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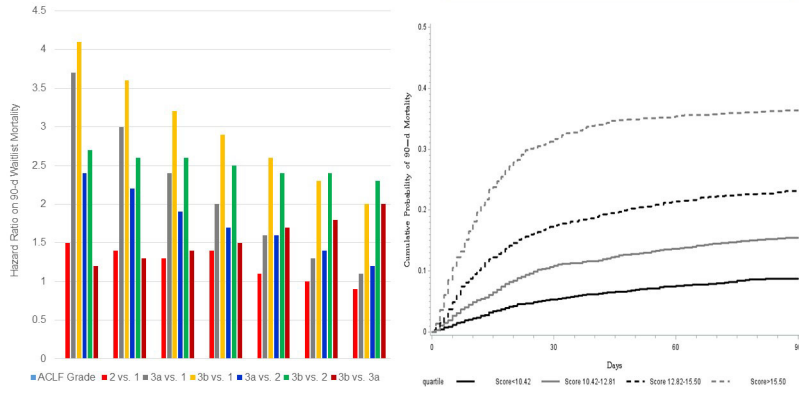
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MELD 10   15   20   25   30   35   40

ACLF Grade ■ 2 vs. 1 ■ 3a vs. 1 ■ 3b vs. 1 ■ 3a vs. 2 ■ 3b vs. 2 ■ 3b vs. 3a

Waitlist mortality according to the new risk score

quartile — Score<10.42 — Score 10.42-12.81 -- Score 12.82-15.50 -- Score>15.50

Validating a novel score based on interaction between ACLF grade and MELD score to predict waitlist mortality

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ABSTRACT

Background and Aim: Among candidates listed for liver transplant (LT), MELD score may not capture acute on chronic liver failure (ACLF) severity. Data on interaction between ACLF and MELD score in predicting waitlist (WL) mortality are scanty. **Methods**: UNOS database (01/2002 to 06/2018) on LT listings for adults with cirrhosis and ACLF (without HCC) was analyzed. ACLF grades 1, 2, 3a, and 3b- were defined using modified EASL-CLIF criteria. **Results**: Of 18,416 candidates with ACLF at listing (mean age 54 years, 69% males, 63% Caucasians), 90-d WL mortality (patient death or being too sick for LT) was 21.6% (18%, 20%, 25%, and 39% for ACLF grades 1, 2, 3a, and 3b respectively). Fine and Gray regression model identified interaction between MELD and ACLF grade, with higher impact of ACLF at lower MELD score. Other variables included candidate's age, gender, liver disease etiology, listing MELD, ACLF grade, obesity, and performance status. A score developed using parameter estimates from the interaction model on the derivation cohort (N=9181) stratified the validation cohort (N=9235) to four quartiles Q1 (score <10.42), Q2 (10.42-12.81), Q3 (12.82-15.50), and Q4 (>15.50). WL mortality increased with each quartile from 13%, 18%, 23%, and 36% respectively. Observed versus expected deciles on WL mortality in validation cohort showed good calibration (goodness of fit P=0.98) and correlation (R=0.99). **Conclusion**: Among selected candidates who are in ACLF at listing, MELD score and ACLF interact in predicting cumulative risk of 90-d WL mortality, with higher impact of ACLF grade at lower listing MELD score. Validating these findings in large prospective studies will support to factor in both MELD and ACLF in prioritizing transplant candidates and allocation of liver grafts.

Keywords: ACLF; Cirrhosis; Mortality; OLT

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Lay Summary

In cirrhosis patients listed for liver transplantation, the presence of multi organ failure, a condition referred to as acute on chronic liver failure has high mortality rates while patients are on the waiting list. Current organ allocation policy disadvantages these patients. This study describes and validates a new scoring method that performs better than the currently available scoring systems. Further validation of this approach may reduce the deaths of patients with cirrhosis and acute on chronic liver failure on the transplant waiting list.

INTRODUCTION

Acute on chronic liver failure (ACLF) occurs frequently among hospitalized patients with cirrhosis and chronic liver disease, with a significant disease burden and high short-term mortality due to multiple organ failure [1-3]. For example, prevalence of ACLF among hospitalized patients with cirrhosis is reported at 5-30%, with mortality rate of 25-42% and 40-56% at 28 and 90 days respectively [4-7]. Worldwide, liver transplantation (LT) provides survival benefit among select patients with ACLF [8-11].

