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Primary biliary cholangitis has highest waitlist mortality in patients with cirrhosis and acute on chronic liver failure awaiting liver transplant

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Abstract:	Background: Data are sparse on etiology specific outcomes on waitlist (WL) and post-transplant outcomes among patients with acute on chronic liver failure (ACLF). Methods and Results: Of 14,774 adults listed for LT with cirrhosis and ACLF in the UNOS database (01/2013-06/2019), 40% were due to alcohol-associated liver disease (ALD), followed by hepatitis C virus (HCV) at 20%, non-alcoholic steatohepatitis (19%), cryptogenic cirrhosis (7%), autoimmune hepatitis (5%), primary sclerosing cholangitis (PSC) at 3%, and 2% each for hepatitis B, primary biliary cholangitis (PBC), and metabolic etiology. Using competing risk analysis, cumulative risk of WL mortality was highest for PBC at 20.5% and lowest for PSC at 13.3%, P<0.001. Compared with ALD as reference, WL mortality was higher for PBC [1.45 (1.16-1.82)], and similar for other etiologies, P<0.001. Of this cohort, 9650 (65.3%) patients received LT, with 1-yr. patient survival of 91.6% for PBC, worst for cryptogenic cirrhosis (89.5%) and best for PSC and ALD (93.4%), P<0.001. Conclusion: Among listed candidates with ACLF, those with PBC have highest WL mortality. 1-yr. post-transplant survival was excellent among recipients for PBC. If these findings are validated in prospective studies, liver disease etiology should be considered for LT selection among patients in ACLF.

Primary biliary cholangitis has highest waitlist mortality in patients with cirrhosis and acute on chronic liver failure awaiting liver transplant

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Author Contribution: AKS conceived the study idea and designed the study. **SA** and **RJ** provided important input into designing the study. **YFK** performed statistical analyses. **AKS, RJ** and **YFK** interpreted the data. **AKS** wrote the initial draft. All the authors reviewed the final version and approved for submission.

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Abbreviations (in order of their appearance in the manuscript)
ACLF: Acute on chronic liver failure; **ALD**: Alcohol-associated liver disease; **AH**: Alcoholic hepatitis; **AIH**: Autoimmune hepatitis; **CCLD**: Chronic cholestatic liver disease; **CC**: Cryptogenic cirrhosis; **EASL-CLIF**: European association for study of liver disease-chronic liver failure **HBV**: Hepatitis B virus; **HCV**: Hepatitis C virus; **LT**: Liver transplantation; **MELD**: Model for end-stage liver disease; **NASH**: Non-alcoholic steatohepatitis; **PBC**: Primary biliary cirrhosis; **PSC**: Primary sclerosing cholangitis; **UNOS**: United network for organ sharing; **WLM**: Waitlist mortality

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Abstract

Background: Data are sparse on etiology specific outcomes on waitlist (WL) and post-transplant outcomes among patients with acute on chronic liver failure (ACLF). **Methods and Results**: Of 14,774 adults listed for LT with cirrhosis and ACLF in the UNOS database (01/2013-06/2019), 40% were due to alcohol-associated liver disease (ALD), followed by hepatitis C virus (HCV) at 20%, non-alcoholic steatohepatitis (19%), cryptogenic cirrhosis (7%), autoimmune hepatitis (5%), primary sclerosing cholangitis (PSC) at 3%, and 2% each for hepatitis B, primary biliary cholangitis (PBC), and metabolic etiology. Using competing risk analysis, cumulative risk of WL mortality was highest for PBC at 20.5% and lowest for PSC at 13.3%, P<0.001. Compared with ALD as reference, WL mortality was higher for PBC [1.45 (1.16-1.82)], and similar for other etiologies, P<0.001. Of this cohort, 9650 (65.3%) patients received LT, with 1-yr. patient survival of 91.6% for PBC, worst for cryptogenic cirrhosis (89.5%) and best for PSC and ALD (93.4%), P<0.001. **Conclusion**: Among listed candidates with ACLF, those with PBC have highest WL mortality. 1-yr. post-transplant survival was excellent among recipients for PBC. If these findings are validated in prospective studies, liver disease etiology should be considered for LT selection among patients in ACLF.

