ORIGINAL ARTICLE

Disease-specific waitlist outcomes in liver transplantation – a retrospective study

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SUMMARY

This study aimed to evaluate possible discrepancies in waitlist outcomes between liver diseases, including alcohol-related liver disease (ALD), nonalcoholic steatohepatitis (NASH), hepatitis C virus infection (HCV), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). Patients registered for liver transplantation from January 11, 2016, to June 30, 2018, were evaluated using OPTN/UNOS registry. Waitlist outcomes were compared between the five-disease groups. Patients were categorized by initial MELD-Na-score (6–20, 21–29, and ≥30) to identify outcome variations. Prognostic impact of transplantation was assessed according to final MELD-Na scores using Cox regression analysis modeling transplantation as a time-dependent covariate. 6053 with ALD, 3814 with NASH, 1558 with HCV, 602 with PBC, and 819 with PSC were eligible. Compared to ALD with comparable MELD-Na-scores, NASH with lower [adjusted hazard ratio (aHR) = 1.30, $P = 0.042$] and mid-scores (aHR = 1.35, $P = 0.008$) showed significantly higher risk of 1-year waitlist mortality, and PBC with higher scores showed significantly higher risk of 90-day (aHR = 1.69, $P = 0.03$) and 1-year waitlist mortality (aHR = 1.69, $P = 0.02$). Positive prognostic impact of transplantation was not seen until score of 24–27 in ALD, 18–20 in HCV, 15–17 in NASH, and 24–27 in PBC and PSC. There are significant differences in waitlist outcomes among etiologies, which may differ the optimal transplant timing.

Transplant International 2021; 34: 499–513

Key words
alcohol-related liver disease, cholestatic liver disease, hepatitis C, nonalcoholic steatohepatitis, prognosis

Received: 2 November 2020; Revision requested: 24 November 2020; Accepted: 1 January 2021

Introduction

In the United States, all adult liver transplant (LT) candidates are ranked based on a Model for End-Stage Liver Disease-Sodium (MELD-Na) score regardless of liver disease etiology, unless they meet criteria for exception scores [1–3]. In patients with alcohol-related liver disease (ALD), there may be less ongoing hepatic injury during the waiting period because of mandatory alcohol abstinence [4,5], whereas liver damage may progress in patients with other chronic liver diseases including nonalcoholic steatohepatitis (NASH), untreated hepatitis C virus (HCV) infection, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). However, disease-specific characteristics are not taken into consideration in the current liver

doi:10.1111/tri.13814

allocation system. Because the MELD-Na score system does not distinguish liver disease etiology, current liver allocation may not stratify patient medical urgency accurately [6].

We hypothesize that disease progression in liver transplant candidates might differ according to liver disease etiology, and risk stratification might need to be altered in the allocation system based on disease and patient characteristics. This study aims to evaluate possible difference of disease progression and discrepancies in waitlist outcomes between major liver disease groups, including ALD, HCV, NASH, PBC, and PSC, and to explore better risk stratification among liver transplant candidates.

Methods

Study population

The Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) registry was used to obtain data for this study. All adults (≥18 years) registered for liver transplantation from January 11, 2016, to June 30, 2018, under the MELD-Na score-based allocation system were evaluated. Primary and secondary liver disease etiology was reviewed and five major groups, ALD, NASH, HCV, PBC, and PSC, were evaluated. Patients with overlapping diseases, in which two of the five diagnoses were recorded, were excluded. Patients with alcoholic hepatitis were not included in the ALD group. Patients with MELD exception for hepatocellular carcinoma (HCC) and other reasons (non-HCC condition) were evaluated separately. Other exclusion criteria included the following: liver transplantation combined with thoracic organ(s), pancreas, and/or intestine; Status 1A; registration for re-transplantation.

This study used the Standard Transplant Analysis and Research file provided by the OPTN/UNOS in which all individually identifiable information is encrypted. Henry Ford Institutional Review Board (IRB) exempted IRB approval to conduct this study using this database.

Analysis for waitlist outcomes

Waitlist outcomes including mortality, liver transplantation, or recovery (too well for transplantation) were studied. Removal from waitlist due to clinical deterioration (too sick for transplant) was included in mortality. Mortality, transplantation, recovery, and removal from waitlist for other reasons were considered competing risk events. Patients who were still active on the waitlist and those who received living donor liver transplant were censored. Patients who did not receive MELD exceptions were categorized into three groups, according to initial MELD-Na score at listing (score of 6–20, 21–29, and ≥30), and 90-day and 1-year waitlist outcomes were compared among the five etiologies. Risks were adjusted for UNOS region (1 through 11) and recipient characteristics at registration, including age, gender, race, body mass index, diabetes, ascites, encephalopathy, Karnofsky score, life support use, and registration for liver–kidney transplantation. Another multivariable Cox regression model was created in each etiology group to determine risk factors for 90-day and 1-year waitlist mortality. Patients who received MELD exceptions for hepatocellular carcinoma (HCC) and non-HCC were separately analyzed and initial MELD-Na score was included in the risk adjustment. For patients with HCC exception, 180-day and 1-year waitlist outcomes were assessed, because of mandatory 6-month waiting rule before being granted for an exception score [7]. For those with MELD exception for other reasons, 90-day and 1-year outcomes were evaluated.

Disease progression according to underlying liver disease etiologies

To assess disease progression, delta MELD-Na score, change in status of ascites, encephalopathy and dialysis requirement were assessed. Delta MELD-Na score was calculated by dividing the change in score by the interval between reported dates of change [6,8]. The STAR waitlist database was queried for initial laboratory MELD-Na scores at listing, and we further identified MELD-Na scores at the closest date to 90 days after listing using STAR waitlist history database. Delta MELD-Na score was calculated only when patients were listed over 14 days. We estimated the 90-day average delta MELD-Na.

- 90-day average Delta MELD-Na = (MELD-Na score recorded on the day closest to 90 days after listing – initial MELD-Na score) × 90 days/Day difference between two points

Patients were dichotomized at 90-day average delta MELD-Na of 15 (30-day average MELD-Na of 5) which is considered as a cut-off value associated with higher waitlist mortality [9].

Status of ascites, encephalopathy, and dialysis requirement at registration were obtained. We identified patients who newly developed moderate ascites, grade 3 or 4 encephalopathy, and/or required dialysis within

90 days after registration. Delta MELD-Na, ascites, encephalopathy, and dialysis status were compared between liver disease etiologies according to initial MELD-Na score groups (score of 6–20, 21–29, and ≥30). To determine possible differences in disease progression between diseases, patients who received MELD exception were not included in this analysis.

Prognostic impact of liver transplantation

To assess possible differences in optimal timing of liver transplantation, intention-to-treat survival was analyzed in each disease group in patients who did not receive MELD exceptions. Living donor liver transplantation was excluded from this analysis. A Cox regression analysis that modeled liver transplantation as a time-dependent covariate was created to estimate the prognostic impact of liver transplantation in each disease group. Patients were categorized according to final MELD score and prognostic impact was assessed. Waitlist and post-transplant mortality were considered as endpoints. Patients removed from waitlist because they were too ill were considered as mortality. Patients who were removed from the waitlist due to recovery and other reasons, those who were still on the waitlist, and those who were alive post-transplant were censored on the last day of follow-up in this analysis. Risks were adjusted by UNOS regions and recipient characteristics at the time of removal from waitlist. Donor characteristics were not included in the risk adjustment because of inclusion of patients who did not undergo transplantation.