However, 20-30% of patients remain at risk to be delisted from the transplant list due to wait list (WL) mortality due to death or being too sick for LT [12, 13]. Although, MELD and MELD-Na scores are also used to predict WL mortality and prioritize for LT among patients with ACLF, [14, 15] organ failure/s based scores have been shown to perform better than MELD based assessment [7, 16, 17]. As serum bilirubin, creatinine, and institutional normalized ratio are used in calculation of MELD score as well as ACLF grade, there is likely to be interaction between these two variables. However, data are scanty on examining this interaction of ACLF grade and MELD score in predicting WL mortality among patients with cirrhosis and ACLF.[18, 19] We performed this study on a cohort of patients with ACLF due to three commonest liver diseases (HCV, ALD, and NASH), with two specific objectives. Our first objective was to examine the interaction of ACLF grade with MELD score at the time of listing for LT in predicting WL mortality at 90 days from listing. The second objective was to develop and validate a new score in predicting WL mortality at 90 days using the interaction model.

METHODS

Study population

United Network for Organ Sharing (UNOS) database was used to extract a retrospective cohort of patients listed for LT for HCV, ALD, or NASH. This database has clinical information on candidates listed for LT and reason for removal from the list. We included adults (≥18 years of

age) listed for LT between 01/2002 and 06/2018. UNOS codes were used to identify candidates listed for HCV (4204), ALD (4215), and NASH (4214). 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 [20]. Listings for concomitant hepatocellular carcinoma or HCC (4400.4 4401, 4402), acute liver failure or status 1A, or with previous LT were excluded. Organ failure/s, ACLF with its grades were defined using the European Association for the Study of the Liver (EASL)-Chronic Liver Failure [CLIF] (EASL-CLIF) definition [7]. As the UNOS dataset does not provide granular information to define circulatory and pulmonary failure, modified definitions were used for these organ failures (**Supplementary Table 1**).

Data collection

Data on the study cohort of candidates on LT list with ACLF at listing was extracted on demographics (age, gender, race, BMI); liver disease etiology (HCV, ALD, or NASH); comorbidities (diabetes mellitus and obesity); MELD score; organ failure and severity of ACLF; candidate's performance status using the Karnofsky's performance status scale (KPSS), and reason for removal from LT list (WL mortality, too sick for LT, improvement in liver disease, or receipt of LT). KPSS is a scale from 0 to 100%, with 0% being dead, 10% being moribund, and 100% being completely normal.

Study Outcome

The study outcome is WL mortality due to candidate dying or being too sick for LT. The WL mortality was examined using competing risk analysis, with receipt of LT being the main competing event. As MELD score is a good predictor for 90 days outcomes and mortality, the outcome was studied at 90 days from listing for LT.[15]

Data and statistical analyses

The study population was analyzed for baseline characteristics at the time of listing. With the availability of potent therapies for HCV in the last five years resulting in changing etiology and transplant demographics, we examined baseline characteristics over time. For this analysis, the study population was stratified to three time periods: 2002-2007, 2008-2013, and 2014-2018. Categorical and continuous variables were analyzed using chi-square and analysis of variance, respectively.

For the first objective, Fine and Gray competing risk model was generated to examine interaction between MELD score and ACLF grade (MELD*ACLF). We graded ACLF to four levels taking into account the number and type of organ failures as these factors are known to be associated with WL mortality (**Supplementary Table 2**). Other confounding variables included in this model were candidate demographics (age, gender, and race), obesity status (body mass index ≥30), liver disease etiology, MELD score, ACLF grade, and calendar year of listing. As candidate's performance status is known to be associated with WL outcomes, the model also included KPSS, which was categorized to good (80-100%) or poor (10-70%) performance. The interaction model was compared with two other models incorporating MELD score alone in one and ACLF grade in the other model, with other variables remaining unchanged. This analysis was repeated using calendar year as categorical variable (2002-07, 2008-13, and 2014-18) instead of continuous variable.

Once an interaction between MELD and ACLF grade was confirmed and this model performed better than the other two models, we examined our second objective of developing and validating a new score useful in predicting WL mortality at 90 days from listing. For this analysis, the whole cohort was randomly split to derivation and validation cohorts.