Key Words: ACLF; Cirrhosis; Organ failure; Waitlist Mortality; UNOS

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INTRODUCTION

Acute on chronic liver failure (ACLF) occurs frequently among hospitalized patients with cirrhosis and yields high short-term mortality due to multiple organ failure [1-4]. The worldwide prevalence of ACLF among hospitalized is reported at 5-30%, with mortality rate of 25-42% and 40-56% at 28 and 90 days respectively [5-8]. Liver transplantation (LT) among select patients provides survival benefit among patients with ACLF, including patients with multiple organ failure with grade 3 ACLF [9-13].

We earlier showed that patients with primary biliary cholangitis (PBC) have highest mortality waiting on the liver transplant (LT) list,[14] and excellent post-transplant outcomes among LT recipients.[15] However, similar data remain scarce among patients who are in ACLF at the time of listing or at transplantation. Prospective studies have proposed a definition of ACLF with high short-term mortality. However, these studies did not address effect of etiology on the mortality in patients with ACLF.[2,8,16-18] We performed this study among candidates listed for LT in the US, to examine and compare liver disease etiologies for waitlist (WL) mortality among listed candidates and for patient survival among transplanted patients.

MATERIAL AND METHODS

Study Population

United Network for Organ Sharing (UNOS) database was used to extract a retrospective cohort of patients listed for LT, who had ACLF at the time of listing. With improvement of HCV related waitlist and post-transplant outcomes since the introduction of direct acting antivirals in 2013, the cohort consisted of listed patients between 01/2013 and 06/2019 [19-21]. Organ failure/s and ACLF and severity (ACLF grades 1, 2, and 3) were defined using the European Association for the Study of the Liver (EASL)-Chronic Liver Failure [CLIF] (EASL-CLIF) definition (**Supplementary Tables 1 and 2**) [8]. As the information on PaO2, FiO2, and mean arterial

pressure are unavailable in the UNOS database, mechanical ventilation or requirement of life support were used to identify patients with pulmonary failure or circulatory failure respectively [9].

We included adults (≥18 years of age) listed for HCV, ALD, NASH, CC, primary sclerosing cholangitis (PSC), HBV, metabolic diseases, autoimmune hepatitis (AIH), and primary biliary cirrhosis (PBC). UNOS codes were used to stratify for liver disease etiology (**Supplementary Table 3**) Candidates listed for Wilson's disease, hereditary hemochromatosis, and alpha-1 antitrypsin deficiency were included in the metabolic etiology [15]. Patients with a dual diagnosis of HCV and ALD (4216) were included in the HCV group, as their outcomes have been reported to be similar to those with HCV [22]. Candidates listed for diagnosis of alcoholic hepatitis were included in the ALD group, as their outcomes are similar as compared to LT performed for decompensated ALD cirrhosis without alcoholic hepatitis [23]. Listings for concomitant hepatocellular carcinoma (4400.4 4401, 4402), listings for acute liver failure or status 1A, or with previous LT were excluded. From this cohort of listed patients, a subgroup of LT recipients was examined for etiology specific one year post-transplant patient survival.

Data Collection

Data on the study cohort was extracted on demographics (age, gender, race, BMI); liver disease etiology; comorbidities (diabetes mellitus and obesity); organ failure and grade of ACLF; and removal from LT list due to WL mortality (death or being too sick for LT). Variables at the time of listing and at the time of LT were used to stratify patients with ACLF with its grade at listing or at receipt of LT respectively (**Supplementary Table 1**).

Study Outcomes

As MELD score predicts 3 months mortality in patients with cirrhosis, the study outcome among listed patients was WL mortality within 90 days from listing [24]. As patient survival at one year after LT is unlikely to be impacted by the acute illness and organ failure in patients with ACLF, patient survival at one year was the outcome studied among recipients of LT [9].

Data Analyses

Overall and etiology specific frequency of listings for ACLF were examined. Chi-square statistical test was used for this analysis. Baseline characteristics among both the cohorts (listed and transplant recipients) were compared for liver disease etiology. Categorical and continuous variables were analyzed using chi-square and analysis of variance, respectively. Cumulative incidence rates on removal from LT list at ninety days from listing due to WLM were generated using competing risk analysis. Competing outcome was removal from transplant list for receiving LT. Patients surviving at 90 days were censored. Gray's statistical test was used for these analyses. Fine and Gray regression models were built to derive independent predictors of removal from LT at ninety days from listing due to WLM, with specific focus to identify impact of liver disease etiology. Variables different at baseline and other clinically relevant variables at the time of listing were entered into the model. Kaplan Meier survival curves were obtained on graft and patient survival at one year after LT among transplant recipients. Log Rank test was used for statistical significance. Cox proportional hazard regression analyses models were built to determine predictors of graft and patient survival at one year after LT. Variables at the time of transplant which are clinically relevant for the studied outcomes were entered into these models. P-values <0.01 was considered significant for all the analyses, given that multiple liver disease etiologies were compared. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analyses.