Statistical analysis

Continuous variables were expressed as median with interquartile range and compared using Kruskal–Wallis test. Descriptive variables were expressed as proportions and compared using chi-square test. P values in comparisons between more than two variables were calculated by a Bonferroni correction. Odds ratio was calculated by logistic regression model. Waitlist outcomes were analyzed using cumulative incidence of competing events and compared using Gray test. Fine-Gray proportional hazard regression for competing events was used to compare 90-day and 1-year waitlist outcomes. Multivariable models to identify risk factors for waitlist mortality in each disease etiology were performed using Fine-Gray proportional hazard regression for competing risk events. Prognostic impact of liver transplantation was assessed using Cox proportional hazard regression model with time-dependent covariate. In this model, liver transplantation was modeled as a time-dependent covariate. Statistical significance was defined at P value <0.05. All analyses were performed with SPSS v26 and R v3.2.2.

Results

Based on the inclusion and exclusion criteria, 6094 with ALD, 1653 with HCV, 3848 with NASH, 602 with PBC, and 819 with PSC were registered with their laboratory MELD-Na scores. The rest of patients were granted for MELD exception. Patient demographics for patients without MELD exceptions are shown in Table 1.

Comparison of waitlist outcomes between ALD and each liver disease etiology

Unadjusted cumulative incidence of waitlist outcomes in patients with the five major liver diseases is shown in Fig. 1. PBC patients showed the higher mortality rate ($P < 0.001$). ALD patients showed the highest transplant rate ($P < 0.001$) and highest recovery rate ($P < 0.001$).

Adjusted risks for waitlist mortality in each liver disease etiology vs ALD according to MELD-Na score category

Adjusted hazards of 90-day and 1-year waitlist mortality, transplant, and recovery in HCV, NASH, PBC, and PSC groups were estimated and compared to the ALD group (Fig. 2a–c). In comparison to ALD, risk of 90-day waitlist mortality was significantly higher in NASH [adjusted hazard ratio (aHR) 1.20, 95% CI 1.00–1.44, $P = 0.042$] and PBC (aHR 1.48, 95% CI 1.08–2.04, $P = 0.02$), whereas HCV and PSC had similar risk (aHR 1.06 and 1.27, 95% CI 0.85–1.35 and 0.90–1.81, $P = 0.58$ and 0.2, respectively). Ninety-day transplant probability and recovery were similar between ALD and other diseases. Adjusted hazards of 1-year waitlist outcomes were assessed (Fig. 2d–f). Overall risk of mortality, compared to ALD, was significantly higher in NASH (aHR 1.21, 95% CI 1.05–1.39, $P = 0.008$) and PBC (aHR 1.52, 95% CI 1.20–1.93, $P < 0.001$).

When evaluating outcomes according to initial MELD-Na score categories, PBC with higher scores showed significantly higher risk of 90-day mortality (aHR 1.69, 95% CI 1.06–2.68, $P = 0.03$) and lower 90-day transplant probability (aHR 0.68, 95% CI 0.48–0.96, $P = 0.03$) than ALD. Because the number of patients who recovered and were removed from the list in 90 days was very limited, likelihoods of recovery were

Table 1. Characteristics of waitlisted patients according to liver disease etiology.

	ALD *n* = 6094	HCV *n* = 1653	NASH *n* = 3848	PBC *n* = 602	PSC *n* = 819	*P* value
Age (year) [IQR]	53.0 [47.0, 60.0]	58.0 [54.0, 62.0]	61.0 [55.0, 65.0]	58.0 [51.0, 65.0]	49.0 [37.0, 59.0]	<0.001
Age group (%)						
<40	703 (11.5)	54 (3.3)	100 (2.6)	36 (6.0)	270 (33.0)	<0.001
40–49	1600 (26.3)	187 (11.3)	461 (12.0)	108 (17.9)	177 (21.6)	
50–59	2457 (40.3)	813 (49.2)	1348 (35.0)	208 (34.6)	207 (25.3)	
60 or higher	1334 (21.9)	599 (36.2)	1939 (50.4)	250 (41.5)	165 (20.1)	
Ethnicity						
White	4707 (77.2)	1027 (62.1)	3051 (79.3)	430 (71.4)	600 (73.3)	<0.001
Black	220 (3.6)	258 (15.6)	71 (1.8)	40 (6.6)	134 (16.4)	
Hispanic	917 (15.0)	306 (18.5)	595 (15.5)	108 (17.9)	56 (6.8)	
Others	250 (4.1)	62 (3.8)	131 (3.4)	24 (4.0)	29 (3.5)	
Gender (%)						
Male	4260 (69.9)	1077 (65.2)	1910 (49.6)	83 (13.8)	557 (68.0)	<0.001
Female	1834 (30.1)	576 (34.8)	1938 (50.4)	519 (86.2)	262 (32.0)	
BMI [IQR]	27.5 [24.2, 31.6]	28.1 [24.9, 32.3]	31.9 [28.0, 36.5]	26.3 [23.2, 30.2]	24.9 [22.4, 27.9]	<0.001
Diabetes (%)						
No	5084 (83.7)	1178 (71.5)	1581 (41.2)	495 (82.5)	730 (89.2)	<0.001
Yes	993 (16.3)	469 (28.5)	2256 (58.8)	105 (17.5)	88 (10.8)	
Ascites (%)						
None/mild	3702 (60.7)	1142 (69.1)	2510 (65.2)	464 (77.1)	704 (86.0)	<0.001
Moderate/severe	2392 (39.3)	511 (30.9)	1338 (34.8)	138 (22.9)	115 (14.0)	
Dialysis (%)						
No	5366 (88.1)	1403 (84.9)	3468 (90.2)	572 (95.0)	801 (97.8)	<0.001
Yes	728 (11.9)	250 (15.1)	378 (9.8)	30 (5.0)	18 (2.2)	
Life support requirement (%)						
No	2552 (86.8)	711 (91.4)	1638 (90.8)	589 (97.8)	810 (98.9)	<0.001
Yes	389 (13.2)	67 (8.6)	166 (9.2)	13 (2.2)	9 (1.1)	
Karnofsky score (%)						
70–100%	2197 (36.3)	686 (42.0)	1515 (39.9)	295 (50.3)	475 (58.9)	<0.001
40–60%	2358 (39.0)	693 (42.4)	1677 (44.2)	217 (37.0)	245 (30.4)	
10–30%	1492 (24.7)	254 (15.6)	604 (15.9)	75 (12.8)	87 (10.8)	
Encephalopathy (%)						
None/mild	5401 (88.6)	1520 (92.0)	3553 (92.3)	572 (95.0)	801 (97.8)	<0.001
Moderate/severe	693 (11.4)	133 (8.0)	295 (7.7)	30 (5.0)	18 (2.2)	
Registered for liver–kidney transplantation						
No	5425 (89.0)	1336 (80.8)	3294 (85.6)	562 (93.4)	790 (96.5)	<0.001
Yes	669 (11.0)	317 (19.2)	554 (14.4)	40 (6.6)	29 (3.5)	

Table 1. Continued.

