ORIGINAL ARTICLE

Primary biliary cirrhosis has high wait-list mortality among patients listed for liver transplantation

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SUMMARY

Patients with primary sclerosing cholangitis (PSC) have frequent episodes of cholangitis with potential for high mortality while waiting for liver transplantation. However, data on wait-list mortality specific to liver disease etiology are limited. Using United Network for Organ Sharing (UNOS) database (2002–2013), of 81 592 listed patients, 11 284 (13.8%) died while waiting for transplant. Primary biliary cirrhosis (PBC) patients ($N = 3491$) compared to PSC ($N = 4905$) differed with age (56 vs. 47 years), female gender (88% vs. 33%), black race (6% vs. 13%), and BMI (25 vs. 27), $P < 0.0001$ for all. A total of 993 (11.8%) patients died while waiting for the transplant list. Using competing risk analysis controlling for baseline recipient factors and accounting for receipt of liver transplantation (LT), PBC compared to patients with PSC had higher overall and 3-month wait-list mortality (21.6% vs. 12.7% and 5.0% vs. 2.9%, respectively, Gray's test $P < 0.001$), [1.25 (1.07–1.47)]. Repeat analysis including all etiologies showed higher wait-list mortality for PBC compared to most etiologies, except for patients listed for diagnosis of alcoholic liver disease (ALD) + hepatitis C virus (HCV). Patients with PBC have high mortality while waiting for liver transplantation. These novel findings suggest that patients with PBC listed for LT may be considered for model for end-stage disease (MELD) exception points.

Transplant International 2017; 30: 454–462

Key words
cirrhosis, transplantation, wait-list mortality

Received: 4 July 2016; Revision requested: 1 August 2016; Accepted: 14 October 2016; Published online: 14 November 2017

Introduction

Liver transplantation (LT) is a definitive treatment option for patients with end-stage liver disease [1,2]. However, patients have a risk of dying while waiting for LT due to shortage of donor livers secondary to imbalance between demand and supply [2–4]. The model for end-stage liver disease (MELD) score, introduced in 2002, is quite accurate in predicting 3 months mortality and has since been used for listing patients for LT [5]. MELD score does not take into consideration the liver disease etiology in predicting wait-list mortality (WLM) [5].

Survival after LT varies by liver disease etiology and patients with chronic cholestatic liver disease due to primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) have excellent survival [1,2]. However, data on WLM based on liver disease etiology especially on comparing for PBC listed with PSC listed patients are limited. In one study, patients with PSC compared

doi:10.1111/tri.12877

to other liver disease etiologies were less likely to become too sick or die while waiting for LT [6]. Another recently reported study from Japan on listing patients based on the Child-Turcotte-Pugh score showed higher WLM among patients with PBC compared to patients listed for hepatitis C virus (HCV) related cirrhosis [7]. However, this difference was not observed when the analysis was controlled for MELD score [7].

Patients with PSC frequently develop bacterial cholangitis, which could potentially impact the WLM [6,8]. Hence, we hypothesized that WLM will be higher among patients listed for LT due to cirrhosis secondary to PSC as compared to patients listed for PBC. We performed this study among candidates listed for LT during the MELD era with aim of examining the impact of liver disease etiology on the WLM among patients with end-stage liver disease and cirrhosis due to PSC or PBC.

Materials and methods

Establishing the study population

The United Network for Organ Sharing (UNOS) database was queried for candidate listings for first LT in adults (age >18 years) between 2002 and 2013. The study population was stratified into eight groups using the UNOS etiology codes at the time of listing for transplantation: PBC, PSC, HCV infection, alcoholic liver disease (ALD), ALD + HCV, nonalcoholic steatohepatitis (NASH), cryptogenic cirrhosis (CC), and hepatitis B virus (HBV) infection. Patients with concomitant hepatocellular carcinoma (HCC) were excluded to keep the study population homogeneous as these patients as these patients receive MELD exception points for listing and also the risk for HCC varies for liver disease etiology.

Analyses

As the mortality while waiting on the transplant list is dependent upon receipt of liver transplant, withdrawal from the waiting list due to deteriorating condition and withdrawal from the waiting list due to improved condition, we used the competing risk analysis to analyze WLM accounting for these events. Candidates listed for liver transplant were analyzed for WLM specific to liver disease etiology. Further analysis was focused on patients listed for PSC or PBC as both these conditions are grouped as chronic cholestatic liver diseases with excellent post-transplant survival. Baseline characteristics at listing were compared for patients listed for PBC or for PSC. Categorical variables were compared using chi-squared test. Continuous variables were compared using the *t*-test and analysis of variance test.