All human studies have been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008. All persons gave their informed consent prior to their inclusion in the study.

RESULTS

Study Population

Of 51,957 candidates listed for LT between 01/2013 and 06/2019, 14,774 (28.4%) with ACLF at listing formed the study cohort. The proportion of cirrhosis patients with ACLF at listing was 26% in 2013 and 29% in 2019, P<0.02. (**Supplementary Figure 1**). Of 14,774 candidates with ACLF at listing, ALD contributed the most (39.7%) followed by HCV (20.3%), NASH (19.4%), CC (7%), AIH (4.7%) PSC (2.6%), PBC (2.4%), HBV (2.2%), and metabolic (1.7%) etiology (**Figure 1**).

Baseline Characteristics of Candidates with ACLF at Listing

Baseline characteristics of the study cohort are depicted in **Table 1**. Patients with ALD, PSC, AIH, and metabolic etiology were younger compared to other etiologies. Candidates listed for NASH etiology were older and more likely to be females, obese, and diabetic**.** Proportion of African Americans was higher at 16-25% for candidates with HCV, PSC, AIH, and HBV etiology compared to 3-11% for other etiologies. Average MELD score at listing was highest at 34 among candidates with HBV etiology, followed by 32 for AIH and metabolic, 31 for ALD and PSC, and 28-29 for other etiologies. Severe ACLF (grade 2 or 3) was most frequent in AIH at 77%, followed by HBV and metabolic etiologies at 72%, PSC at 67%, 64% in ALD, and 41-52% for NASH, HCV, and CC etiologies. Frequency of organ failures also followed the same distribution for etiology, except renal failure which was most common at 83% and 80% in NASH and HCV etiologies respectively.

Removal from LT List at Ninety Days

On competing risk analysis of all candidates with ACLF at the time of listing, 12.5% experienced WL mortality within ninety days of listing. The cumulative incidence of WL mortality was highest for PBC at 20.1%, and lowest for PSC at 13.3%. WL mortality for other etiologies was 16.6% for CC, 16.4% for AIH, 15.1% for HBV and metabolic etiologies, 14.8% for NASH, 14.5% for ALD,

and 14.1% for HCV etiology, P<0.001 (**Figure 2**). On Fine and Gray competing risk model, risk of removal from the transplant list at ninety days from listing was 53% higher for PBC etiology compared to HCV etiology. The risk was similar for other etiologies (**Table 2**). Other factors at listing predictive of WL mortality within 90 days were candidate's age, female gender, ACLF grade, and MELD score. Risk of WL mortality decreased by 7% annually and was 35% lower among Hispanics compared to Caucasians.

Subgroup Analyses

As PBC was four times more frequent in females and WL mortality was 27% higher in females as compared to males, separate analyses among males and females were performed to examine independent effect of PBC etiology on WLM. In adjusted analysis of 9,148 males, the cumulative risk of WL mortality was highest among candidates listed for AIH or for PBC at 19.0% and 18.8% respectively (**Supplementary Table 4 and Supplementary Figure 2A**). Compared to ALD in Fine and Gray model, the WL mortality was numerically higher for PBC, however due to small sample size (N=52) this did not reach statistical significance, 1.49 (0.85-2.60), P=0.16 (**Supplementary Table 5**). Male candidates listed for AIH (N=207) also had higher WL mortality compared to ALD, 1.52 (1.09-2.12), P<0.02. However, WL mortality was similar comparing PBC vs. AIH etiology, 1.02 (0.54-1.94), P=0.95.

Similarly, among 5626 females, cumulative risk of WL mortality was highest among candidates listed for PBC in both unadjusted and adjusted analyses at 26.9% and 23.6% respectively (**Supplementary Table 4 and Supplementary Figure 2B**). Compared to ALD in Fine and Gray model, the WL mortality was higher for PBC, 1.41 (1.09-1.83), P<0.01 (**Supplementary Table 5**). Female candidates listed for metabolic etiology (N=166) also tended to have WL mortality compared to ALD, 1.65 (1.06-2.58), P<0.03. However, WL mortality was similar comparing PBC vs. AIH etiology, 1.15 (0.71-1.86), P=0.58.

