probability of receiving ME points (HR 10.1; CI 6.39–16.0; $P < 0.001$) compared to PSC, whereas patients with alcoholic and patients with viral liver disease had a lower chance (HR 0.32; CI 0.12–0.83; $P = 0.020$ and HR 0.23; CI 0.05–0.98; $P = 0.026$), respectively.

Outcomes on the liver transplantation waiting list

At the end of follow-up of median 214 (IQR 62–435) days (range 8.8 years), 609 patients (71.5%) underwent LTx, 159 (18.7%) died or were withdrawn due to clinical deterioration, 60 (7.0%) were withdrawn for other reasons, and 25 (2.9%) were still on the waiting list as of the November 2016 (Fig. S1). The causes of death or removal due to clinical deterioration are presented in Table 2. A total of 36 (4.2%) patients were removed because of clinical improvement and 24 (2.8%) for other reasons (refusal, addiction or mental problems).

A total of 112/146 (76.7%) PSC patients and 397/706 (56.2%) non-PSC patients underwent LTx. Six of the 146 (4.1%) PSC patients were removed because of clinical improvement and 2/146 (1.4%) for other reasons. For non-PSC patients, these numbers were 30/706 (4.2%) and 22/706 (3.1%), respectively. In the PSC group, a total of 18/146 (12.3%) died or were removed due to clinical deterioration on the liver transplantation waiting list compared to 141/706 (20.0%) in the non-PSC group. None of the PSC patients died or deteriorated due to cholangitis (Table 2). Three of the 18 PSC patients were removed because of clinical deterioration (assumed to have died in our analyses): two patients developed cholangiocarcinoma and one patient gallbladder carcinoma. Two of these patients died within 81 and 138 days after waitlist removal, respectively. One patient was still alive 908 days after waitlist removal. In the non-PSC group, 54/141 were removed because of clinical deterioration. Data on survival after removal from the liver transplantation waiting list were available for 50/54 patients. Three patients were still alive at 118, 370 and 708 days after waitlist removal, respectively. The other 47 patients died after waitlist removal within a median of 181 (IQR 44–400, range 2–1282) days. Most patients (33/47) died within 1 year after waitlist removal.

Eighteen (14.5%) of the 124/146 (84.9%) PSC patients prioritized on laboratory MELD scores died; 8 (6.5%) were removed from the waiting list, 90 (72.6%) underwent LTx, and 8 (6.5%) were still alive on the waiting list as of the November 2016. None of the PSC patients prioritized on (N)SE MELD scores (22/146; 15.1%) died during follow-up, and all these patients received a LTx. Therefore, Table 2 shows the causes of death or removal for the laboratory MELD-prioritized PSC patients.

One hundred and fourteen patients (23.8%) in the LM non-PSC group [478/706 (67.7%)] died, 44 (9.2%) were removed from the waiting list, 309 (64.6%) received LTx, and 12 (2.5%) were still alive on the waiting list as of the November 2016 (Fig. S1). Twenty-seven patients (12%) in the ME non-PSC

Table 2. Waitlist removal due to death or clinical deterioration.

	Total cohort (n = 159)	PSC patients (n = 18)	Non-PSC patients (n = 141)*
End-stage liver disease/Acute on chronic liver failure	62 (39)	8 (44)	54 (38)
Infection/sepsis	20 (13)	6 (33)	14 (9.9)
SBP	6	2	4
Pneumonia	3	1	2
Focus unclear	11	3	8
Bleeding	11	0	11 (7.8)
Progression malignancy	45 (28)	4 (22)	41 (29)
CCA	2	2	0
HCC	39	0	39
Other	4	2†	2
Other (nonliver related)	12 (7.5)‡	0	12 (8.5)‡
Unknown	9 (5.7)	0	9 (6.4)

SBP, spontaneous bacterial peritonitis; CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma.

Data are presented as number (and percentage) and represent the cumulative occurrence of endpoints in the period from waiting list acceptance until the end of the study in November 2016.