The Fine and Gray competing risk interaction model was generated on the derivation cohort. The estimated parameters from this model were applied to the validation cohort to develop new

score in predicting 90-d WL mortality. Using the cut-off score for each quartile, the validation

cohort was categorized to four quartiles. Cumulative incidence curves on 90-d WL mortality

were generated comparing these quartiles. The validation cohort was also examined for

calibration between observed and expected cumulative incidence of 90-d WL mortality. For this

analysis, the expected cumulative incidence rates were categorized into deciles and the mean

of each decile was compared with the actual observed cumulative incidence rates on 90-d WL

mortality estimated by non-parametric competing risk analyses. Correlation between the deciles

of observed and expected cumulative incidence of 90-d WL mortality was derived.

The study did not require IRB approval as database study using the de-identified data. The data

user agreement was completed with the UNOS for permission to use the database for this

study. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analyses

(Supplementary CTAT Table). P-values < 0.05 were considered significant.

RESULTS

Of 286,082 candidates listed for LT until 06/2018 for cirrhosis, 81,862 adults without HCC were

listed since 01/2002 for cirrhosis due to HCV, ALD, and NASH. Of these, 20,083 (24.5%) were

in ACLF at the time of listing for LT. A total of 18,416 candidates with complete data on KPSS,

type of organ failure, and on listing MELD score were analyzed (Figure 1). Renal failure was the

most common organ failure in 14,132(77%), followed by liver failure in 7104 (39%), coagulation

failure in 5881 (32%), brain failure in 3923 (21%), cardiovascular failure in 2009 (11%), and

pulmonary failure in 1489 (9%).

Waitlist mortality at 90 days

Of all the candidates listed for ACLF, 63% were removed for receiving LT, 10.4% died while

awaiting LT, and 11.2% were removed as they were too sick for receiving LT. Remaining

patients are either still waiting or removed due to improved liver disease.

Based on type of organ failure, 90-d WL mortality was higher in patients for all organ failures except for renal failure (20 vs. 20%, P>0.05). For example, 90-d WL mortality compared to candidates with liver failure at listing vs. without liver failure was 25 vs. 20%, P<0.001. Similarly, 90-d WL mortality was higher for coagulation failure (24 vs. 21%), cardiovascular failure (36 vs. 20%), pulmonary failure (41 vs. 20%), and brain failure (27 vs. 20%), P<0.001 for all.

On Fine and Gray analysis, presence of pulmonary failure had strongest association with WL mortality with cumulative 90-d WL mortality risk over two folds compared to patients without pulmonary failure. The risk with other organ failures varied from 1.08 folds in presence of renal failure and 1.16 folds in presence of brain failure (Supplementary Table 2). For stratification of ACLF grade, patients with ACLF-3 were stratified to ACLF-3a with 3 organ failures and ACLF-3b with ≥4 organ failures (Supplementary Figure 1). Pulmonary failure in any ACLF grade was allocated two points. With a maximum of seven points on this modified stratification, 8720 candidates were in ACLF-1, 5586 in ACLF-2, 2232 in ACLF-3a, and 1878 in ACLF-3b (Figure 1). Based on these ACLF grades, 18%, 20%, 25%, and 39% experienced 90-d WL mortality for ACLF grades 1, 2, 3a, and 3b respectively (Supplementary Figure 1).

Baseline Characteristics

Of 18,416 listed candidates, 3421 (19%) were listed until 12/2007, 7191 (39%) between 01/2008 and 12/2013, and remaining 7804 (42%) between 01/2014 and 06/2018 (Table 1). Among candidates listed until 12/2007, HCV was the commonest etiology in 58% followed by ALD in 34%, and NASH in 8%. Contribution of HCV, ALD, and NASH among candidates listed between 01/2014 and 06/2018 was 26%, 50%, and 24% respectively. This change overtime was associated with increasing proportion of females, obesity as comorbidity, ACLF higher than grade 1, and poor functional status. Liver, coagulation, and cardiovascular failures were more frequent with time, without any difference on renal, brain, and pulmonary failure. The average

MELD score was higher among candidates listed since 2008 compared to those listed before 2008 (Table 1).