A prior study has shown that patients with ACLF grades 2 and 3 at listing and MELD score ≤25 are disadvantaged with higher WL mortality compared to patients with higher MELD score.[9] Hence, we plotted etiology specific MELD score in the whole dataset and at each ACLF grade. Although, 32% of PBC patients had listing MELD ≤25, 38% of patients with NASH had listing MELD ≤25 (**Supplementary Figure 3**).

We also examined causes of death stratified for etiology of liver disease among candidates who died while waiting for LT (**Supplementary Table 6**). Among 1854 candidates dying within 90 days after listing for LT, about 70% had documented known cause of death. Common causes were multi-organ failure in 31-45%, infection in 13-26%, cardiopulmonary in 5-17%, and bleeding in 5-13% candidates. Cardiopulmonary cause was commonest cause of WL mortality among candidates listed for PBC, AIH, or NASH etiologies at 17%, 17%, and 15% respectively. Similarly, multi-organ failure was the most common cause of death in AIH and ALD, infection in PSC and metabolic etiology, and bleeding in those listed for PSC.

Etiology Specific Baseline Characteristics of LT Recipients

Between 01/2013 and 06/2019, a total of 9650 received LT of which 4050 for ALD, 1886 for HCV, 1780 for NASH, 603 for CC, 454 for AIH, 273 for PSC, 220 for HBV, 203 for PBC, and 181 for metabolic etiology. Baseline characteristics of these patients specific to liver disease etiology are depicted in **Table 3**. At the time of LT, 10% of 9650 recipients were not in ACLF, 24% were in ACLF-1, 31% in ACLF-2, and 35% in ACLF-3. Among candidates with ACLF-1 at the time of listing, 13% improved to no ACLF at LT, 32% worsened (22% ACLF-2 and 10% ACLF-3), and 55% remaining in ACLF-1. Similar respective figures for ACLF-2 at listing were 21% (11% without ACLF and 10% ACLF-1), 31%, and 48%. Among candidates with ACLF-3 at listing, 19% improved (15% ACLF-2, 2% ACLF-1, and 2% no ACLF), while 81% remained in ACLF-3 at LT (**Figure 3**). We also examined progression of ACLF grade from listing to the time of LT. Proportion of listed candidates in whom ACLF progressed from the time of listing to LT

was highest for PBC at 27% and lowest for ALD and HCV at 16%. ACLF and disease severity among the remaining patients either stable or improved (**Supplementary Figure 4**).

Etiology Specific Patient Survival of LT Recipients

Kaplan Meier curves were generated on one year outcomes comparing liver disease etiologies. With overall patient survival rate of 91.2% at one year after transplantation, etiology specific survival rates were around 93% for PSC and for ALD, 91.7% for metabolic, 91.6% for PBC, 90.1% for AIH, 89.8% for NASH, 89.5% for CC and HCV, and 89.3% for HBV, Log Rank P<0.001 (**Figure 4**). In a cox proportional hazard regression model, transplant recipients for ALD etiology were 22% less likely to die at one year after LT compared to recipients for HCV etiology. Patent survival at one year was similar for other etiologies (**Table 2**). Other predictors for patient survival were donor risk index, ACLF grade 3 at transplant, and age at transplant.

DISCUSSION

About 28% of candidates with cirrhosis at the time of listing for LT have ACLF, and this condition is highest among patients with cirrhosis due to HBV or ALD. Among candidates who are in ACLF at the time of listing for LT, ALD is the leading etiology in about 40%, while PBC contributes to only about 2% of these cases. However, once ACLF develops, cumulative risk WL mortality within ninety days of listing is highest for patients with PBC. Among LT recipients, one year patient survival is good for all etiologies of liver disease, with best survival rate at 93.4% among recipients for ALD and 91.6% among those transplanted for PBC.

Our study showed the highest waitlist mortality was in PBC patients. The WL mortality of 20.1% in PBC and 13.3% in PSC within 90 days of listing is similar to our earlier study in patients with cirrhosis [14]. In another study from Japan, PBC patients compared to HCV patients experienced higher WLM [25]. Similarly, s study from Austria on 176 cirrhosis patients listed for LT (100 with PBC), the WL mortality was higher in PBC as compared to 76 patients with PSC (16 vs.

5.3%).[26] To our knowledge, however, the high WL mortality associated with PBC has not been demonstrated among patients who are in ACLF at the time of listing for LT.