*Fifty-four patients were assumed to have died after waitlist removal due to clinical deterioration The cause of clinical deterioration could be identified for 51/54 patients: 35 patients suffered progression of HCC, one patient developed HCC, six developed end-stage liver disease, two patients had cancer, and seven patients had a nonliver-related cause of clinical deterioration.

†One patient was removed because of gallbladder carcinoma.

‡One Non-Hodgkin's mantel cell lymphoma, one bladder carcinoma, one Alzheimer's disease, two heart failure/cardiac decompensation, one oropharyngeal cancer, one cardiopulmonary problems, three cerebral vascular accident, one melanoma and one lung carcinoma.

group [228/706 (32.3%)] died, 8 (3.5%) patients were removed from the waiting list, 188 (82%) received a LTx, and 5 (2.2%) were still alive on the waiting list as of November 2016.

Outcome on the LTx waiting list: longer waiting time and low mortality for PSC patients

Although PSC patients had a significantly longer waiting time until delisting compared to non-PSC patients (HR 0.73; CI 0.61–0.88; $P = 0.001$), they had significant better waiting list survival ($HR_{univariate}$ 0.48; CI: 0.29–0.78; $P = 0.003$) in the cumulative incidence curves of the competing risk analyses (Fig. 1a and b). There were no differences in the rate of liver transplantation between PSC and non-PSC candidates (HR 0.84; CI 0.69–1.03; $P = 0.101$; Fig. 1a and b).

Patients who had received MELD exception points had a higher chance of LTx (HR obtained by considering MELD exception points as a time-dependent covariate (HR^{ME}) 3.59 CI 3.01–4.28; $P < 0.001$; Table 3). In addition, ME PSC patients had a significantly higher probability of LTx than had LM PSC patients (HR^{ME} 9.86 CI 6.14–15.85; $P < 0.001$) and ME non-PSC patients (HR^{ME} in ME non-PSC patients 4.60 CI 3.78–5.61; $P < 0.001$). The analyses revealed that the effect of age at listing was not significantly different between PSC and non-PSC patients (P-value for effect modification 0.442).

In univariate analyses, ME points (considered as a time-dependent covariate) had a numerical benefit, however not significant ($P = 0.069$), whereas in multivariable analyses those receiving ME points had lower risk of waiting list mortality (Table 4). In addition, the multivariate analyses showed that the differences in waiting list survival between PSC and non-PSC patients observed in competing risk analyses are largely explained by age and MELD scores at listing and ME points. Older age and higher MELD scores were associated with a poorer prognosis, whereas receiving ME points was associated with a better prognosis (Table 4). The analyses revealed that the effect of ME points and age at listing was not significantly different between PSC and non-PSC patients (P-value for effect modification of PSC 0.944 for ME points and 0.815 for age at listing).

Post-transplant survival is better in PSC patients, although relisting is more common

Analysis of the data of 609 transplanted patients with a mean follow-up after the first liver transplantation of