Cumulative incidence rates for WLM and each competing event were generated comparing PSC and PBC for WLM. As the MELD score accurately predicts 3-month mortality, similar cumulative incidence rates were generated for mortality at 3 months from listing. Patients surviving at 3 months from listing were censored for this subgroup analysis. Gray's test was used for these analyses. Fine and Gray regression model was built to determine independent effect of disease etiology (PBC versus PSC) after accounting for competing events and controlling for variables that were significantly different between the two groups at baseline and other clinically relevant variables, which could have confounded the outcomes. Effect size on Fine and Gray regression analyses was given as hazard ratio (HR) with 95% confidence interval CI. The two etiologies were also compared for (i) cause specific mortality while waiting for LT and (ii) causes of removal from LT list other than WLM. As patients with PSC often receive exception MELD points for episodes of cholangitis, we performed subgroup analyses after excluding patients who had received MELD exception points. As PBC is more common in females and there are data suggesting higher wait-list mortality in females compared to males, we performed subgroup analysis in male patients. To understand how the PBC and PSC are different from other liver disease etiologies on WLM and other causes of removal from the transplant list, we repeated our analyses of cumulative incidence rates on WLM including all liver disease etiologies. All analyses were performed using the STATISTICAL ANALYSIS Software 9.4 (SAS Institute, Cary, NC, USA) and R software version 3.1.3 (www.r-project.org). *P* values less than 0.05 were considered significant.

Results

Prevalence of wait-list mortality

Of 81 592 candidates listed for LT during 2002–2013 in the USA for eight selected indications, 11 284 (13.8%) died while waiting for LT. On competing risk analysis, the rate of WLM was 27.8%, 27.1%, 26.8%, 25.2%, 22.9%, 21.6%, 16.6%, and 15.6% for PBC (n = 3491), ALD + HCV (6998), CC (n = 7865), HCV (n = 32 591), ALD (n = 16 606), NASH (n = 6343), PSC (n = 4905), and HBV (n = 2793), respectively.

Baseline characteristics: candidates listed for PSC versus for PBC

A total of 8396 candidates were listed for end-stage liver disease and cirrhosis secondary to PSC ($N = 4905$) or PBC ($N = 3491$). At the time of listing for LT, patients with PBC compared to PSC were more likely to be elderly females and diabetic and less likely to be Blacks. Compared to PSC, patients with PBC were more likely being overweight, having lower serum bilirubin and MELD score at the time of listing for LT. The ABL blood groups were similar comparing the two liver disease etiologies (Table 1).

Wait-list mortality and other causes of removal from the transplant list: PSC versus PBC

Patients listed for PBC as compared to PSC had similar median time to removal from the list after being listed for LT (214 vs. 203 days, $P = 0.34$). Over this period, 993 patients (418 listed for PSC) were removed because of death while waiting for LT. WLM was higher for patients listed for PBC compared to PSC listed patients (21.6% vs. 12.7%, Gray's test $P < 0.001$). The WLM for patients listed for PSC varied from 11% to 22% across 11 UNOS regions with lowest mortality in region 3 and highest in region 5. Similarly, the WLM for patients listed for PBC varied from 9% to 53.7% with lowest mortality in region 3 and highest in region 5.

Among patients who survived on the LT list, causes of removal from the list were deceased donor LT, live donor LT, being too sick for LT, and improved clinical condition of the patient (Fig. 1). Comparing patients listed for PSC with patients listed for PBC, the respective proportions for these causes of removal from LT list were 54.4%, 7.5%, 5.7%, and 2.6%, vs. 55.8%, 6.0%, 9.3%, and 3.1% (Fig. 1). About 29.8% and 25.8% of patients listed for PBC and PSC and surviving on the transplant list were removed from reasons other than receipt of liver transplantation or change in their clinical condition.

The cumulative incidence of WLM was higher for PBC compared to patients with PSC (21.6% vs. 12.7%, Gray's test $P < 0.001$, Fig. 2). Compared to patients with PSC, cumulative incidence of removal from the wait list was higher for patients with PBC due to deteriorating condition (11.2% vs. 8.0%, Gray's test $P < 0.001$) and was lower for receipt of liver transplant (58.6% vs. 68.6%, Gray's test $P < 0.001$). The cumulative incidence of wait-list removal was similar for

Table 1. Baseline listing characteristics comparing patients listed for PSC or PBC.