Females compared to males have higher WL mortality and less access to LT due to differences in height and underestimation of renal function due to their small stature and muscle volume.[27] Given PBC is a disease of females, impact of PBC etiology on WL mortality may be a gender effect. However, our findings on trend for male candidates with PBC also for high WL mortality, suggests that this is not entirely a gender effect. Patients with PBC may also be disadvantaged and have higher WL mortality, as a relatively higher proportion of these patients are listed with MELD score ≤25. However, this also does not explain the entire effect, as proportion of such patients was even higher among candidates listed for NASH. Although, PBC patients were not at higher risk of any specific organ failures or higher grade of ACLF at the time of listing, they had highest rate of progression to higher grade/s of ACLF after being listed for LT. It is likely that higher WL mortality in PBC patients is multifactorial due to higher candidate's age, female gender, relatively higher proportion listed at lower MELD, and more frequent of progression of ACLF grade. Our findings on cardiovascular and pulmonary complications resulting in WL mortality among PBC patients is also reported earlier.[14,26]

ACLF is a major cause of health care burden in the US with prevalence of 5-40% among hospitalized patients with cirrhosis, [8,17,28,29] similar to prevalence of 28.4% of cirrhosis patients listed for LT in this study. Although, LT provides significant survival benefit to select ACLF patients, the outcomes remain suboptimal compared to recipients for cirrhosis without ACLF, especially for recipients with ACLF-3 at the time of LT.[13] Ours is the first study to examine etiology specific post-transplant outcomes among recipients with ACLF at LT. Patients receiving LT for ALD had the best post-transplant outcomes after controlling severity of liver disease and patient demographics. Reasons for better outcomes in ALD patients may be speculated due to

younger age with less number of comorbidities and more rigorous psychosocial evaluation in these candidates.

Large sample size with patients listed for LT across the nation from several regions is a strength of our study. Further, we limited our study to the era when effective treatment for HCV is available to overcome the era effect on pre- and post-transplant outcomes. However, our study suffers from limitations of any analysis using the retrospective cohort. Using the UNOS database, there is a potential for misclassification of pulmonary or circulatory organ failure. For example, use of mechanical ventilation which was used to adjudicate pulmonary failure could have been for airway protection and not really for respiratory failure. Similarly, use of life and vasopressor support which was used to adjudicate circulatory failure could have been for treating hepatorenal syndrome and not truly for circulatory failure or shock. Although, information on ACLF and its grade was available at listing and at the time of transplant, how the ACLF grade evolved from listing to removal of the candidate from list due to WL mortality was not available. Information on precipitant of ACLF such as infection or other precipitants was also unavailable. However, we feel that these limitations do not affect our study conclusions as our aim was to examine the effect of liver disease etiology on the WL mortality and on post-transplant survival. We do feel though, that these limitations do limit implementation of our findings in routine practice pending validation in large prospective multicenter studies. The database also lacked information on use of etiology specific treatment which could have impacted the outcomes, though it would be expected that that patients listed for PBC would be taking ursodeoxycholic acid.

In summary, our study shows for the first time the importance of liver disease etiology in patients with ACLF, in defining the risk of death on the transplant waiting list and on post-LT survival. The highest waitlist mortality was observed in PBC patients, whilst the best one year post-LT survival was noted in ALD patients with ACLF at the time of listing. These data suggest

that if these findings are validated in other large prospective studies, liver disease etiology should be considered in patient selection for LT among ACLF patients [9].

Table 1 Baseline characteristics of candidates with acute on chronic liver failure (ACLF) at listing for liver transplant

Variable	HCV (N=3012)	ALD (N=5860)	NASH (N=2852)	CC (N=1036)	PSC (N=387)	HBV (N=329)	Metabolic (N=256)	AIH (N=692)	PBC (N=350)
Age in years*	57, 7	51, 10	59, 9	56, 11	51, 14	53, 10	50, 14	49, 14	58, 9
Males (%)	70	71	48	53	70	81	68	30	15
% Race (C, AA, H)	53, 20, 23	67, 5, 25	67, 3, 26	57, 9, 30	58, 26, 12	27, 17, 20	79, 4, 16	46, 24, 26	58, 11, 27
Body Mass Index*	29, 6	29, 6	33, 7	29, 6	26, 5	29, 6	30, 7	30, 7	29, 6
Diabetes mellitus (%)	34	18	62	36	21	32	21	24	24
Obesity (%)	35	38	64	38	20	34	45	45	35
Listing MELD*	29, 9	31, 8	28, 8	29, 8	31, 8	34, 9	32, 8	32, 8	29, 8
ACLF 1, 2, 3 (%)	53, 27, 20	36, 40, 24	59, 27, 14	48, 33, 19	34, 52, 14	30, 37, 33	33, 43, 24	25, 43, 33	44, 39, 17
Liver failure (%)	33	51	27	40	76	68	54	70	53
Renal failure (%)	80	72	83	77	61	63	61	56	73
Coagulation failure (%)	33	41	25	33	26	56	52	53	27
Brain failure (%)	20	25	19	18	15	18	23	29	19
Pulmonary failure (%)	7	7	5	7	3	11	8	14	7
CV failure (%)	11	13	9	12	9	13	13	18	10