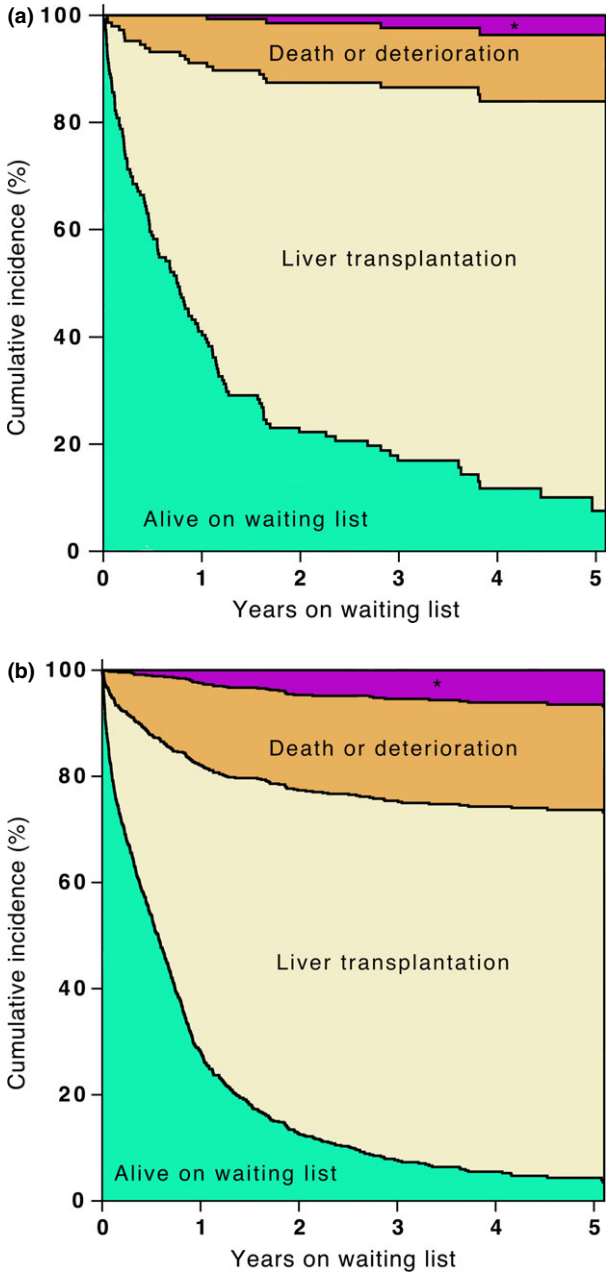

Figure 1 Competing risk analyses with cumulative incidence curves comparing the outcomes on the liver transplantation waiting list (removal, death or clinical deterioration, Ltx and still alive) in PSC patients (a) and non-PSC patients (b). The cumulative incidence curves show that although PSC patients had a longer waiting time on the LTx waiting list, they had better waiting list survival compared to non-PSC patients in univariable analyses. The transplantation rate between both groups was equal. *Other reasons for removal from the waiting list including clinical improvement, patients' refusal and addiction or mental problems.

5.89 years (range: 0 days–9.07 years) revealed no differences between PSC and non-PSC patients for the combined endpoint of death or relisting for LTx ($P = 0.332$; Fig. 2a). Interestingly, in subanalyses, PSC patients had a significantly lower risk of death than non-PSC patients (HR 0.51; CI 0.27–0.95; $P = 0.035$; Fig. 2b). The post-transplant survival rate at 1, 3 and 5 year(s) of follow-up was 91.7%, 90.5% and 90.5% in PSC patients, while these rates were 91.2%, 83.5% and 75.6% in non-PSC patients. Proportions of patients relisted for LTx did not significantly differ between the PSC and non-PSC groups ($P = 0.763$). However, after 3 years of follow-up, there was a clear distinction between PSC and non-PSC patients in this respect. The relisting rates for LTx at 1, 3 and 5 year(s) were 10.7%, 14.7% and 26.8% in PSC patients, while these rates were 12.8%, 15.4% and 17.5% in non-PSC patients. An increased HR of relisting was observed in PSC patients still alive at 3 years of follow-up, and over the period 1 year and 3 years post-transplant (HR hazard of relisting 7.94; CI 1.98–31.85; $P = 0.003$), as compared to non-PSC patients according to the landmark method [23] (Fig. 2c).

Discussion

The results of this nationwide study in the Netherlands demonstrate that under current policy for liver donation prioritization the waiting time for PSC patients is longer than that of patients with other indications for liver donation. However, this does not result in increased waiting list mortality or a lower probability of liver transplantation. Although receiving ME points on the LTx waiting list during follow-up is associated with better survival and higher probability of LTx across all indications for liver donation, this finding is most pronounced in PSC patients. PSC patients who have received MELD exception points have a higher probability of liver transplantation than non-PSC patients, and no mortality during waiting for LTx was observed in these patients. Lastly, our study suggests that post-transplant PSC patients have better post-transplant survival than non-PSC patients, although they are more often relisted for liver transplantation.