Predictors of removal from transplant list at ninety days

A Fine and Gray regression model was built to examine interaction of ACLF grade and MELD score in predicting 90-d WL mortality. We describe the distribution of seven confounders (age at listing, gender, race, liver disease etiology, calendar year of listing, obesity status, and performance status or KPSS) for ACLF grade and for MELD score. For this analysis, we stratified the listing MELD score to ≤15, 16-25, 26-35, and >35 (Supplementary Table 3). We also performed univariate analysis of the impact of each of these confounders on the 90-d waitlist mortality (Supplementary Table 4). Although, the effect size of obesity on the outcome is not significant, we still included this in the multivariate model given clinical significance of obesity in ACLF patients as per some previous analyses. Results of the multivariate analyses including age in year at listing, gender, race, calendar year of listing, liver disease etiology, obesity, and KPSS are shown in Table 2. As can be seen, the interaction model performed better with lower Akaike Information Criterion (AIC) value at 75,394 compared to separate model with ACLF grade alone (AIC 75,510) or MELD score alone (AIC 75,688).

Candidate age at listing, female gender, and KPSS were associated with higher risk of WL mortality, while the risk was lower among Hispanics compared to Caucasians. The risk of 90-d WL mortality decreased by 3% with each calendar year of listing (Table 2). Stratified to three time periods, the cumulative 90-d WL mortality was 18.7%, 21.2%, and 16% among candidates listed during 2014-2018, 2008-13, and 2002-07 respectively, P<0.001 (Supplementary Figure 2).

Interaction of ACLF grade and MELD score on cumulative 90-d WL mortality

Using the Fine and Gray model with ACLF*MELD interaction, cumulative incidence of WL mortality comparing ACLF grades were estimated at listing MELD score of 10, 20, 30, and 40 respectively. The cumulative 90-d WL mortality at ACLF grades 1, 2, 3a, and 3b for MELD score 10 were estimated at 6.7%, 11.7%, 28.4%, and 26.9% respectively (Supplementary Figure 3A). Similar estimated figures on cumulative 90-d WL mortality were 10.2%, 14%, 26.9%, 30% at listing MELD score of 20; 15.5%, 16.8%, 25.4%, 35% for listing MELD score 30; and 23.1%, 20%, 23.9%, 40% at listing MELD score of 40 respectively (Supplementary Figure 3 B-D). Similar estimates were also derived comparing listing MELD 10 vs. 20 vs. 30 vs. 40 for each of the ACLF grades (Supplementary Figure 4 A-D).

Pairwise comparison of ACLF grades were also estimated at listing MELD score of 10 and then at every 5 units increase until score of 40, and reported as hazard ratio (HR) with 95% confidence intervals (Table 3). This analysis showed a linear effect with increasing ACLF grade at every MELD strata, except for comparing ACLF grade 2 vs. 1 at listing MELD score ≥30 and comparing ACLF grade 3b vs. 3a at listing MELD score ≤15. Further, the magnitude of effect of ACLF grade for all the comparisons was higher at lower MELD score and decreased with increasing MELD score at listing (Table 3). Every unit increase in listing MELD score was associated with 5% [1.05 (1.04-1.06), P<0.001], 3% [1.03 (1.02-1.04), P<0.001], and 2% [1.02 (1.00-1.03), P<0.014] increase in risk of 90-d WL mortality among candidates in ACLF -1, ACLF-2, and ACLF-3b respectively. Similar association was not observed among candidates with ACLF grade 3a at the time of listing, 1.005 (0.99-1.02), P=0.39.

Derivation and Validation of Score Predicting 90-d WL Mortality

For this objective, the whole cohort was randomly divided into derivation and validation cohorts, and these were similar on baseline characteristics (Supplementary Table 5).

Univariate and multivariate analyses using the Fine and Gray competing risk interaction (ACLF*MELD) model were built on the derivation cohort of 9181 listed candidates (Supplementary Table 6). Variables in the model included age in years at the time of listing for LT, gender, race, calendar year of listing, liver disease etiology, ACLF grade, MELD score at listing, obesity, and KPSS. The three models (ACLF grade alone, MELD score alone, and ACLF*MELD interaction) were examined separately in the derivation and validation cohorts. In both the cohorts. ACLF*MELD interaction model was only numerically superior as compared to models with MELD and ACLF alone (Supplementary Table 7). The parameter estimates on these variables from the Fine and Gray model were standardized with every 5 years increases in age and used on the validation cohort on 9235 listed candidates to derive a risk score for 90-d WL mortality: *(Candidate age in years-18)/5+(MELD-6)*0.28+(ALD Etiology)*-0.35+(NASH etiology=3)*-0.62+(ACLF=2)*3.5+(ACLF=3a)*8.4+(ACLF=3b)*10.1 +(MELD-6)*(ACLF=2)*-0.1+(MELD-6)*(ACLF=3a)*-0.2+(MELD-6)*(ACLF=3b)*0.1+(Listing Year-2002)*-0.3+(African American)*-0.4+(Hispanic)*-3.1+(Other race)*-0.6+(Obesity)*0.003+(Female)*1.4+(KPSS 10-70%)*1.7*.