AA: African American, ALD: alcoholic liver disease, BMI: Body mass index, C: Caucasian, H: Hispanic, HCV: Hepatitis C virus infection, MELD: Model for end-stage liver disease, NASH: Non-alcoholic steatohepatitis; CC: Cryptogenic cirrhosis; PSC: Primary sclerosing cholangitis; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; CV: Cardiovascular.

**Results expressed as mean, standard deviation.*

Table 2 Predictors listing for liver transplantation of ninety day risk of waitlist mortality and at transplant for one year patient survival.

		Waitlist Mortality at 90 days		Post-transplant patient survival at one year	
Variable		**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
	HCV vs. ALD	0.95 (0.84-1.07)	0.40	1.24 (1.06-1.45)	<0.007
	NASH vs. ALD	1.00 (0.89-1.14)	0.97	1.18 (0.99-1.40)	<0.06
	CC vs. ALD	1.17 (0.99-1.38)	<0.07	1.17 (0.92-1.48)	0.20
	PSC vs. ALD	0.92 (0.69-1.21)	0.54	1.08 (0.77-1.53)	0.66
Liver Disease Etiology	HBV vs. ALD	0.99 (0.74-1.31)	0.92	1.07 (0.75-1.55)	0.70
	Metabolic vs. ALD	1.08 (0.79-1.48)	0.63	0.96 (0.51-1.52)	0.87
	AIH vs. ALD	1.21 (0.99-1.47)	<0.06	1.33 (1.02-1.72)	<0.03
	PBC vs. ALD	1.45 (1.16-1.82)	<0.002	0.96 (0.64-1.46)	0.96
Age in years		1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	<0.001
Females vs. Males		1.27 (1.17-1.39)	<0.001	0.93 (0.80-1.08)	0.35
	AA vs. Caucasian	0.89 (0.77-1.03)	0.13	0.99 (0.79-1.25)	0.93
Race	Hispanic vs. Caucasian	0.65 (0.59-0.73)	<0.001	0.85 (0.72-1.01)	<0.06
	Other vs. Caucasian	1.06 (0.88-1.28)	0.55	0.89 (0.63-1.26)	0.52
Obesity		0.999 (0.92-1.09)	0.98	0.92 (0.82-1.03)	0.14
ACLF grade	ACLF 2 vs. ACLF 1	1.44 (1.29-1.62)	<0.001	1.12 (0.97-1.29)	0.14
	ACLF 3 vs. ACLF 1	2.63 (2.29-3.01)	<0.001	1.45 (1.24-1.70)	<0.001
Calendar Year		0.93 (0.91-0.95)	<0.001	1.03 (0.99-1.07)	0.15
MELD score		1.02 (1.01-1.03)	<0.001		
Donor risk index				1.64 (1.38-1.93)	<0.001

ALD: alcohol associated liver disease, HCV: Hepatitis C virus infection, NASH: Non-alcoholic steatohepatitis; CC: Cryptogenic cirrhosis; PSC: Primary sclerosing cholangitis; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; HR: Hazard ratio; CI: Confidence interval; ACLF: Acute on chronic liver failure.