	ALD *n* = 6094	HCV *n* = 1653	NASH *n* = 3848	PBC *n* = 602	PSC *n* = 819	*P* value
MELD-Na score [IQR]	23 [17, 30]	20 [14, 25]	19 [15, 26]	19.0 [14.0, 24.0]	18.0 [13.0, 24.0]	<0.001
MELD-Na group (%)						
6–20	2457 (40.3)	877 (53.1)	2140 (55.6)	357 (59.3)	514 (62.8)	<0.001
21–29	1933 (31.7)	533 (32.2)	1095 (28.5)	171 (28.4)	208 (25.4)	
30 or higher	1704 (28.0)	243 (14.7)	613 (15.9)	74 (12.3)	97 (11.8)	
Total bilirubin (mg/dl) [IQR]	4.1 [2.1, 9.8]	2.4 [1.3, 4.4]	2.6 [1.6, 4.8]	4.7 [2.3, 9.7]	5.9 [2.5, 12.6]	<0.001
INR [IQR]	1.63 [1.40, 2.20]	1.46 [1.20, 1.90]	1.50 [1.30, 1.80]	1.30 [1.20, 1.62]	1.30 [1.10, 1.60]	<0.001
GFR (ml/min) [IQR]	68.9 [40.9, 96.8]	65.6 [33.8, 93.9]	59.8 [37.5, 87.8]	75.8 [50.1, 99.8]	102.2 [73.8, 132.2]	<0.001
CKD stage (%)						
Stage 1 or 2 (GFR 60 or higher)	3573 (59.6)	911 (56.0)	1915 (50.8)	396 (66.4)	683 (84.1)	<0.001
Stage 3 (GFR 30–59)	1439 (24.0)	358 (22.0)	1187 (31.5)	145 (24.3)	89 (11.0)	
Stage 4 or 5 (GFR < 30)	978 (16.3)	357 (22.0)	666 (17.7)	55 (9.2)	40 (4.9)	
Serum sodium level (%)						
Normal (135–145 mmol/l)	3356 (55.1)	1084 (65.6)	2452 (63.7)	367 (61.0)	606 (74.0)	<0.001
Mild hyponatremia (130–134 mmol/l)	1729 (28.4)	389 (23.5)	961 (25.0)	167 (27.7)	154 (18.8)	
Severe hyponatremia (<130 mmol/l)	939 (15.4)	166 (10.0)	404 (10.5)	63 (10.5)	54 (6.6)	
Hypernatremia (>145 mmol/l)	69 (1.1)	14 (0.8)	31 (0.8)	5 (0.8)	5 (0.6)	

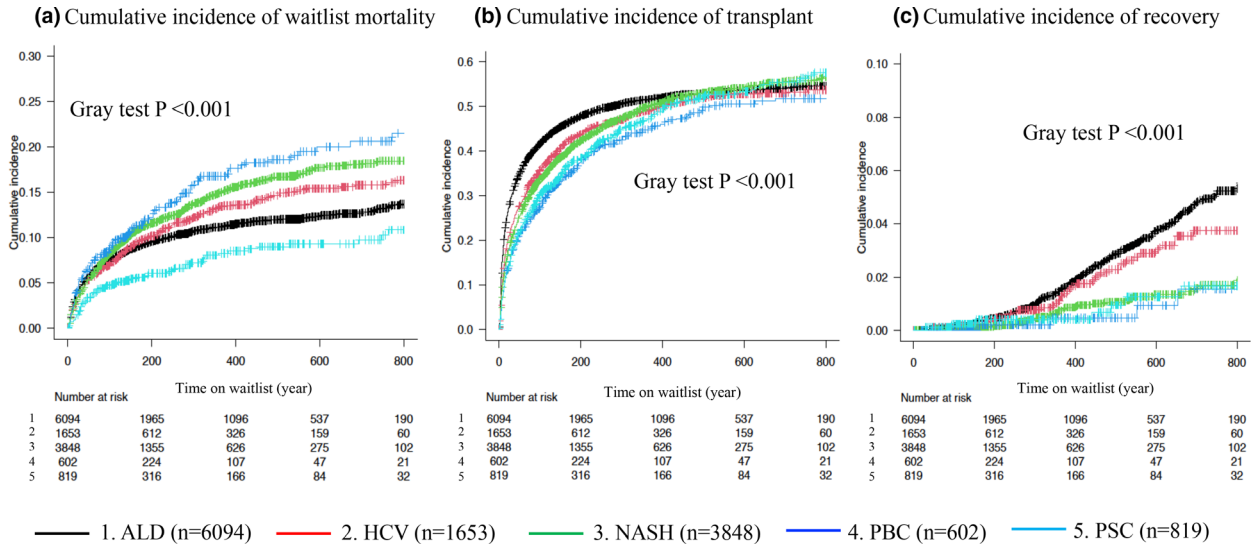

Figure 1 Cumulative incidence curves showing (a) waitlist mortality, (b) transplant probability, and (c) recovery on waitlist among ALD, HCV, NASH, PBC, and PSC patients (Gray test).

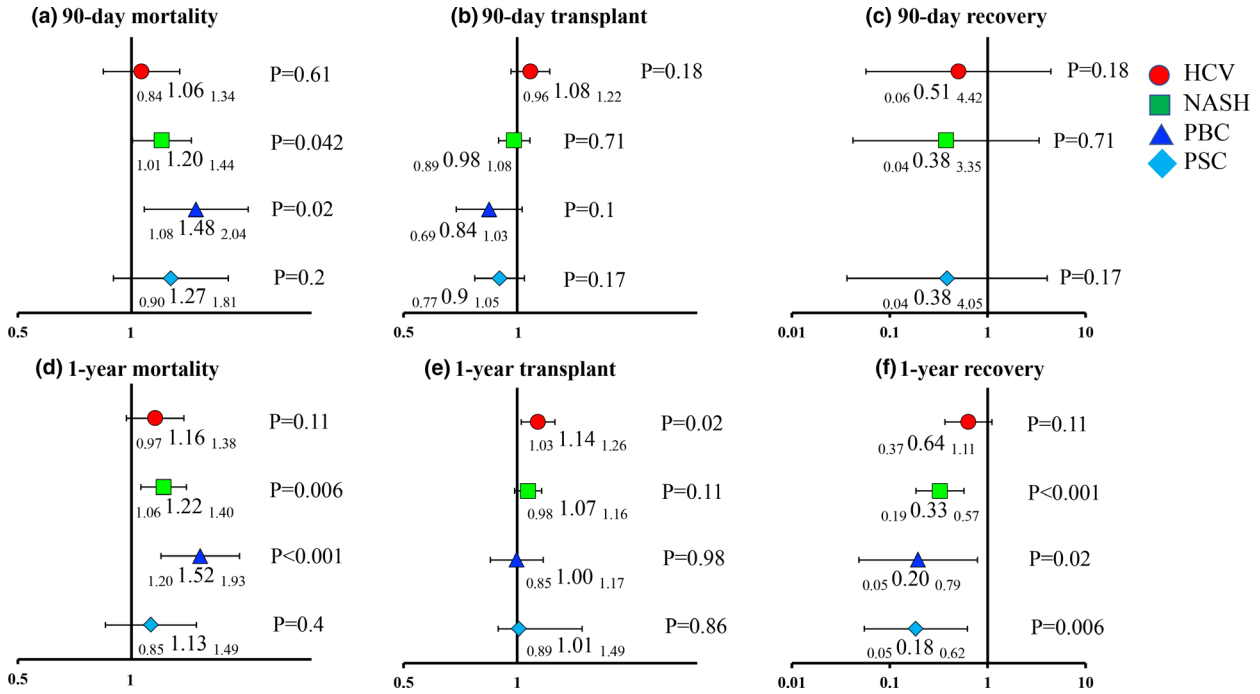

Figure 2 Forest plots summarizing adjusted hazards of 90-day and 1-year waitlist outcomes in ALD, HCV, NASH, PBC, and PSC, compared to ALD. The numbers and subscripts show hazard ratio and 95% confidence interval.

not compared between ALD and other etiology groups (Fig. 3a).

A significantly higher risk of 1-year mortality was found in NASH with lower (aHR 1.30, 95% CI 1.01–1.67, $P = 0.042$) and mid-scores (aHR 1.35, 95% CI 1.08–1.68, $P = 0.008$), and in PBC with lower and higher scores (aHR 1.54 and 1.69, 95% CI 1.04–2.29 and 1.09–2.63, $P = 0.042$ and 0.02), compared to ALD in respective score groups. In the lower score group, 1-year transplant probability was significantly higher in HCV (aHR 1.76, 95% CI 1.50–2.07, $P < 0.001$), NASH (aHR 1.38, 95% CI 1.21–1.57, $P < 0.001$), PBC (aHR 1.56, 95% CI 1.24–1.97, $P < 0.001$), and PSC (aHR 1.57, 95% CI 1.29–1.91, $P < 0.001$) than in ALD.