	Listing diagnosis		
	PSC ($N = 4886$)	PBC ($N = 3473$)	*P*
Age in years (mean, SD)	47, 14	56, 9	<0.001
Median (25–75% IQR)	49 (37–58)	57 (50–63)	
% Females	33	88	<0.001
% Blacks	13	6	<0.001
BMI in kg/m^2 (mean, SD)	25.3, 4.7	27.0, 5.7	<0.001
Median (25–75% IQR)	24.6 (22.1–27.8)	26.1 (22.9–30.1)	
% Blood group A	39	37	
% Blood group B or AB	15	15	0.08
% Blood group O	46	48	
% Diabetes mellitus	13	15	<0.001
Serum bilirubin (mean, SD)	7.4, 8.7	6.7, 8	<0.001
Median (25–75% IQR)	4 (1.7–9.8)	3.6 (1.8–8.1)	
INR (mean, SD)	1.38, 0.61	1.38, 0.50	0.75
Median (25–75% IQR)	1.2 (1.1–1.5)	1.2 (1.1–1.5)	
Serum creatinine (mean, SD)	1.06, 0.86	1.09, 0.80	0.06
Median (25–75% IQR)	0.86 (0.7–1.1)	0.9 (0.7–1.2)	
Serum albumin (man, SD)	3.1, 0.7	3.0, 0.6	<0.001
Median (25–75% IQR)	3.1 (2.6-3.6)	3.0 (2.5-3.4)	
Listing MELD (mean, SD)	16.2, 7.6	16.5, 7.6	0.11
Median (25–75% IQR)	15 (11–20)	15 (11–19)	

PSC, primary clerosing cholangitis; PBC, primary biliary cirrhosis; WLM, wait-list mortality; SD, standard deviation; INR, institutional normalized ratio; MELD, model for end-stage liver disease; BMI, body mass index.

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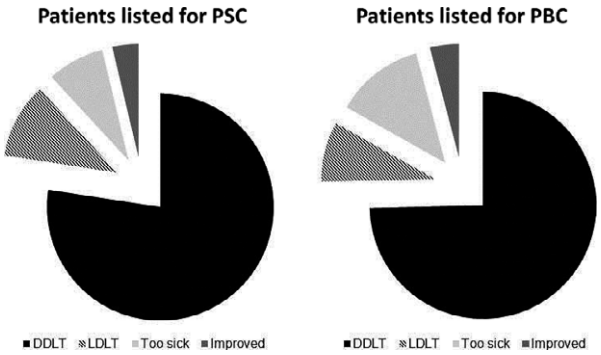

Figure 1 Proportion of patients removed from the liver transplant list secondary to receipt of deceased donor liver transplantation (DDLT), living donor liver transplantation (LDLT), becoming too sick for transplantation (Sick), or improvement in clinical condition (Improved). Results show that patients listed for primary sclerosing cholangitis (PSC, left panel) compared to patients listed for primary biliary cirrhosis (PBC, right panel) were more likely to be removed for receipt of LDLT (7.5% vs. 6.0%, $P = 0.015$). In contrast, patients with PBC compared to patients with PSC were more often removed from the list for becoming too sick for transplantation (9.3% vs. 5.7%, $P < .0001$). Proportion of patients removed from the list for improvement in clinical condition and removed for receipt of DDLT was similar comparing PSC and PBC (2.6% vs. 3.1%, $P = 0.24$, 54.4% vs. 55.8%, $P = 0.26$, respectively).

patients with PBC and patients with PSC due to improved clinical condition of the patient (5.2% vs. 5.8%, Gray's test $P = 0.45$) (Fig. 2). In the Fine and Gray regression analysis, PBC listed patients as compared to those listed for PSC diagnosis were about 25% more likely to die while waiting for LT. Other predictors of WLM were listing year with lower WLM if listing after 2007, age at listing, blood groups A or O, lower serum albumin at listing, UNOS region 5, and listing MELD score (Table 2). With 10-year increase in age of the candidate, the risk for WLM increased by about 35%. Candidate gender, race, and diabetes status were not predictors of the WLM (Table 2).