Our study results are in accordance with those of Freeman *et al.* [29], who reported a lower risk of death or removal from the LTx waiting list in PSC patients compared to other indications for LTx after the introduction of MELD allocation in the USA. Moreover, our findings match those from a Scandinavian study that found an equal probability of LTx for PSC and non-PSC patients and lower waiting list mortality in PSC patients [30]. These results are not directly applicable to the Netherlands or the USA, as Scandinavian countries do not use the MELD score for liver allocation. Lastly,

Table 3. The association of time-dependent MELD exception points with liver transplantation.

	Univariable analysis				Multivariable analysis			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Male sex	0.97	0.82	1.15	0.725				
Age at listing	1.01	1.00	1.02	0.046	1.02	1.01	1.02	<0.001
MELD score at listing	1.10	1.08	1.12	<0.001	1.10	1.09	1.12	<0.001
PSC vs. non-PSC	0.84	0.69	1.03	0.101				
Without exception points					0.95	0.74	1.21	0.654
With exception points*					2.27	1.45	3.56	<0.001
ME points vs. LM*,†	3.59	3.01	4.28	<0.001				
PSC	6.87	4.24	11.13	<0.001	9.86	6.14	15.85	<0.001
Non-PSC	3.38	2.78	4.10	<0.001	4.60	3.78	5.61	<0.001

HR, hazard ratio; MELD, model for end-stage liver disease; PSC, primary sclerosing cholangitis; ME, MELD exception; LM, laboratory MELD.

*These hazard ratios were obtained by considering MELD exception points as a time-dependent covariate in univariable and multivariable analyses.

†The effect of receiving MELD exception points on the probability of liver transplantation was significantly different between PSC and non-PSC patients (interaction, $P = 0.003$). PSC patients that received MELD exception points during follow-up were more likely to receive liver transplantation than non-PSC patients that received ME points.

Table 4. The association of time-dependent MELD exception points with death or clinical deterioration.

	Univariable analysis				Multivariable analysis			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Male sex	1.11	0.80	1.54	0.538				
Age at listing	1.04	1.02	1.06	<0.001	1.05	1.04	1.07	<0.001
PSC vs. non-PSC	0.48	0.29	0.78	0.003	0.72	0.43	1.21	0.211
MELD score at listing	1.11	1.09	1.13	<0.001	1.15	1.13	1.18	<0.001
MELD exception points*	0.67	0.44	1.03	0.069	0.43	0.28	0.68	<0.001

HR, hazard ratio; MELD, model for end-stage liver disease; PSC, primary sclerosing cholangitis.

*These hazard ratios were obtained by considering MELD exception points as a time-dependent covariate in univariable and multivariable analyses.

also consistent with our findings, a recent nationwide study from the USA in more than 79 000 patients reported that MELD score-allocated PSC patients were less likely to die or be removed from the LTx waiting list due to clinical deterioration compared to non-PSC patients, irrespective of MELD exception points [15].

The MELD score comprises laboratory parameters that may not reflect PSC disease severity [6,7,31]. As such, as observed in the current study, time on the LTx waiting list may be longer for PSC patients, thereby increasing the risk of development of PSC-associated complications [14,15]. In this regard, cholangiocarcinoma (CCA), which develops in 6%–36% of PSC patients, is an important complication [9,12,32,33]. Nonetheless, only 3 (2%) patients were withdrawn because of biliary tract cancer (2 CCA and 1 gallbladder carcinoma) in our study. This can be explained by CCA being a contraindication for liver transplantation during the study period [19]. Interestingly, but in keeping with Goldberg *et al.* [16], none of the PSC patients died or deteriorated due to fulminant cholangitis; one of the PSC-associated complications suggested to affect waiting list mortality and for which standard ME points can be granted [19,20].