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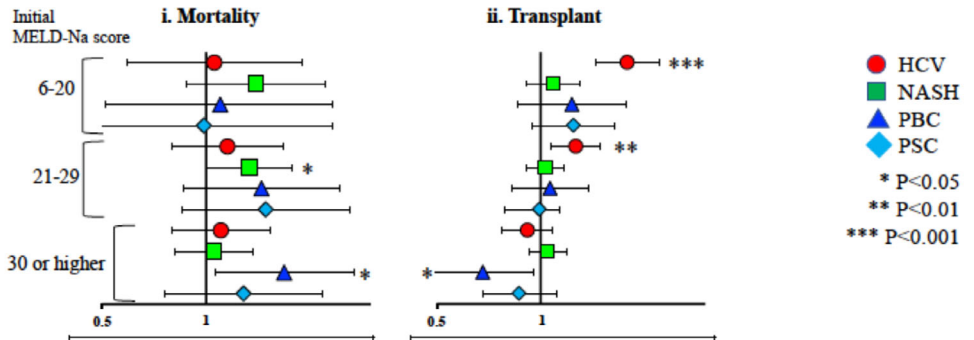
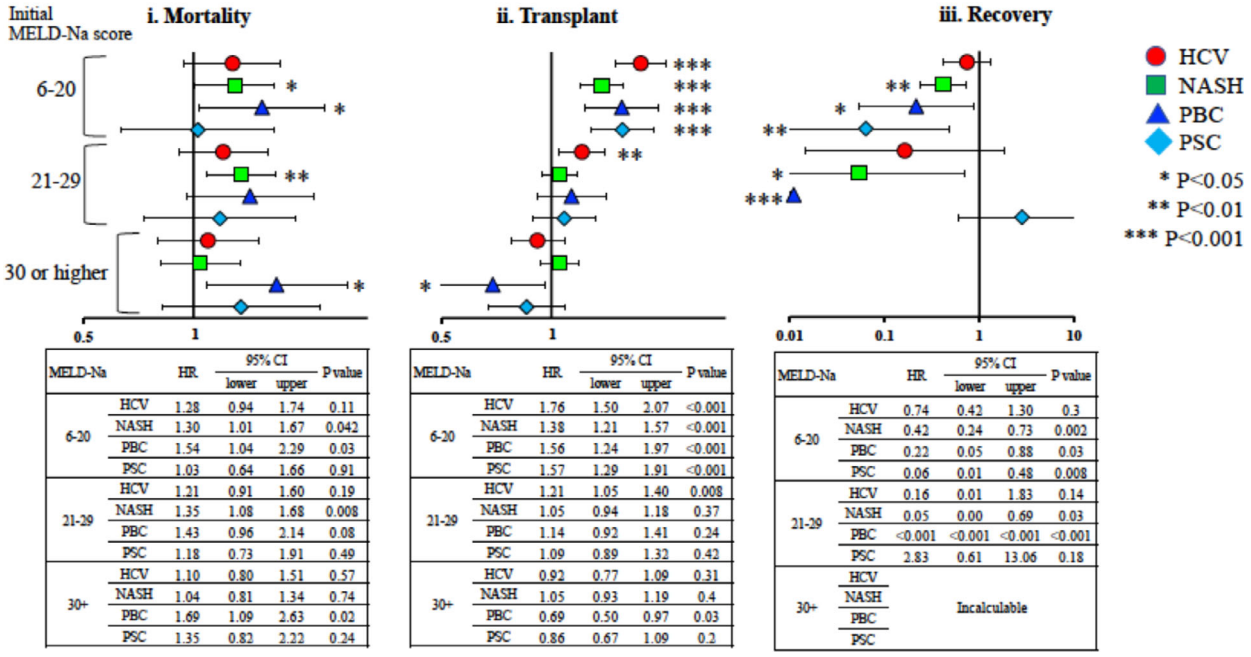
(a)



MELD-Na		HR	95% CI lower	95% CI upper	P value
6-20	HCV	1.06	0.59	1.90	0.85
	NASH	1.39	0.88	2.21	0.16
	PBC	1.10	0.51	2.32	0.81
	PSC	0.98	0.42	2.31	0.97
21-29	HCV	1.15	0.79	1.68	0.45
	NASH	1.34	1.01	1.77	0.045
	PBC	1.45	0.86	2.44	0.17
	PSC	1.49	0.85	2.60	0.16
30+	HCV	1.10	0.80	1.53	0.55
	NASH	1.06	0.81	1.37	0.69
	PBC	1.69	1.06	2.68	0.03
	PSC	1.29	0.76	2.18	0.35

MELD-Na		HR	95% CI lower	95% CI upper	P value
6-20	HCV	1.79	1.45	2.20	<0.001
	NASH	1.09	0.91	1.31	0.37
	PBC	1.23	0.86	1.77	0.25
	PSC	1.25	0.94	1.65	0.12
21-29	HCV	1.27	1.08	1.49	0.005
	NASH	1.03	0.91	1.17	0.65
	PBC	1.07	0.83	1.38	0.63
	PSC	0.99	0.79	1.14	0.95
30+	HCV	0.92	0.77	1.09	0.31
	NASH	1.05	0.93	1.19	0.44
	PBC	0.68	0.48	0.96	0.03
	PSC	0.87	0.68	1.11	0.26

(b)



MELD-Na		HR	95% CI lower	95% CI upper	P value
6-20	HCV	1.28	0.94	1.74	0.11
	NASH	1.30	1.01	1.67	0.042
	PBC	1.54	1.04	2.29	0.03
	PSC	1.03	0.64	1.66	0.91
21-29	HCV	1.21	0.91	1.60	0.19
	NASH	1.35	1.08	1.68	0.008
	PBC	1.43	0.96	2.14	0.08
	PSC	1.18	0.73	1.91	0.49
30+	HCV	1.10	0.80	1.51	0.57
	NASH	1.04	0.81	1.34	0.74
	PBC	1.69	1.09	2.63	0.02
	PSC	1.35	0.82	2.22	0.24

MELD-Na		HR	95% CI lower	95% CI upper	P value
6-20	HCV	1.76	1.50	2.07	<0.001
	NASH	1.38	1.21	1.57	<0.001
	PBC	1.56	1.24	1.97	<0.001
	PSC	1.57	1.29	1.91	<0.001
21-29	HCV	1.21	1.05	1.40	0.008
	NASH	1.05	0.94	1.18	0.37
	PBC	1.14	0.92	1.41	0.24
	PSC	1.09	0.89	1.32	0.42
30+	HCV	0.92	0.77	1.09	0.31
	NASH	1.05	0.93	1.19	0.4
	PBC	0.69	0.50	0.97	0.03
	PSC	0.86	0.67	1.09	0.2

MELD-Na		HR	95% CI lower	95% CI upper	P value
6-20	HCV	0.74	0.42	1.30	0.3
	NASH	0.42	0.24	0.73	0.002
	PBC	0.22	0.05	0.88	0.03
	PSC	0.06	0.01	0.48	0.008
21-29	HCV	0.16	0.01	1.83	0.14
	NASH	0.05	0.00	0.69	0.03
	PBC	<0.001	<0.001	<0.001	<0.001
	PSC	2.83	0.61	13.06	0.18
30+	HCV	Incalculable			
	NASH				
	PBC				
	PSC				

Figure 3 Forest plots summarizing adjusted hazards of (a) 90-day and (b) 1-year waitlist outcomes (i. Mortality, ii. Transplant, iii. Recovery), categorized by initial MELD-Na score, between ALD (ref.) and other liver disease (HCV, NASH, PBC, and PSC; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, Fine-Gray proportional hazard model).