At 3 months from the time of listing, the cumulative incidence of removal from the wait list remained higher for PBC compared to PSC listed patients due to WLM (5.0% vs. 2.9%; Gray's test $P < 0.001$) or due to deteriorating patient's condition (2.1% vs. 1.4%, Gray's test $P < 0.001$) (Fig. 3). Similarly, the cumulative incidence of removal from the list was lower for patients with PBC due to receipt of liver transplant (24.2% vs. 26.1%, $P < 0.001$) and was similar for removal due to improving patient's condition (Fig. 3). Using the Fine and Gray regression analysis, patients with PBC compared to PSC remained at 35% higher risk for WLM at 3 months from listing for LT with HR of 1.34 (95% CI: 1.01–1.76, $P = 0.047$).

Causes of wait-list mortality: candidates listed for PSC versus for PBC

We also examined the causes of death among patients who died waiting for LT. The cause of death information was available for about 60% of patients. Common causes of deaths while waiting for LT were cardiovascular related, organ failure, infection, hemorrhage, and miscellaneous or other causes (Table 3). Respective proportions of these causes comparing patients listed for

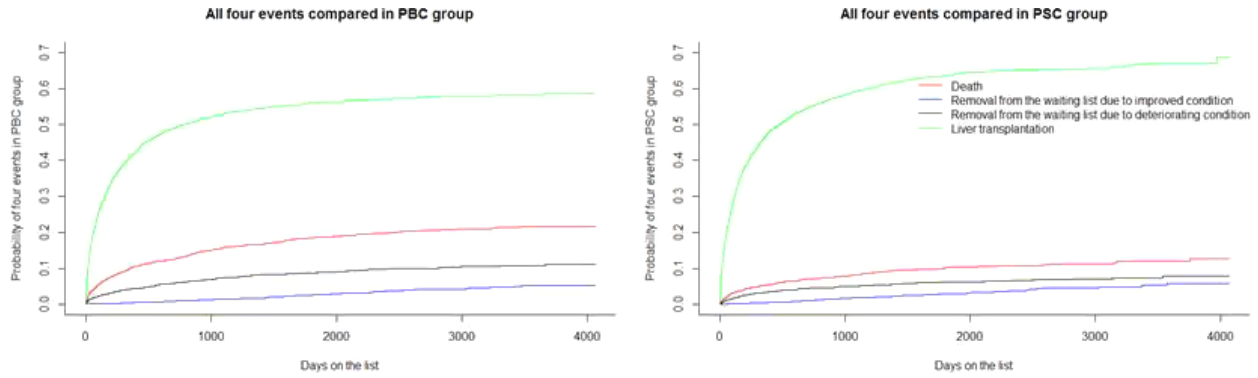

Figure 2 Cumulative incidence function for probability of wait-list mortality (WLM) for overall waiting time in primary sclerosing cholangitis (PSC) group (left) and in primary biliary cirrhosis (PBC) group (right). Results show that the WLM cumulative probability was higher for patients listed for PBC compared to patients listed for PSC for overall WLM (21.6% vs. 12.7%; Gray's test $P < 0.001$). patients with PBC, compared to patients with PSC, had higher cumulative incidence on removal from the waiting list due to deteriorating condition (11.2% vs. 8.0%; Gray's test $P < 0.001$) but lower cumulative incidence on removal from the waiting list due to liver transplantation (58.6% vs. 68.7%; Gray's test $P < 0.001$). The cumulative incidence on removal from the waiting list due to improved condition was lower for PBC compared to PSC, but it is not statistically significant (5.2% vs. 5.8%, Gray's test $P = 0.45$).

Table 2. Fine and Gray regression model for predictors of wait-list mortality.

Variable	Hazard ratio*	95% Confidence interval	*P*
Listing diagnosis: PBC versus PSC	1.25	1.07–1.47	0.006
Listing year	0.96	0.94–0.98	<.001
Age at listing in years	1.03	1.02–1.04	<0.001
Female versus male gender	1.31	1.12–1.54	0.001
Whites versus nonwhite race	1.00	0.85–1.17	0.95
BMI in kg/m^2 at listing	1.00	0.99–1.01	0.17
Diabetes versus no diabetes	1.07	0.90–1.29	0.44
Blood group B or AB versus A or O	0.74	0.61–0.91	0.003
MELD score at listing	1.02	1.01–1.03	<0.001
Serum albumin at listing	0.63	0.56–0.70	<0.001
UNOS regions			
5	Reference group		
1	0.89	0.64–1.23	0.48
2	0.81	0.64–1.03	0.09
3	0.32	0.24–0.44	<.001
4	1.00	0.80–1.24	0.97
6	0.49	0.33–0.73	<0.001
7	0.52	0.39–0.68	<0.001
8	0.81	0.63–1.04	0.09
9	0.95	0.74–1.23	0.71
10	0.53	0.41–0.70	<0.001
11	0.78	0.60–1.02	0.07
10 years increase in age	1.35	1.26–1.44	<0.001

PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MELD, model for end-stage liver disease; BMI, body mass index.