Although the exact reasons for relisting after the first liver transplantation in the current study are unknown, one might speculate that the observed higher probability of relisting in PSC patients was due to recurrent disease. While the 5 year post-transplant survival of PSC patients exceeds 80% [3–5], approximately 20% of PSC

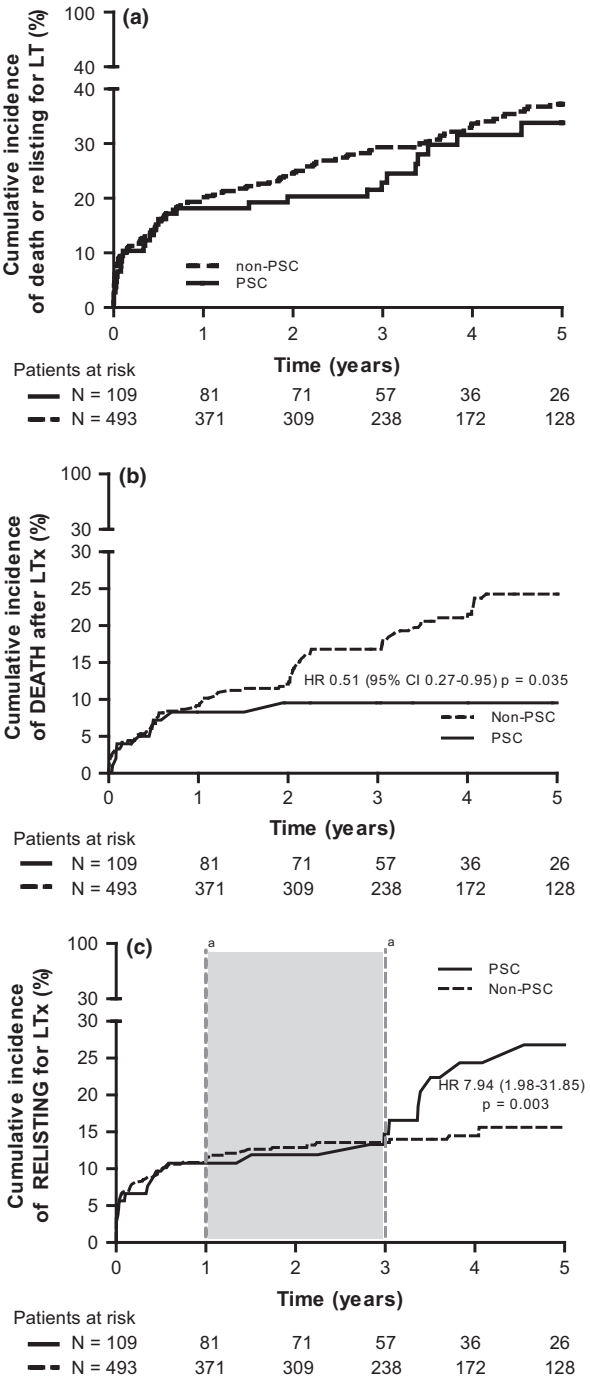

Figure 2 Cumulative incidence of post-transplant relisting and death Kaplan–Meier estimates of post-transplant outcomes, stratified according to main indication for liver transplantation (PSC versus non-PSC). The solid line shows values for PSC patients and the dotted line for non-PSC patients. (a) Cumulative incidence of relisting for liver transplantation or death, whichever came first. There were no differences between PSC and non-PSC patients ($P = 0.301$). (b) PSC patients alive after 3 years post-transplant follow-up had higher probability of relisting for LTx compared to non-PSC patients. (c) Overall, PSC patients had a lower risk of post-transplant death compared to non-PSC patients. [a]Grey area represents interval in which the landmark method was applied.

patients will develop recurrent disease within a median time of 3–5 years [24–28]). This is associated with increased risk of graft loss and mortality [27,28,34]. Interestingly, recently published data from the United Network for Organ Sharing (UNOS) by Henson *et al.* [35] indicate that PSC patients with a late retransplantation for recurrent disease have an excellent 5-year graft survival of approximately 75.7%. Based on these and our results, PSC patients have a high 'transplant benefit', meaning a high post-transplant survival in addition to postacceptance survival. From an economic and ethical perspective, this is an important consideration in the prioritization for liver donation. The high transplant benefit in PSC patients may warrant currently observed waiting list advantage.