Likelihood of 1-year recovery was significantly lower in the NASH (aHR 0.42, 95% CI 0.24–0.73, $P = 0.002$), PBC (aHR 0.22, 95% CI 0.05–0.88), $P = 0.03$), and PSC patients (aHR 0.06, 95% CI 0.01–0.48, $P < 0.001$) than ALD. In the higher score group, PBC showed significantly lower 1-year transplant probability than ALD (aHR 0.69, 95% CI 0.50–0.97, $P = 0.03$; Fig. 3b).

Risk factors for waitlist mortality in each liver disease

Risk factors for 90-day and 1-year waitlist mortality in each etiology were identified by multivariable Fine-Gray models (Table S1 and Table 2). In ALD, older age groups (40–59, 50–59, 60 years or older), compared to those <40 years, showed significantly higher risk of 90-

day and 1-year mortality. Lower Karnofsky scores (10–30% and 40–60%) were risk factors for 90-day and/or 1-year mortality across all diseases. Among factors comprising the MELD-Na score, kidney dysfunction (CKD stage 3 or higher) and hyponatremia were significantly associated with mortality in ALD, HCV, and NASH. Higher serum total bilirubin level was an independent risk factor for 90-day mortality in PSC and PBC. Hyponatremia was an independent risk factor for 90-day and 1-year mortality in PSC.

Co-existing conditions according to MELD-Na score at listing in each liver disease group

Dialysis requirement, status of grade 3 or 4 encephalopathy and moderate ascites at listing were assessed in each disease group according to the initial MELD-Na score. In the higher MELD-Na score group, a rate of dialysis requirement in NASH patients was highest of all disease groups (38%, $P = 0.001$). While dialysis requirement in PBC patients was less likely than other diseases in all score categories, an increasing risk of dialysis requirement from the mid to higher MELD-Na score groups was more prominent [from 2.3% to 35.1%, odds ratio (OR) 22.62, 95% CI 7.52–67.97], compared to other disease groups (Fig. 4a). PSC patients, compared to other disease groups, showed lower rates of grade 3 or 4 encephalopathy and moderate ascites in all score categories (Fig. 4b,c).

Comparisons of disease progression between liver disease etiologies

In the lower MELD-Na score group, NASH patients had significantly higher 90-day delta MELD-Na [0.61, IQR (0, 3.27)] than ALD [0, IQR (−0.55, 1.81), $P < 0.001$], HCV [0, IQR (0, 1.96), $P < 0.001$], PBC [0, IQR (0, 2.1), $P < 0.001$], and PSC patients [0, IQR (0, 2.5), $P = 0.008$]. Delta MELD-Na > 5/month was observed in 3.2% in ALD patients which was significantly lower than in NASH (5.0%, $P = 0.01$). In the mid-MELD-Na score group, PBC and PSC patients showed significantly higher 90-day delta MELD [1.65, IQR (−1.8, 7.8)] and 1.91 [−2.5, 9.3] than ALD [0 IQR (−3.0, 5.1)] and HCV patients [0, IQR (−2.6, 4.8)] ($P = 0.003$). PBC and PSC patients showed significantly higher rate of delta MELD > 5/month (15.8% and 14.9%) than ALD (9.7%) and HCV patients (7.5%; $P = 0.001$). In the higher MELD-Na score group, 90-day delta MELD was similar between disease groups (Table 3).

Prognostic impact of liver transplantation

Intention-to-treat survival was assessed in patients who were registered with their laboratory MELD-Na score in each disease group. The positive prognostic impact of liver transplantation became significant with a MELD-Na score category of at least 24–26 in ALD (HR 0.33, $P < 0.001$), 18–20 in HCV (HR 0.15, $P = 0.004$), 15–17 in NASH (HR 0.44, $P = 0.02$), and 24–26 in PBC and PSC (HR 0.16 and 0.15, $P = 0.02$ and 0.02; Fig. 5).

Waitlist outcomes in patients with MELD exception

A total of 4805 patients were granted for MELD exception for HCC, of whom 832, 2950, 922, 46, and 55 were ALD, HCV, NASH, PBC, and PSC, respectively. Risk of 180-day mortality was significantly higher in HCV and NASH, compared to ALD. Risk of 1-year waitlist mortality and transplant probability was comparable between disease groups. There were very few patients who were removed from the waitlist due to improvement and likelihood of recovery was not able to be compared between groups (Table 4).

A total of 297 with ALD, 275 with HCV, 330 with NASH, 66 with PBC, and 298 with PSC were granted for MELD exceptions for other reasons (non-HCC conditions). In this group, NASH patients showed significantly higher risk of 1-year mortality, compared to ALD patients. One-year transplant probability was significantly higher in the HCV, PBC, and PSC group, compared to ALD. There was no difference in likelihood of recovery between disease groups (Table 4).

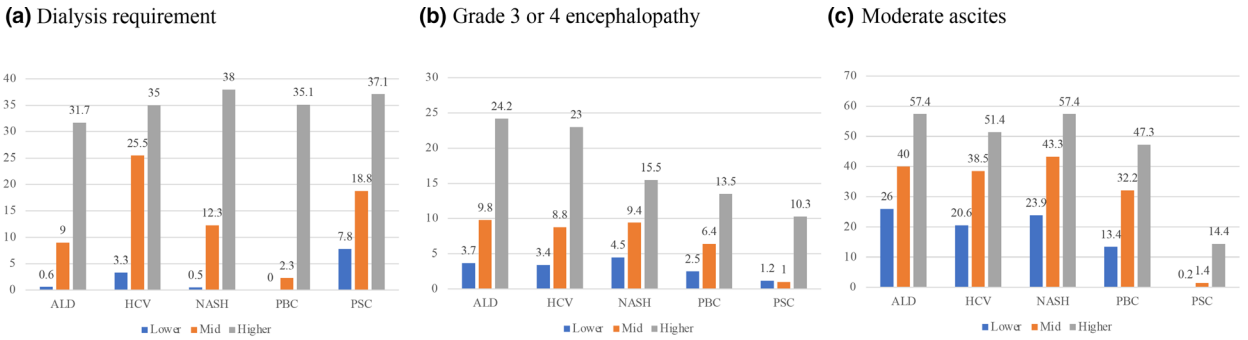
Discussion

Transplant priority based on MELD and MELD-Na scores has been the mainstay of liver organ allocation in the United States since 2002. However, with significant recent shifts in underlying liver diseases, the ability of MELD to predict 90-day mortality as declined [10]. This study evaluated different disease progression and disease-specific waitlist outcomes according to underlying etiologies of liver transplant candidates. Importantly, unlike the previous studies, we focused on patients registered after implementation of MELD-Na score-based allocation (January 11, 2016), because waitlist outcomes have been significantly affected by this allocation change and because of recent marked shifts in liver diseases underlying liver transplant in the United States [6]. In addition, effects of DAA on outcomes in HCV population should be saturated during our study period and

Table 2. Risk factors associated with 1-year waitlist mortality in each liver disease etiology.