*It is subdistribution hazard ratio as calculated from the Fine and Gray regression model.

PSC with patients listed for PBC were 4.8, 28.5, 15.8, 5, and 8.1 vs. 8.2, 27.1, 15.1, 4, and 8.5; $P = 0.43$. Cause of death was unknown as identified from the UNOS database in about 38% of deaths among patients with PSC and 37% of patients listed for PBC (Table 3).

Subgroup analyses after excluding patients receiving exception MELD points

A total of 757 patients (502 PSC) had received exception MELD points at the time of removal from the list

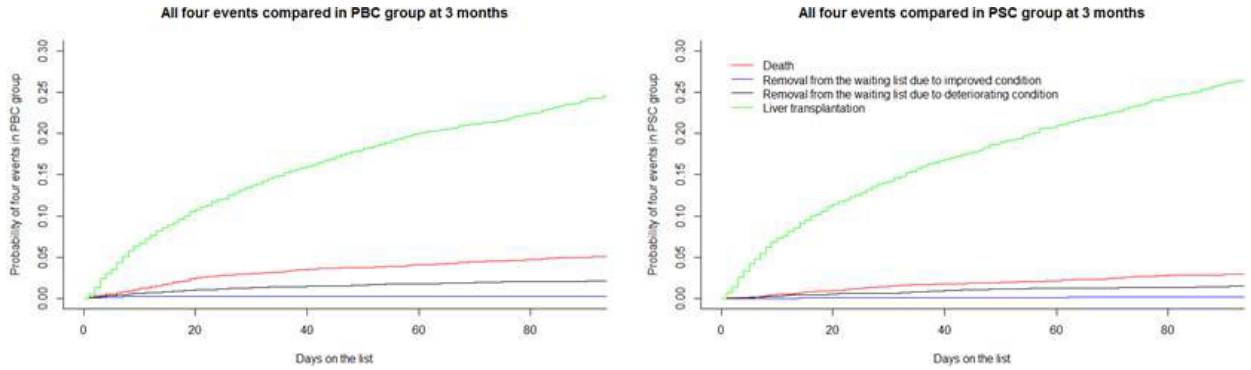

Figure 3 Cumulative incidence function for probability of wait-list mortality (WLM) at 3-monthswaiting time in primary sclerosing cholangitis (PSC) group (left) and in primary biliary cirrhosis (PBC) group (right). Results show that the WLM cumulative probability was higher for patients listed for PBC compared to patients listed for PSC for WLM at 3 months(5% vs. 2.9%; Gray's test $P < 0.001$). Patients with PBC experienced a higher cumulative incidence on removal due to deteriorating condition (2.1% vs. 1.4%, Gray's test $P < 0.001$) but a lower cumulative incidence on removal due to liver transplantation (24.2% vs. 26.1%, Gray's test $P < 0.001$) compared to patients with PSC. The cumulative incidence on removal due to improved condition for patients with PBC and patients with was 0.3% and 0.2%, respectively. *P* value for Gray's test was 0.45.

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Table 3. Causes of death on wait-list mortality: comparison of patients listed for PBC or PSC.

	PSC (N = 418)	PBC (N = 575)
Cardiovascular N (%)	20 (4.8)	47 (8.2)
Organ failure N (%)	119 (28.5)	156 (27.1)
Infection N (%)	66 (15.8)	87 (15.1)
Hemorrhage N (%)	21 (5)	23 (4)
Other N (%)	34 (8.1)	49 (8.5)
Unknown N (%)	158 (37.8)	213 (37.1)

PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis.

or waiting for the transplantation. Proportion of patients receiving exception MELD points was higher in PSC compared to PBC (10.2% vs. 7.3%, $P < 0.001$). After excluding these cases and controlling for listing characteristics, patients with PBC compared to PSC remained at higher 3-month unadjusted wait-list mortality compared to patients with PSC (5.3% vs. 3.2%, Gray's test $P < 0.001$). However, the adjusted wait-list mortality was nonsignificant, 1.33 (0.98–1.81) (*data not shown*). Patients with PBC experienced a higher cumulative incidence on removal due to deteriorating condition (2.2% vs. 1.6%, Gray's test $P = 0.045$), but a lower cumulative incidence on removal due to liver transplantation (23.2% vs. 25.7%, Gray's test $P = 0.01$) compared to patients with PSC. The cumulative incidence on removal due to improved condition for patients with PBC and patients with PSC was 3.2% and 2.1%, respectively, Gray's test $P = 0.37$).