Table 3 Baseline characteristics of candidates with acute on chronic liver failure (ACLF) at the time of liver transplantation (LT)

Variable	HCV (N=1886)	ALD (N=4050)	NASH (N=1780)	CC (N=603)	PSC (N=273)	HBV (N=234)	Metabolic (N=217)	AIH (N=747)	PBC (N=204)
Age in years*	57, 8	50, 10	58, 9	55, 11	50, 13	53, 11	48, 14	46, 15	57, 10
Males (%)	71	71	49	54	71	79	72	29	16
% Race (C, AA, H)	52, 19, 25	65, 4, 28	65, 3, 29	56, 9, 32	56, 24, 15	28, 15, 25	75, 4, 19	43, 24, 28	57, 10, 30
Body Mass Index*	28, 6	28, 6	32, 7	29, 6	26, 6	28, 7	29, 6	30, 7	28, 6
Diabetes mellitus (%)	30	16	58	32	20	31	18	22	20
Obesity (%)	37	40	65	40	19	35	46	46	34
ACLF 1, 2, 3 (%)*	35, 27, 31	19, 33, 36	35, 28, 27	26, 33, 32	15, 41, 28	18, 32, 44	19, 34, 35	10, 36, 44	21, 32, 36
Liver failure (%)	42	56	36	52	82	75	58	74	63
Renal failure (%)	77	66	78	71	62	61	59	57	73
Coagulation failure (%)	36	44	30	38	26	59	57	53	29
Brain failure (%)	24	26	21	20	15	24	25	27	21
Pulmonary failure (%)	5	7	4	6	3	9	6	11	6
CV failure (%)	20	23	19	21	14	19	15	25	21
Wait time in days	11 (4-48)	8 (4-22)	12 (5-47)	9 (4-35)	11 (4-32)	6 (3-13)	3 (2-6)	4 (2-10)	10 (5-31)
MELD at LT*	31, 8	32, 8	30, 8	31, 8	32, 8	35, 8	32, 8	32, 9	30, 8

**Results expressed as mean, standard deviation. **Remaining patients were not in ACLF at the time of transplantation. AA: African American, ALD: alcohol associated liver disease, C: Caucasian, H: Hispanic, HCV: Hepatitis C virus, MELD: Model for end-stage liver disease, NASH: Non-alcoholic steatohepatitis, CC: Cryptogenic cirrhosis, PSC: Primary sclerosing cholangitis; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; SD: Standard deviation; CV: Cardiovascular*

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Legends to Figures

Figure 1 Proportion of liver disease etiologies among candidates with acute on chronic liver failure (ACLF) at the time of listing for liver transplantation.
HCV: Hepatitis C virus; ALD: Alcohol-associated liver disease; NASH: Non-alcoholic steatohepatitis; CC: Cryptogenic cirrhosis; PSC: Primary sclerosing cholangitis; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis.

Figure 2 Etiology specific cumulative incidence of waitlist mortality within 90 days from listing among candidates with acute on chronic liver failure at the time of listing.
HCV: Hepatitis C virus; ALD: Alcohol-associated liver disease; NASH: Non-alcoholic steatohepatitis; CC: Cryptogenic cirrhosis; PSC: Primary sclerosing cholangitis; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis.

Figure 3 Acute on chronic liver failure (ACLF) and its grade at the time of liver transplant stratified for ACLF-1, ACLF-2, or ACLF-3 at the time of listing.

Figure 4 Etiology specific Kaplan Meir curves on one year post-transplant patient survival among transplant recipients.
HCV: Hepatitis C virus; ALD: Alcohol-associated liver disease; NASH: Non-alcoholic steatohepatitis; CC: Cryptogenic cirrhosis; PSC: Primary sclerosing cholangitis; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis.