With a median (range) score of 12.8 (-0.06 to 27.6), quartiles risk categories were generated: quartile 1 (score <10.42, N=2288), quartile 2 (score 10.42-12.81, N=2366), quartile 3 (score 12.82-15.50, N=2308), and quartile 4 (score >15.50, N=2273). The cumulative 90-d WL mortality (95% Confidence Interval) was 13.2 (11.9-14.7) %, 17.5 (16.0-19.0) %, 22.7 (21.0-24.5) %, and 36.3 (34.3-38.3) % for quartiles 1-4 respectively, P<0.001. Using Fine and Gray competing risk model, 90-d WL mortality increased linearly with increasing quartile on the score (Figure 2). The score was further validated with calibration of deciles in the validation cohort on observed cumulative incidence of WL mortality against deciles on the expected cumulative incidence, Goodness of fit chi-square P=0.98 (**Figure 3**). Deciles on observed and expected cumulative risk also showed excellent correlation, with R coefficient of 0.9996, P<0.001.

Patient examples of risk score calculation and predicted 90-d WL mortality

Using the novel validated risk score, the probability of 90-d WL mortality of an individual patient varies from 4.6% at risk score of 0 to 90% at risk score of 30 (Supplementary Table 8). We describe two case scenarios as examples to justify factoring ACLF grade along with MELD score in estimating WL mortality among candidates listed for LT and who are in ACLF at the time of listing. A 40 year old Hispanic non-obese male in good functional status (KPSS 80-100%) with MELD score of 35 and ACLF grade 3a at the time of listing will have risk score of 6 with probability of 90-d WL mortality of 10%. However, a 70 year old female with HCV related ACLF grade 3b, poor functional status and MELD score 14 at listing will have risk score of 18 and WL mortality four folds higher at 39%.

DISCUSSION

Main finding of our study demonstrates interaction between ACLF grade and MELD score among candidates with ACLF at listing for LT, with several novel observations. For example, the magnitude of impact of the ACLF grade was higher at lower than at higher MELD score. Finally, we developed a novel score using listing characteristics including both the MELD score and ACLF grade to estimate risk of WL mortality.

In this analysis, 21.6% of candidates with ACLF at listing were removed due to WL mortality within 90 days of listing, similar to another report using the UNOS database [8]. In another study, 108 of 768 (14%) candidates with cirrhosis either died or were delisted within 90 days from listing for LT [13]. Among ACLF patients in this study, 28% candidates were delisted, as observed in our study [13].

As organ failure development is a unique feature to ACLF and also primary driver of mortality, MELD score alone is limited in predicting WL mortality as observed in this study and other

reports. For example, in a recent report using the UNOS database, removal from LT list at 28 days from listing among candidates with ACLF-3 was highest at 43.8% at listing MELD <25 [8]. Relatively low MELD in these patients puts them at disadvantage in receiving LT explaining higher WL mortality due to organ failure/s. This may also explain much higher impact of ACLF grade at lower compared to candidates with higher listing MELD score. In another study on candidates listed for ACLF-3 using the same database, WL mortality at 14 days from listing was independent of MELD-Na score, and was higher compared to candidates listed as status 1a [21].

Our analysis also showed increasing WL mortality with number of organ failures, as candidates with ≥4 compared to those with 3 organ failures had higher risk for WL mortality, similar to other reports [8, 22]. In a recent study using the UNOS database among candidates with ACLF-3 at listing, WL mortality was higher in the presence of 4-6 compared to 3 organ failures. [22]. In another study, brain failure (hepatic encephalopathy grade 3 or 4), but not the other extra-hepatic organ failures was associated with risk of WL mortality [23]. In our analysis, pulmonary failure had strongest impact on WL mortality followed by brain and liver failure. Low frequency of pulmonary failure in ACLF-1 probably explained lack of impact of ACLF grade 2 compared to ACLF grade 1 on WL mortality among candidates at listing MELD higher than 30 [8].