Subgroup analyses among men

A total of 3873 men (489 for PBC) were listed for liver transplantation, of which 328 (8.5%) experienced WLM. Cumulative incidence of WLM over time remained higher for men listed for PBC diagnosis compared to men listed for diagnosis of PSC (17.8% vs. 11.8%, Gray's test $P < 0.001$). Removal from the wait list was similar comparing men listed for PBC to those listed for PSC for deteriorating condition, receipt of transplant, or for improved clinical condition (Fig. 4). After controlling for baseline characteristics as listed in Table 2 using Fine and Gray regression analysis, men listed with PBC diagnosis tended to have 32% higher WLM compared to men listed for PSC diagnosis, $P = 0.06$ (Table 4). Other predictors remained similar as in the overall sample except for blood group of the candidate.

Wait-list mortality and other causes of removal from transplant list: comparison of all etiologies

Table S1 described baseline characteristics on patients listed for various liver disease etiologies. Cumulative probability on WLM and other causes for removal from the transplant list including receipt of LT, too sick for LT, and improved clinical condition were determined for all etiologies (Figs S1–S3). Fine and Gray regression models were built to determine the impact of liver disease etiology on WLM. After adjusting for listing year (as continuous variable), age at listing, gender, race, BMI, diabetes mellitus, blood group, serum albumin at

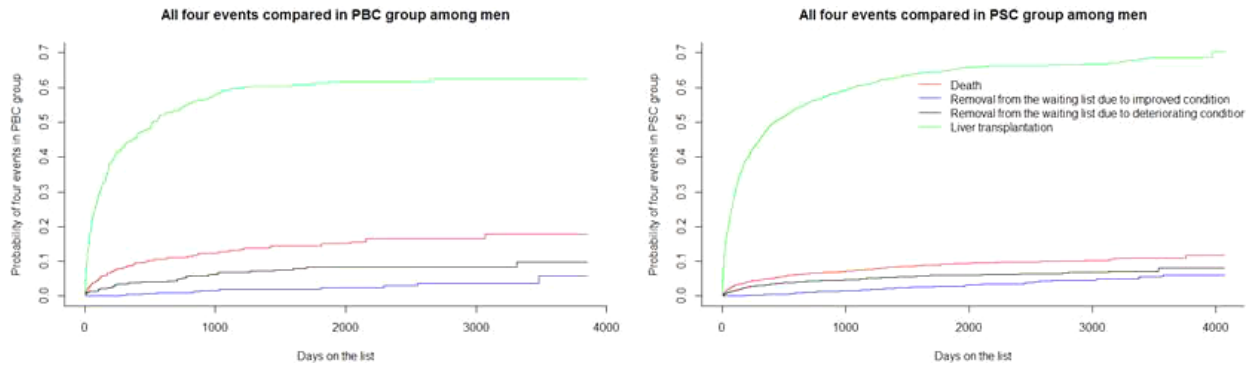

Figure 4 Cumulative incidence function for probability of wait-list mortality (WLM) for overall waiting time in primary sclerosing cholangitis (PSC) group (left) and in primary biliary cirrhosis (PBC) group (right) among men. Results show that the WLM cumulative probability was higher for patients listed for PBC compared to patients listed for PSC for overall WLM (17.8% vs. 11.8%; Gray's test $P < 0.001$). However, patients with PBC, compared to patients with PSC, tended to had a higher cumulative incidence on removal from the waiting list due to deteriorating condition (9.9% vs. 8.0%; Gray's test $P = 0.60$) but a lower cumulative incidence on removal from the waiting list due to liver transplantation (62.6% vs. 70.4%; Gray's test $P = 0.22$). The cumulative incidence on removal from the waiting list due to improved condition tended to be lower for PBC compared to PSC (5.7% vs. 6.1%, Gray's test $P = 0.20$). Only difference of cumulative incidence for death was significant.

Table 4. Fine and Gray regression analysis for predictors of wait-list mortality among men.