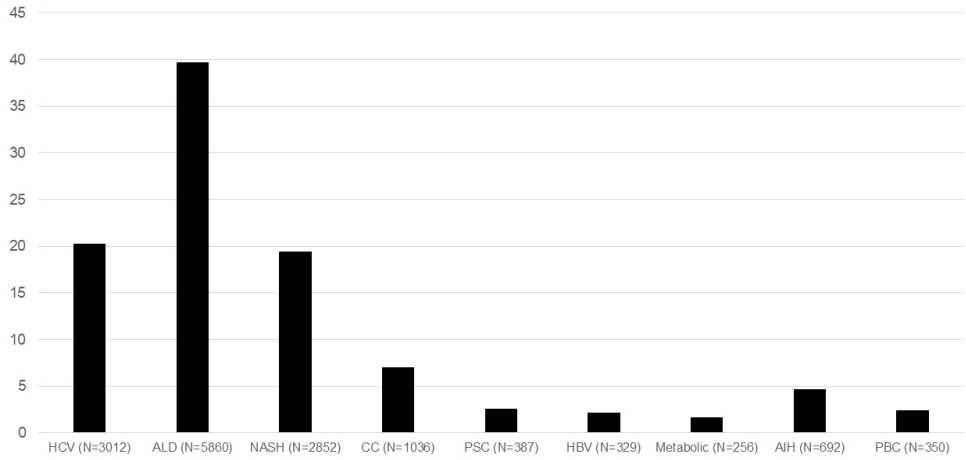

Figure 1

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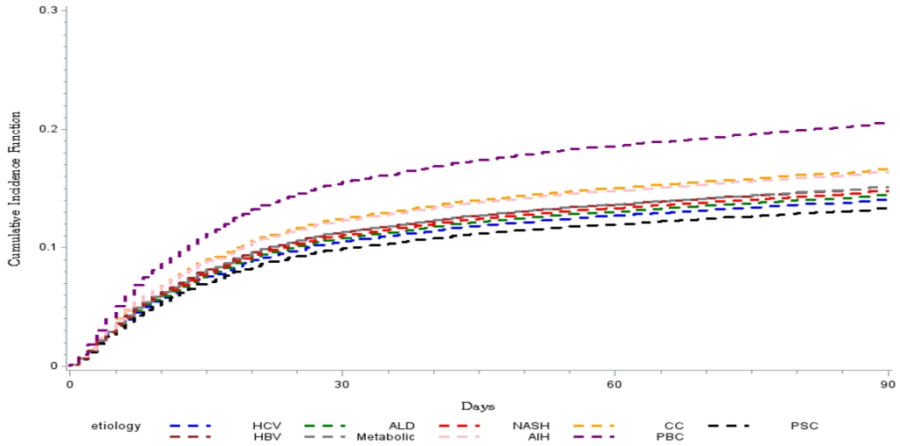

Figure 2

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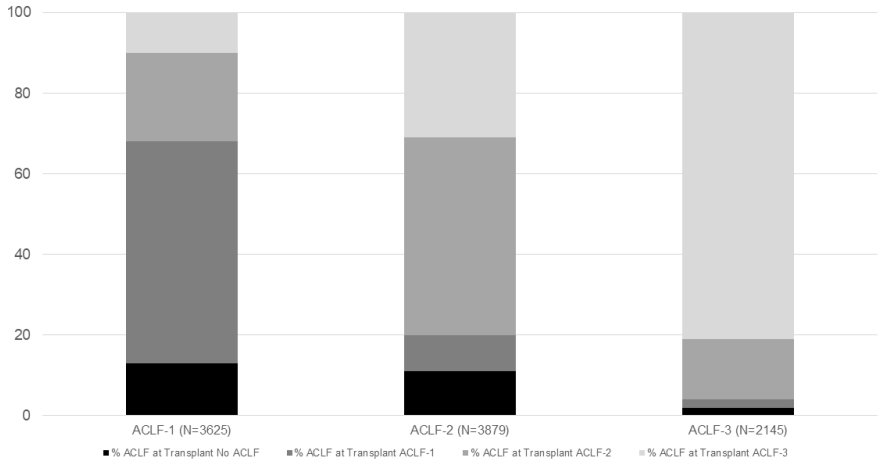

Figure 3

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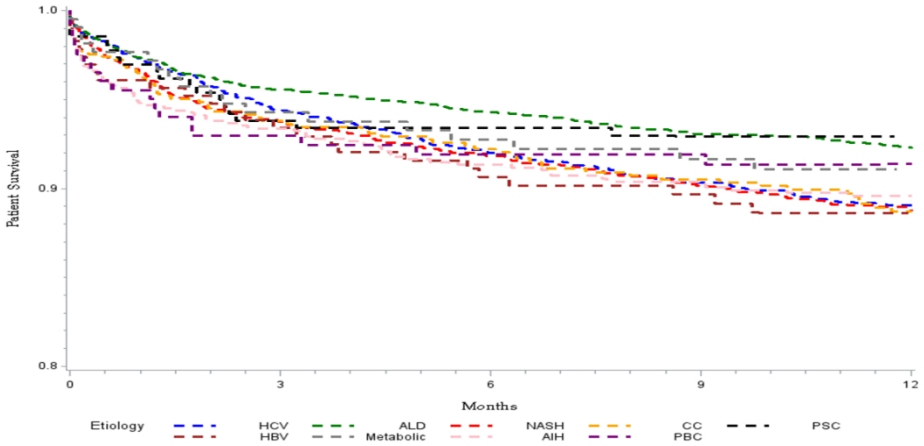

Figure 4

338x190mm (96 x 96 DPI)