Analysis on large number of patients using the UNOS database is a strength of our study. Our study provides a score to estimate WL mortality among LT listed candidates, based on interaction of MELD score and ACLF grade at listing. Further, we internally validated the model with ACLF grade and MELD score interaction. However, our study has certain limitations. For example, misclassification of organ failure(s) can occur when using UNOS database due to lack of granular information on mechanical ventilation indication whether airway protection or true respiratory failure. Other scoring systems and variables including CLIF-SOFA, CLIF-OF, CLIF-ACLF, CLIF-AD, APACHE-III, MELD-lactate, hepatic encephalopathy, and biomarkers like high

density lipoprotein levels, apolipoprotein A, and neutrophil to lymphocyte ratio have also been shown to predict WL mortality among patients with ACLF [7, 16, 24-28]. Unavailability of data in the UNOS dataset on blood pressure readings, number of vasopressors use, PaO2/FiO2 ratio, white blood cell count, and serum lactate to limited calculation of these to further improve the prediction of WL mortality. However, we feel that our analysis to some extent overcomes this limitation as we accounted for number and types of organ failure to stratify ACLF patients to four grades. As ACLF is a dynamic syndrome, it is likely that change in ACLF grade from listing may have impacted the WL mortality. UNOS database has the ability to assess ACLF and its grade at listing and at transplant, and does not provide all the data on follow up from listing until transplant to dynamically assess change in ACLF grade from listing to examine the impact of this change.

In conclusion, ACLF grade and MELD score interact in predicting 90-d risk of WL mortality. Our novel score incorporating MELD score and ACLF grade removes disparities on organ allocation especially for candidates who are in ACLF at listing and MELD score 25 or below. Future large prospective studies are needed to validate these findings and examine the impact of type of organ failure within the same ACLF grade, as a basis to better prioritize organ allocation among patients with cirrhosis and ACLF.

Table 1 Baseline characteristics stratified for time period among candidates with acute on chronic liver failure (ACLF) at listing

Variable	2002-2007 (N=3421)	2008-2013 (N=7191)	2014-2018 (N=7804)	P	2002-2018 (N=18416)
Mean age (Std. Dev.) in yrs.	53 (8)	55 (9)	55 (10)	<0.001	54 (9)
% Females	26	31	35	<0.001	69
% Caucasian, AA, Hispanics	65, 10, 22	63, 11, 23	63, 9, 24	<0.003	63, 10, 24
% HCV, ALD, NASH	58, 34, 8	49, 35, 16	26, 50, 24	<0.001	41, 41, 18
% Obesity	34	41	43	<0.001	40
% KPSS 10-70	70	87	94	<0.001	87
Mean (Std. Dev.) MELD score	28.7 (8.4)	29.7 (8.5)	29.8 (8.3)	<0.001	30 (8)
% ACLF grades 1, 2, 3a, 3b	53, 28, 10, 9	48, 29, 12, 11	44, 32, 13, 11	<0.001	47, 30, 12, 11
% Liver failure	35	39	40	<0.001	39
% Renal failure	76	77	77	0.56	77
% Coagulation failure	27	32	35	<0.001	32
% Cardiovascular failure	8	11	13	<0.001	11
% Pulmonary failure	8	9	8	0.5	9
% Brain failure	22	21	22	0.87	21

S.D.: Standard deviation; C: Caucasians; AA: African Americans; H: Hispanics; HCV: Hepatitis C virus; ALD: Alcohol-associated liver disease; NASH: Non-alcoholic steatohepatitis; KPSS: Karnofsky's performance status scale; MELD: Model for end-stage disease; ACLF: Acute on chronic liver failure

Table 2 Fine and Gray competing risk MELD*ACLF interaction model for variables associated with 90-d waitlist mortality among candidates with ACLF at the time of listing.

Variable	Hazard Ratio (95% Confidence Interval)	P
Age of candidate at listing	1.03 (1.02-1.04)	<0.001
Females vs. Males	1.23 (1.15-1.32)	<0.001
African American vs. Caucasian	0.95 (0.85-1.06)	0.43
Hispanic vs. Caucasian	0.65 (0.59-0.70)	<0.001
Other race vs. Caucasian	1.05 (0.89-1.25)	0.52
ALD vs. HCV etiology	0.94 (0.87-1.01)	<0.06
NASH vs. HCV etiology	0.97 (0.88-1.06)	0.45
Obese vs. non-obese	1.00 (0.94-1.07)	0.88
KPSS (10-70 vs. 80-100%)	1.24 (1.11-1.38)	<0.001
Calendar year of listing	0.97 (0.95-0.96)	<0.001