	ALD			HCV			NASH			PBC			PSC		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age, years															
<40	Ref			Ref			Ref			Ref			Ref		
40–50	1.74	1.20–2.51	**0.003**	1.15	0.37–3.6	0.81	2.39	0.84–6.86	0.1	1.30	0.21–7.94	0.78	0.85	0.32–2.30	0.75
51–59	2.30	1.61–3.27	**<0.001**	1.92	0.69–5.37	0.21	3.02	1.10–8.34	**0.03**	1.98	0.33–11.75	0.45	2.10	0.91–4.84	0.08
≥60	3.42	2.37–4.94	**<0.001**	2.11	0.74–6.02	0.16	5.11	1.87–14.0	**0.002**	3.03	0.53–17.45	0.21	2.87	1.13–7.25	**0.03**
Gender, female	1.12	0.93–1.34	0.24	0.92	0.67–1.27	0.61	1.20	0.99–1.45	0.054	1.73	0.68–4.36	0.25	2.34	1.24–4.40	**0.009**
Race															
Caucasian	Ref			Ref			Ref			Ref			Ref		
African American	1.41	0.96–2.07	0.08	0.90	0.56–1.43	0.65	0.94	0.48–1.87	0.87	1.46	0.57–1.53	0.51	1.01	0.44–2.33	0.98
Hispanic	1.39	1.10–1.74	**0.005**	1.11	0.74–1.67	0.62	1.19	0.93–1.54	0.17	0.90	0.44–1.88	0.79	1.17	0.31–4.42	0.82
Others	1.46	1.00–2.11	**0.048**	1.07	0.52–2.21	0.86	1.02	0.62–1.69	0.93	0.60	0.16–2.25	0.45	2.00	0.53–7.58	0.62
Diabetes	1.19	0.97–1.47	0.1	1.16	0.83–1.64	0.39	1.09	0.90–1.32	0.38	0.80	0.42–1.53	0.51	1.23	0.49–3.10	0.66
Grade 3 or 4 encephalopathy	1.55	1.23–1.94	**<0.001**	1.28	0.78–2.10	0.34	1.27	0.92–1.74	0.15	0.63	0.17–.2.36	0.50	2.00	0.39–.10.37	0.41
Moderate/severe ascites	1.16	0.97–1.38	0.11	1.01	0.71–1.42	0.98	1.20	0.97–1.48	0.09	1.47	0.87–2.49	0.15	0.89	0.38–2.06	0.31
Karnofsky score, %															
70–100	Ref			Ref			Ref			Ref			Ref		
40–60	1.45	1.16–1.81	**0.001**	1.45	1.01–2.07	**0.045**	1.36	1.09–1.68	**0.005**	0.99	0.56–1.75	0.98	0.89	0.43–1.82	0.74
10–30	1.89	1.43–2.49	**<0.001**	1.67	0.96–2.92	0.07	1.37	0.99–1.89	0.059	1.68	0.76–3.68	0.2	4.58	1.42–14.80	**0.01**
Life support	1.80	1.33–2.44	**<0.001**	2.03	1.13–3.67	**0.02**	1.32	0.78–2.24	0.3	2.35	0.61–8.90	0.21	1.65	0.12–22.19	0.71
MELD-Na components															
Serum total bilirubin	1.01	0.99–1.02	0.09	1.02	0.99–1.04	0.1	1.02	1.01–1.03	**<0.001**	1.04	1.01–1.07	**0.004**	1.02	0.98–1.06	0.24
Chronic kidney disease stage															
Stage 1 or 2	Ref			Ref			Ref			Ref			Ref		
Stage 3	1.13	0.92–1.39	0.23	1.32	0.90–1.95	0.16	1.24	0.99–1.55	0.056	2.09	1.25–3.51	**0.005**	0.62	0.25–1.54	0.3
Stage 4 or 5	1.31	1.04–1.65	**0.02**	1.77	1.16–2.69	**0.008**	1.58	1.21–2.07	**<0.001**	0.89	0.36–2.23	0.81	0.83	0.24–2.88	0.77
INR	1.09	0.98–1.21	0.1	1.12	0.89–1.41	0.35	1.16	1.03–1.31	**0.01**	1.54	0.96–2.46	0.07	0.94	0.63–1.39	0.76
Serum sodium concentration															
Normal	Ref			Ref			Ref			Ref			Ref		
Mild to moderate hyponatremia	1.22	1.00–1.48	**0.046**	1.96	1.39–2.75	**<0.001**	1.35	1.10–1.67	**0.005**	0.86	0.48–1.54	0.6	2.33	1.15–4.71	**0.02**
Severe hyponatremia	1.41	1.13–1.77	**0.003**	1.68	1.03–2.74	**0.04**	1.31	0.98–1.75	0.07	0.90	0.42–1.54	0.78	2.99	1.26–7.12	**0.01**
Hypernatremia	1.65	0.95–2.87	0.08	0.71	0.13–3.78	0.69	2.04	0.88–4.68	0.1	0.47	0.03–7.79	0.6	—	—	—

Statistical significant *P* values are shown in bold.



	Lower to Mid	Mid to Higher
ALD	17.26 (9.98-29.857)	4.69 (3.89-5.65)
HCV	10.02 (6.59-15.22)	1.57 (1.13-2.18)
NASH	29.93 (15.67-57.14)	4.36 (3.42-5.56)
PBC	-	22.62 (7.52-67.97)
PSC	7.51 (0.78-72.59)	11.53 (3.23-41.16)

	Lower to Mid	Mid to Higher
ALD	2.82 (2.28-3.65)	2.95 (2.45-3.56)
HCV	2.73 (1.70-4.38)	3.10 (2.23-4.73)
NASH	2.19 (1.64-2.92)	1.77 (1.31-2.38)
PBC	2.66 (1.08-6.54)	2.27 (0.92-5.61)
PSC	0.82 (0.17-4.11)	11.84 (2.54-55.15)

	Lower to Mid	Mid to Higher
ALD	1.90 (1.67-2.16)	2.02 (1.77-2.30)
HCV	2.40 (1.89-3.05)	1.70 (1.25-2.30)
NASH	2.43 (2.08-2.84)	1.77 (1.45-2.16)
PBC	3.05 (1.96-4.75)	1.89 (1.08-3.31)
PSC	2.74 (1.70-4.40)	2.56 (1.49-4.39)

Increasing risk (odds ratio) of co-existing conditions from lower to mid-score and from mid to higher-score categories

Figure 4 Co-existing conditions at listing according to liver diseases and initial MELD-Na score categories. (a) Dialysis requirement. (b) Presence of grade 3 or 4 encephalopathy. (c) Presence of moderate ascites. Tables show odds ratio and 95% confidence interval of each condition in the mid-MELD-Na score group, compared to the lower MELD-Na score group, and in the higher MELD-Na score group, compared to the mid-MELD-Na score group. Increasing risks for all comparisons were significant ($P < 0.001$), except for the risk of dialysis requirement between the lower and mid-score groups in PSC and the risk of grade 3 or 4 encephalopathy between mid to higher score groups in PBC.

better reflect the current clinical practice, compared to previous studies [11]. Our study showed that each major liver disease had different disease progression depending on MELD-Na scores. NASH patients in the lower (score of 6–20) and mid (score of 21–30) MELD-Na score groups showed faster disease progression which was represented by significantly higher 90-day delta MELD-Na score, compared to ALD, HCV, PBC, and PSC in the comparable score category groups. This may account for the differences in waitlist outcomes between disease groups found in this study. Compared to ALD patients, NASH patients had higher risk of mortality and lower chance of recovery in the lower to mid-score categories. Abstinence in transplant candidates with ALD and eradication of HCV in infected patients could stabilize or improve liver function in those patients. These disease-specific characteristics might lead to the discrepancies in disease progression and waitlist outcomes. Wong *et al.* [12] evaluated disease-specific waitlist outcomes in patients who were registered from 2004 to 2013 in the United States. They showed that, compared to patients with NASH, the risk of 1-year waitlist mortality was significantly higher in patients with HCV and lower in those with ALD. The waitlist outcomes in HCV patients reported in their study should be carefully interpreted, because data used in their study were from pre-DAA era. Further, waitlist outcomes were not compared according to their MELD scores. The results of our study suggest an increasing importance of risk stratification and priority of liver allocation that considers underlying liver disease.