Strengths of our study are its nationwide coverage and long-term follow-up period from 2006 to 2016. Furthermore, we used competing risk analyses. Whereas normal survival analyses would have provided an overestimation of the risk of death or clinical deterioration and an underestimation of the probability of LTx, our analyses provide a reliable overview of LTx waiting list survival. Moreover, in addition to an in-depth analysis of the influence of ME points on waiting list survival, we assessed 'transplant benefit' (the combination of postacceptance survival and post-transplant survival) of the current allocation system. As such, we provide a comprehensive overview of LTx waiting list dynamics of PSC patients in the Netherlands.

However, some limitations need to be considered. First, the considerable proportion of HCC patients may have influenced the results, as early-stage HCC patients receive standard ME points. Still, when we excluded the HCC group from analysis, we found no differences in granting ME points in PSC versus non-PSC patients, and the results of all other analyses remained unchanged. Second, our study only indicates that the advantage obtained from current ME policy is greater than appropriate. To obtain a definite answer on the appropriateness of ME priority, a study to determine the outcomes of all patients in the counterfactual case they had not been given ME priority would be needed. However, the current data do not allow for such a comparative analysis. In addition, to study this in a prospective study would raise ethical issues. Third, in our study, removal due to clinical deterioration was considered equal to death. However, studies using the US Organ Procurement and Transplantation Network (OPTN) have shown that removal for medical deterioration is not always a reliable indicator of death [36]. While in the USA a marked variability in the use of

removal codes among the different OPTN regions may significantly impact the estimates of deaths, this variation is negligible in the Netherlands as LTx is centralized in three centres. Moreover, in our study, most patients that deteriorated died within 1 year after removal (2/3 PSC and 33/50 non-PSC). Therefore, it is reasonable to assume that the impact of considering clinical deterioration equal to death has a negligible impact on our results. Finally, this nationwide study may be difficult to generalize. However, several European countries use the same standard MELD exceptions that are common to the Eurotransplant system. Consequently, variability mainly concerns the non-standard ME points. Furthermore, in the USA, the PSC aspect of exception points and other challenges regarding the ME system (including lack of standardization, geographical differences in the approval of exceptions and limited evidence base to support certain exceptions [17,37,38]) have already triggered a broader effort to change the exception point system [17,18]. Our data warrant reconsideration of the ME system in Europe, similar to initiatives in the USA.

In conclusion, this nationwide study in the Netherlands confirms previously reported challenges in granting equal access to donor livers across patients with various end-stage liver diseases. Despite a longer waiting time, current MELD score prioritization does not result in increased waiting list mortality or a lower probability of liver transplantation in PSC patients, while the MELD exception point system advantages PSC patients on the liver transplantation waiting list in the Netherlands. These findings need to be weighed against higher transplant benefit in PSC patients during the continuous process of reassessment and adjustment of liver transplantation prioritization.

Authorship

JCG, ACV and BEH: Had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analyses. JCG, ACV, MT, HJM, BEH, BH, APB, WGP, JD, RJP, CK and RAM: Participated in study concept and design. JCG, MT, ACV and CK: Involved in acquisition of data. JCG, MT, ACV and BEH: Performed analysis and interpretation of data. JCG, MT and ACV: Drafted the manuscript. JCG, ACV, MT, HJM, BEH, BH, APB, WGP, JD, RJP, CK and RAM: Critically revised the manuscript for important intellectual content. JCG, MT, ACV and BEH: Performed statistical analysis. ACV, HJM and BEH: supervised the study.

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Conflict of Interest

The authors declare that they have not anything to disclose regarding funding or conflict of interest with respect to this manuscript.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Flow diagram of outcomes. Patients granted MELD Exception (ME) points in the period from waiting list acceptance (cumulative) until the end of the study in November 2016 are included in the group 'Exception points'. Numbers represent cumulative occurrence of endpoints in the period from waiting list acceptance until the end of the study in November 2016.

Table S1. Main indications for liver transplantation.

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