Table 3 Pairwise comparison of acute on chronic liver failure (ACLF) grade on estimated 90-d WL mortality at listing MELD score

Comparison	MELD=10	MELD=15	MELD=20	MELD=25	MELD=30	MELD=35	MLD=40
ACLF-2 vs. 1	1.51 (1.11-2.05)	1.38 (1.09-1.75)	1.26 (1.06-1.50)	1.38 (1.09-1.75)	1.05 (0.96-1.16)	0.96 (0.86-1.08)	0.88 (0.75-1.04)
ACLF-3a vs. 1	3.65 (2.31-5.75)	2.98 (2.06-4.31)	2.44 (1.83-3.24)	1.99 (1.62-2.45)	1.63 (1.41-1.88)	1.33 (1.18-1.51)	1.09 (0.93-1.28)
ACLF-3b vs. 1	4.08 (2.71-6.12)	3.63 (2.61-5.04)	3.23 (2.51-4.16)	2.88 (2.40-3.46)	2.56 (2.25-2.92)	2.28 (2.03-2.57)	2.03 (1.74-2.38)
ACLF-3a vs. 2	2.42 (1.45-4.02)	2.16 (1.43-3.27)	1.93 (1.40-2.66)	1.73 (1.37-2.17)	1.55 (1.33-1.79)	1.38 (1.24-1.54)	1.24 (1.07-1.43)
ACLF-3b vs. 2	2.70 (1.70-4.30)	2.63 (1.80-3.83)	2.56 (1.92-3.42)	2.50 (2.03-3.07)	2.43 (2.12-2.79)	2.37 (2.14-2.63)	2.31 (2.00-2.65)
ACLF-3b vs. 3a	1.17 (0.66-2.07)	1.27 (0.80-2.03)	1.39 (1.09-1.75)	1.51 (1.16-1.97)	1.65 (1.38-1.96)	1.80 (1.59-2.02)	1.95 (1.69-2.25)

REFERENCES

[1]   Arroyo V, Moreau R, Kamath PS, Jalan R, Gines P, Nevens F, et al. Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primers 2016;2:16041.

[2]   Singal AK, Kamath PS. Acute on chronic liver failure in non-alcoholic fatty liver and alcohol associated liver disease. Transl Gastroenterol Hepatol 2019;4:74.

[3]   Jalan R, Moreau R, Kamath PS, Arroyo V. Acute-on-Chronic Liver Failure: A Distinct Clinical Condition. Semin Liver Dis 2016;36:107-108.

[4]   Hernaez R, Kramer JR, Liu Y, Tansel A, Natarajan Y, Hussain KB, et al. Prevalence and short-term mortality of acute-on-chronic liver failure: A national cohort study from the USA. J Hepatol 2019;70:639-647.

[5]   Singal AK, Arora S, Wong RJ, Satapathy SK, Shah VH, Kuo Y-F, et al. Increasing Burden of Acute-On-Chronic Liver Failure Among Alcohol-Associated Liver Disease in the Young Population in the United States. The American journal of gastroenterology 2020;115:88-95.

[6]   Mahmud N, Kaplan DE, Taddei TH, Goldberg DS. Incidence and Mortality of Acute-on-Chronic Liver Failure Using Two Definitions in Patients with Compensated Cirrhosis. Hepatology 2019;69:2150-2163.

[7]   Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426-1437, 1437 e1421-1429.

[8]   Sundaram V, Jalan R, Wu T, Volk ML, Asrani SK, Klein AS, et al. Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation. Gastroenterology 2019;156:1381-1391 e1383.

[9]   Finkenstedt A, Nachbaur K, Zoller H, Joannidis M, Pratschke J, Graziadei IW, et al. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. Liver Transpl 2013;19:879-886.

[10]   Moon DB, Lee SG, Kang WH, Song GW, Jung DH, Park GC, et al. Adult Living Donor Liver Transplantation for Acute-on-Chronic Liver Failure in High-Model for End-Stage Liver Disease Score Patients. Am J Transplant 2017;17:1833-1842.

[11]   Levesque E, Winter A, Noorah Z, Daures JP, Landais P, Feray C, et al. Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation. Liver Int 2017;37:684-693.

[12]   Singal AK, Fang X, Kaif M, Hasanin M, McGuire BM, Kuo YF, et al. Primary biliary cirrhosis has high wait-list mortality among patients listed for liver transplantation. Transpl Int 2017;30:454-462.