Higher delta MELD (MELD-Na) indicates rapid disease progression. It was reported that Delta MELD of 5 or higher per month was associated with higher waitlist mortality [8,9]. Difference of delta MELD-Na between diseases was more prominent in the lower and mid-MELD-Na score groups. 90-day delta MELD-Na was smaller in ALD than NASH, which indicates that disease was more stable in ALD than NASH. PBC and PSC patients with a lower MELD-Na score also showed relatively stable MELD-Na score after listing. 90-day delta MELD in PBC and PSC was similar to ALD and HCV with a lower MELD-Na score, whereas those patients with a mid-MELD-Na score showed the highest delta MELD-Na and delta MELD-Na > 5/month was most frequently observed among disease groups. These results suggest that disease progression in PBC and PSC patients may be accelerated when severity of disease exceeds a certain level.

Another important finding of this study is different thresholds of MELD-Na score associated with a positive prognostic impact of liver transplantation among the

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Table 3. Clinical deterioration in 90 days after waitlist registration according to liver disease etiologies and MELD-Na score.

MELD-Na	Newly developed condition	ALD	HCV	NASH	PBC	PSC	*P* value
Lower	Encephalopathy, *n* (%)*	65 (2.7)	31 (3.7)	73 (3.6)	11 (3.2)	14 (2.8)	0.49
	Ascites, *n* (%)†	87 (4.8)	47 (6.8)	86 (5.3)	10 (3.2)	15 (3.2)	**0.04**
	Dialysis, *n* (%)‡	28 (1.1)	8 (0.9)	25 (1.2)	4 (1.1)	5 (1.0)	0.98
	90-day Delta MELD-Na§	0 [−0.6, 1.8]	0 [0, 2.0]	0.61 [0, 3.3]	0 [0, 2.1]	0 [0, 2.5]	**<0.001**
	Delta MELD-Na >5/month§	78 (3.2)	25 (2.9)	107 (5.0)	15 (4.2)	18 (3.5)	**0.01**
Mid	Encephalopathy, *n* (%)*	142 (8.1)	31 (6.4)	108 (10.9)	20 (12.5)	19 (9.2)	**0.01**
	Ascites, *n* (%)†	220 (19.0)	53 (16.2)	127 (20.5)	16 (13.8)	21 (12.4)	0.07
	Dialysis, *n* (%) s‡	127 (7.2)	22 (5.5)	86 (9.0)	14 (8.4)	13 (6.3)	0.21
	90-day Delta MELD-Na§	0 [−3.0, 5.1]	0 [−2.6, 4.8]	0.83 [−2.8, 6.7]	1.65 [−1.8, 7.8]	1.91 [−2.5, 9.3]	**0.003**
	Delta MELD-Na >5/month§	188 (9.7)	40 (7.5)	124 (11.3)	29 (17.0)	31 (14.9)	**0.001**
Higher	Encephalopathy, *n* (%)*	212 (16.4)	38 (20.3)	98 (18.9)	12 (18.8)	22 (11.5)	0.29
	Ascites, *n* (%)†	191 (26.3)	42 (35.6)	55 (21.1)	8 (20.5)	16 (26.2)	**0.048**
	Dialysis, *n* (%)‡	234 (20.1)	40 (25.3)	96 (25.3)	12 (25.0)	16 (19.3)	0.17
	90-day Delta MELD-Na§	0 [−7.6, 12.0]	0.99 [−6.8, 18.4]	2.47 [−6.5, 14.3]	6.75 [−4.9, 24.6]	0 [−6.9, 12.9]	0.32
	Delta MELD-Na >5/month§	123 (7.2)	21 (8.6)	53 (8.6)	10 (13.5)	10 (10.3)	0.22

* Including patients who did not have grade 3 or 4 encephalopathy at waitlist registration.

† Including patients who did not have moderate ascites at waitlist registration.

‡ Including patients who did not require dialysis at waitlist registration.

§ Delta MELD-Na was calculated in patients who were listed at least for 14 days.

Statistical significant *P* values are shown in bold.

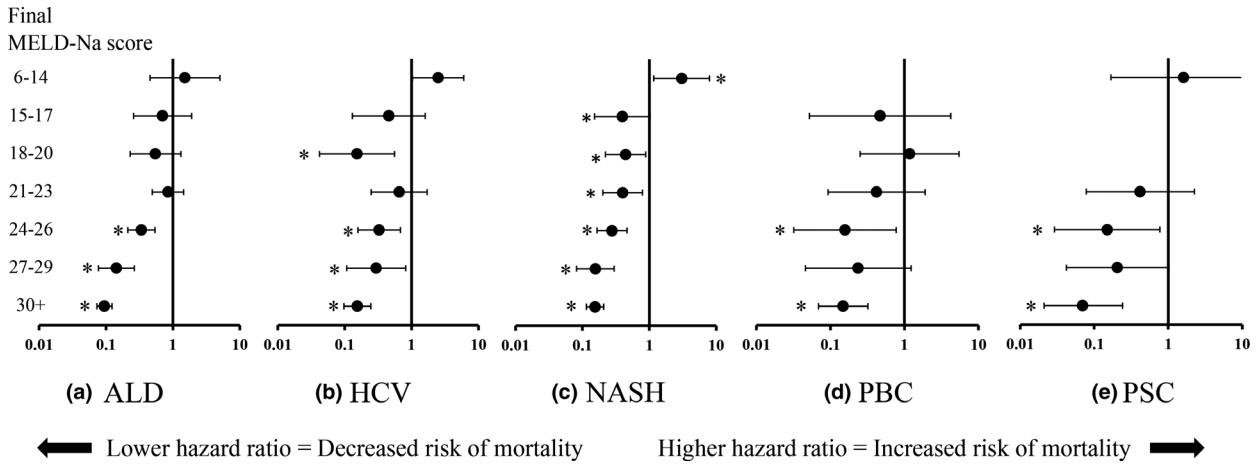

Figure 5 Prognostic impact of liver transplantation in (a) ALD, (b) HCV, (c) NASH, (d) PBC, and (e) PSC. Lower and higher hazard ratios refer positive and negative prognostic impact of liver transplantation.

five liver disease groups. Survival benefit of liver transplantation has been studied by our group and others, with the finding that the threshold MELD-Na score associated with survival benefit is 21 [6,13]. However, previous studies did not distinguish liver disease etiology. Both waitlist and post-transplant outcomes may differ as a function of liver disease [14]. Thresholds of MELD-Na score associated with a positive prognostic impact of liver transplantation were higher in ALD and CLD and lower in NASH. These results indicate that the optimal timing of liver transplantation might be different according to underlying liver disease. While the results should not be interpreted to mean that liver transplantation be done only for those above the MELD-Na score thresholds, the findings do support the concept of disease-specific priority in liver allocation.

Abstinence removes the hepatic insult in ALD patients which may explain the higher waitlist recovery rate in ALD, compared to other liver diseases. Interestingly, ALD had the lowest transplant probability in the lower score category. This may be associated with slow disease progression in this population. Giard et al. recently compared waitlist outcomes between ALD and non-ALD populations from 2002 to 2016 [5], and also found superior waitlist outcomes and higher rates of recovery in liver transplant candidates with ALD. We focus on more detailed disease progression during waiting time and waitlist outcomes for all five major liver disease populations and evaluate the prognostic impact of liver transplantation for each etiology. As noted, our study focused on patients registered after implementation of MELD-Na score-based allocation (January 11, 2016). Our study showed that hyponatremia was more prominently associated with poor waitlist outcomes in ALD and HCV (Table 2 and Table S1). The introduction of MELD-Na based allocation might impact their waitlist outcomes differently. To reflect our current waitlist practice, findings shown in this study using more contemporary data would be more reliable.

With the introduction of DAA as curative therapy for HCV, liver transplant in HCV infected patients offers longer graft survival compared to the past [15]. While the number of waitlisted patients with HCV has decreased because of DAA therapy [15,16], this study demonstrates that HCV patients with lower MELD-Na scores have a higher chance of recovery without transplantation, compared to those with NASH or CLD, and have comparable waitlist outcomes to ALD. Similar to the effects of abstinence in ALD, eradication of virus in HCV patients may lead to a decrease in waitlist mortality and an increase in recovery. It should be noted that data for DAA usage in HCV is not available in the OPTN/UNOS registry and the succinct impact of DAA therapy on waitlist outcomes remains to be elucidated.