Variable	Hazard ratio*	95% Confidence interval	*P*
Listing diagnosis: PBC versus PSC	1.32	0.99–1.78	0.06
Listing year	0.93	0.90–0.97	<0.001
Age at listing in years	1.03	1.02–1.04	<0.001
Whites versus nonwhite race	0.92	0.67–1.25	0.57
BMI in kg/m^2 at listing	1.01	0.98–1.04	0.53
Diabetes versus no diabetes	1.14	0.84–1.53	0.40
Blood group B or AB versus A or O	0.96	0.70–1.33	0.82
MELD score at listing	1.03	1.01–1.05	<0.001
Serum albumin at listing	0.57	0.47–0.68	<0.001
UNOS region			
5	Reference group		
1	0.54	0.28–1.06	0.07
2	1.01	0.68–1.50	0.97
3	0.27	0.15–0.47	<0.001
4	0.74	0.47–1.17	0.19
6	0.66	0.37–1.20	0.17
7	0.59	0.38–0.93	0.02
8	0.78	0.51–1.19	0.25
9	1.07	0.69–1.67	0.75
10	0.50	0.31–0.79	0.003
11	0.70	0.44–1.13	0.14
10 years increase in age	1.32	1.20–1.46	<0.001

PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; CI, confidence interval; MELD, model for end-stage liver disease; UNOS, united network for organ sharing; BMI, body mass index.

*It is subdistribution hazard ratio as derived from the Fine and Gray regression model.

listing, MELD at listing, and 11 UNOS regions, WLM for various liver disease etiologies as compared to PSC were: 1.50 (1.28–1.66) for PBC, 1.72 (1.54–1.93) for ALD + HCV, 1.45 (1.31–1.61) for HCV, 1.35 (1.20–1.52) for CC, 1.35 (1.19–1.53) for NASH, 1.34 (1.20–1.49) for ALD, and 1.09 (0.94–1.28) for HBV (Table S2). Similar analyses performed only in men showed similar data (Table S3).

Discussion

The main findings of our study are as follows: (i) patients listed for PBC as compared to patients with PSC have higher wait-list mortality, independent of the listing MELD score and (ii) the wait-list mortality remains higher among patients with PBC at 3 months from listing. Comparing other liver disease etiologies on WLM, although, patients with PBC still had higher WLM compared to most etiologies including PSC, except those listed for combined HCV and ALD, who had higher WLM compared to PBC, and those listed for HCV, who had similar WLM as compared to PBC.

Any patient listed for liver transplantation is like the sinking titanic ship with liver transplantation as the only lifesaving boat [9]. However, not everyone listed for liver transplantation can be provided with this lifesaving boat due to mismatch between the demand and supply of livers. Depending on the size of this mismatch, about 10–25% of patients listed for liver transplantation may potentially die while waiting for the liver [9–11].

In a recent report from Japan, patients listed for PBC were more likely to die with approximately 8 months shorter survival time on the liver transplant wait list compared to patients listed for hepatitis C virus infection [7]. Another study has described lower WLM in patients with PSC, likely due to lower risk for development of complications of portal hypertension in patients with PSC as compared to other liver diseases [6]. To the best of our knowledge, there are no reports focusing to compare liver disease etiologies on WLM, especially comparing PSC with PBC. Our study showed finding opposite to our initial hypothesis with PBC compared to PSC being an independent predictor of wait-list mortality after adjusting for listing MELD score [5]. Patients with PBC as compared to PSC were also more likely to be taken off the list due to being too sick. Patients with PBC also experienced higher wait-list

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mortality compared to patients with PSC at 3 months from the time of listing in spite of their similar listing MELD. Although, serum albumin was lower in the PBC as compared to patients with PSC, patients listed for PBC remained at 45% higher risk of dying compared to patients with PSC, after controlling for various factors including the listing serum albumin level. Lack of difference in the WLM between PBC and patients with PSC in a subgroup analysis after excluding patients with MELD exception patients is likely due to higher proportion of patients with PSC as compared to PBC receiving MELD exception for listing.

Age, bilirubin, variceal bleeding, serum albumin, and prothrombin time impact the pretransplant mortality and natural history of patients with cholestatic liver disease including PBC and PSC [12]. Factors such as candidate's blood group and height at listing are also known to affect the receipt of LT and may potentially affect the WLM [11]. Serum bilirubin and MELD score at the time of listing among patients with PBC were lower as compared to PSC. Hence, these variables probably are unlikely to explain the higher WLM among patients with PBC. In contrast, PBC compared to patients with PSC differed at the time of listing with higher age, lower serum albumin, and shorter height. Further, patients dying compared to surviving on the LT list differed for ABO blood group. It is also possible that the WLM may have reduced differentially between the two liver disease etiologies. However, the PBC listed patients remained at higher risk for WLM after controlling for listing characteristics of candidates including age, MELD score, height, ABO blood group, listing year, serum albumin, and UNOS region for listing.

Large sample size using the UNOS database is strength of our study. Further, our findings of higher WLM in patients with PBC reflect the real-world situation, as we used the competing risk analysis and controlled the WLM comparing the two etiologies competing for receipt of liver transplantation or change in the clinical condition of the patient. As WLM is reported to be more frequent and likely among females compared to males, it may be argued that the study findings could just be a reflection of the gender difference rather than the real effect of liver disease etiology. However, PBC compared to PSC remained a predictor for higher WLM after controlling for the baseline characteristics including candidate's gender. Further, the study findings remained similar and unchanged on subgroup analysis among men only listed for either PBC or PSC. However, our study may potentially suffer from the limitations of any retrospective study. Although information on most of the clinically relevant variables which could have confounded the outcome among PBC and PSC patients was available from the UNOS dataset, the information on history of variceal bleeding was unavailable. Unavailability of information from the UNOS dataset on causes of removal from the waiting list in 30% of PBC and 26% of PSC cases and on causes of death in about 40% of patients is also limitation of this analysis. Further, there was a huge regional variation on WLM among patients listed for PBCand huge variation on WLM across UNOS regions. The likely explanations for this variation could be organ acceptance, MELD exception points, and technical expertise. Although, we controlled for MELD exception and performed separate analyses after excluding patients with MELD exception, other factors could not be explored as the UNOS database is limited on availability of information on these variables.

From our study, there is a suggestion that patients with PBC tend to die more often from cardiovascular related causes compared to patients with PSC. Older age, diabetes, and slightly higher BMI among patients with PBC may explain this difference. Further, patients with PBC are more likely to be complicated with dyslipidemias. However, the dyslipidemia in PBC is different from inherited dyslipidemia and usually does not by itself should place someone at increased cardiovascular risk [13,14]. Whether this is really a factor in increasing cardiovascular deaths among patients with PBC remains a testable hypothesis in future prospective studies.

Data on comparing liver disease etiologies on WLM are scanty. Our study showing WLM in patients with PBC to be similar to HCV patients is similar to the previously reported study [7]. However, high WLM in all other indications except ALD+HCV has not been shown before. Novel findings of our study suggest that patients with PBC listed for liver transplantation may need to be considered to receive exception points. Further prospective studies are needed to answer this before implementing this in routine practice. Further, patients with PBC should receive more rigorous cardiac evaluation prior to listing as basis for improving post-transplant outcomes of patients listed for PBC.

Authorship

AKS: involved in study design, data interpretation, and writing and critically revising the manuscript. XF: involved in data analysis. MK: involved in writing the manuscript. MH: involved in writing the manuscript the initial draft. BMM: involved in data interpretation

and reviewing the manuscript. YFK: involved in data analysis and interpretation. RWW: involved in study design, data interpretation, and critical revision of the manuscript.

Funding

Faculty development grant to A.K.S from the American College of Gastroenterology.

Conflict of interest

None of the authors have any conflict of interests to disclose.

SUPPORTING INFORMATION

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

Figure S1. Cumulative overall probability of removal from waiting list due to wait-list mortality, due to improved condition, due to deterioration, and for receipt of liver transplantation on all the eight liver disease etiologies.

Figure S2. Cumulative probability of removal from waiting list at three months from listing due to wait-list mortality, due to improved condition, due to deterioration, and for receipt of liver transplantation on all the eight liver disease etiologies.

Figure S3. Cumulative probability of removal from waiting list among men due to wait-list mortality, due to improved condition, due to deterioration, and for receipt of liver transplantation on all the eight liver disease etiologies.

Table S1. Baseline listing characteristics comparing a) patients listed for PBC, PSC, HBV, NASH, ALD, HCV, cryptogenic cirrhosis, and combined ALD and HCV.

Table S2. Fine and Gray regression model for predictors of wait-list mortality.

Table S3. Fine and Gray regression analysis for predictors of wait-list mortality among men.

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