HCV remains the leading underlying disease for transplantation for HCC [17]. Our study evaluated patients with HCC separately and revealed that 180-day mortality risk was significantly higher in HCV and NASH than ALD, whereas there was no significant difference in 1-year waitlist outcomes. Patients awaiting transplant for HCC population have already been subject to disease-specific risk stratification and allocation with being given an exception score for HCC [18]. It should be acknowledged that Younossi *et al.* [19] also evaluated waitlist dropout rate in the HCC population between NASH, ALD, HCV, and hepatitis B infection and showed that waitlist dropout rates were similar between groups. Liver transplant candidates with HCC

Table 4. Comparisons of waitlist outcomes in patients with MELD exception for HCC and non-HCC (Ref. ALD).

	HR (95% CI)	*P* value
HCC exception group		
180-day mortality		
HCV	1.28 (0.94–1.74)	0.11
NASH	1.09 (0.75–1.57)	0.66
PBC	1.35 (0.48–3.75)	0.57
PSC	0.25 (0.03–1.91)	0.18
1-year mortality		
HCV	0.07 (0.87–1.32)	0.54
NASH	0.90 (0.69–1.16)	0.42
PBC	1.25 (0.63–2.45)	0.52
PSC	0.55 (0.23–1.30)	0.17
180-day transplant probability		
HCV	1.43 (1.11–1.85)	**0.006**
NASH	1.35 (1.01–0.39)	**0.04**
PBC	1.37 (0.53–3.52)	0.52
PSC	1.01 (0.39–2.60)	0.98
1-year transplant probability		
HCV	1.05 (0.92–1.18)	0.48
NASH	1.05 (0.91–1.21)	0.053
PBC	0.75 (0.45–1.24)	0.26
PSC	1.06 (0.75–1.50)	0.73
Non-HCC exception group		
90-day mortality		
HCV	0.99 (0.38–2.57)	0.99
NASH	1.76 (0.80–3.87)	0.16
PBC	1.57 (0.07–4.75)	0.6
PSC	1.01 (0.38–2.68)	0.99
1-year mortality		
HCV	1.28 (0.75–2.19)	0.37
NASH	1.98 (1.20–3.28)	**0.008**
PBC	1.42 (0.56–3.60)	0.46
PSC	0.96 (0.54–1.72)	0.9
90-day transplant probability		
HCV	1.52 (1.04–2.25)	**0.03**
NASH	0.68 (0.46–0.99)	**0.047**
PBC	0.85 (0.44–1.64)	0.62
PSC	1.24 (0.82–1.86)	0.31
1-year transplant probability		
HCV	1.33 (1.02–1.74)	**0.04**
NASH	1.01 (0.80–1.29)	0.91
PBC	1.00 (0.66–1.51)	**0.001**
PSC	1.55 (1.19–2.01)	**<0.001**
90-day recovery	Incalculable	
1-year recovery		
HCV	0.27 (0.04–1.69)	0.16
NASH	0.29 (0.07–1.11)	0.07
PBC	0.34 (0.03–3.56)	0.37
PSC	0.34 (0.06–1.82)	0.21

Statistical significant *P* values are shown in bold.

usually have a very low MELD score and difference of disease progression among disease etiologies might not be obvious. It was reported that oncological features were different according to underlying liver disease, which might be associated with the difference in waitlist outcomes at 180 days [20].

NASH patients showed higher mortality and lower chance of recovery, compared to ALD patients. In patients who were granted MELD exception for non-HCC reasons, NASH had significantly higher risk of 1-year mortality compared to ALD. According to our findings, NASH patients are significantly older than other disease groups with over 50% of waitlisted patients being 60 years or older. Of note, older patients have a significantly higher risk of waitlist mortality. Because the NASH group has the largest number of older patients, the impact of older age on waitlist outcomes in NASH would be more prominent than in other disease groups [14]. Currently, liver allocation in the United States does not take patient age into account. It would not be straightforward to incorporate patient age into the allocation system. Allocation of priority to older patients should be carefully considered based on individual risk and benefit of liver transplantation, because older recipient age is a well-known risk factor for post-transplant mortality [14].

When assessing waitlist mortality in the entire group, PBC patients showed the highest risk of waitlist mortality. Interestingly, PSC patients showed the lowest mortality rate among the disease groups, though the difference was not significant after risk adjustment. Although these two diseases may be classified in the same disease category as cholestatic liver disease, disease progression may be quite different between PBC and PSC. In fact, the lower risk of waitlist mortality in PSC patients was reported by other groups [21]. Goldberg *et al.* [22] reported that patients with PSC were less likely to develop complications of portal hypertension, compared to non-PSC patients, which might contribute to the lower risk of waitlist mortality in this group. Our study also revealed that the rates of grade 3 or 4 encephalopathy and moderate ascites at listing were lowest in PSC patients than other disease groups (Fig. 4). However, we should acknowledge that both PBC and PSC patients had higher delta MELD-Na than ALD, HCV, or NASH in the mid-MELD-Na score category. In addition, the increased risk of waitlist mortality in PBC and PSC patients with a higher MELD-Na score was observed, compared with HCV, NASH or ALD (Fig. 3). Given the worse waitlist outcomes in these populations especially in the higher MELD-Na score category, PBC and PSC patients are at a potential disadvantage in the current MELD-Na-based allocation system. In this population, rapid deterioration more likely

occurs when their MELD-Na scores reach mid to higher score range. Given the unique disease progression, it may be important to carefully monitor their MELD-Na score and co-morbidities in this particular population. Acute-on-chronic liver failure might be associated with their poor outcomes, though the OPTN/UNOS registry does not contain sufficient information to identify patients who developed acute-on-chronic liver failure. Their disease status and prognosis may need to be assessed not only by MELD-Na score, but also other models such as the updated Mayo PBC risk score, which is calculated by total bilirubin, prothrombin time, age, albumin, presence of peripheral edema, and requirement of diuretics [23,24].

Limitations of this study include its retrospective nature and usage of the OPTN/UNOS registry which lacks some detailed clinical data, specifically abstinent period, relapse of alcohol pre- and post-transplant, psychosocial status, and DAA usage. Secondly, we included only diagnosis of "alcoholic cirrhosis" as ALD. Because of the increasing interests in liver transplantation for alcoholic hepatitis, waitlist outcomes in this population remain to be elucidated. We acknowledge that it is likely that some alcoholic hepatitis patients were classified as "alcoholic cirrhosis" in the database.

In conclusion, liver transplant candidates with major liver diseases showed different disease progression during their waiting time. ALD and HCV patients show relatively slower disease progression, whereas it may progress faster in NASH. PBC and PSC patients may show rapid deterioration of condition when their MELD-Na score reaches mid to higher rage. These differences lead to the discrepancies in waitlist outcomes between disease groups. ALD patients have lower mortality risk, better recovery chance on waitlist, and NASH and PBC patients have worse waitlist outcomes in particular MELD-Na score categories. The unique characteristics in each liver disease may need to be considered in the assessment of medical urgency. The findings suggest that risk stratification and priority of liver allocation might need to be altered according to liver disease etiology.

Authorship

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Funding

This work received no funding from any agency in the public, commercial, or not-for-profit sectors. No writing assistance. We have partly paid for staff positions from the Benson Ford Endowment for Transplantation.

Conflicts of interest

The authors have declared no conflicts of interest.

Acknowledgements

The data reported here have been supplied by the UNOS as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Risk factors associated with 90-day waitlist mortality in each liver disease etiology.

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