[13]   O'Leary JG, Bajaj JS, Tandon P, Biggins SW, Wong F, Kamath PS, et al. Outcomes after Listing for Liver Transplant in Patients with Acute-on-Chronic Liver Failure (ACLF): The Multicenter NACSELD Experience. Liver Transpl 2019.

[14]   Martin P, DiMartini A, Feng S, Brown R, Jr., Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014;59:1144-1165.

[15]   Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.

[16]   Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Gines P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol 2014;61:1038-1047.

[17]   Engelmann C, Thomsen KL, Zakeri N, Sheikh M, Agarwal B, Jalan R, et al. Validation of CLIF-C ACLF score to define a threshold for futility of intensive care support for patients with acute-on-chronic liver failure. Crit Care 2018;22:254.
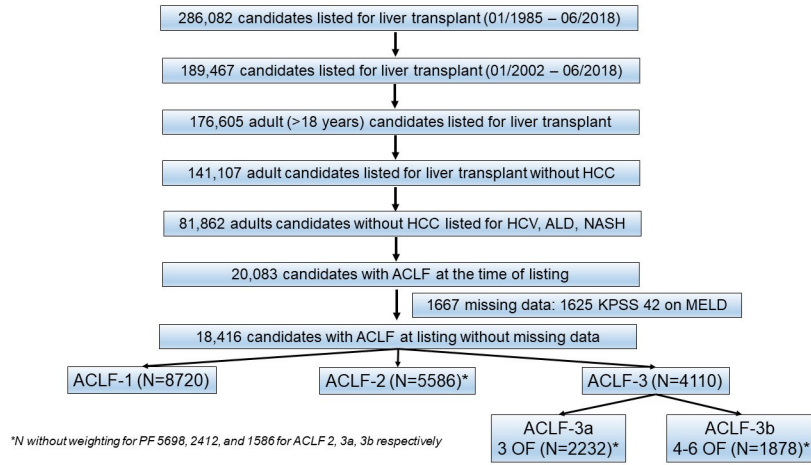
[18]   Karvellas CJ, Garcia-Lopez E, Fernandez J, Saliba F, Sy E, Jalan R, et al. Dynamic Prognostication in Critically Ill Cirrhotic Patients With Multiorgan Failure in ICUs in Europe and North America: A Multicenter Analysis. Crit Care Med 2018;46:1783-1791.
[19]   Agbim U, Sharma A, Maliakkal B, Karri S, Yazawa M, Goldkamp W, et al. Outcomes of Liver Transplant Recipients With Acute-on-Chronic Liver Failure Based on EASL-CLIF Consortium Definition: A Single-center Study. Transplant Direct 2020;6:e544.
[20]   Singal AK, Hmoud BS, Guturu P, Kuo YF. Outcome after liver transplantation for cirrhosis due to alcohol and hepatitis C: comparison to alcoholic cirrhosis and hepatitis C cirrhosis. J Clin Gastroenterol 2013;47:727-733.
[21]   Sundaram V, Shah P, Wong RJ, Karvellas CJ, Fortune BE, Mahmud N, et al. Patients With Acute on Chronic Liver Failure Grade 3 Have Greater 14-Day Waitlist Mortality Than Status-1a Patients. Hepatology (Baltimore, Md) 2019;70:334-345.
[22]   Sundaram V, Shah P, Mahmud N, Lindenmeyer CC, Klein AS, Wong RJ, et al. Patients with severe acute-on-chronic liver failure are disadvantaged by model for end-stage liver disease-based organ allocation policy. Aliment Pharmacol Ther 2020.
[23]   Bajaj JS, O'Leary JG, Tandon P, Wong F, Garcia-Tsao G, Kamath PS, et al. Hepatic Encephalopathy Is Associated With Mortality in Patients With Cirrhosis Independent of Other Extrahepatic Organ Failures. Clin Gastroenterol Hepatol 2017;15:565-574 e564.
[24]   Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243-252.
[25]   Sonika U, Jadaun S, Ranjan G, Rout G, Gunjan D, Kedia S, et al. Alcohol-related acute-on-chronic liver failure-Comparison of various prognostic scores in predicting outcome. Indian J Gastroenterol 2018;37:50-57.
[26]   Sarmast N, Ogola GO, Kouznetsova M, Leise M, Bahirwani R, Maiwall R, et al. Model for End-stage Liver Disease-Lactate and Prediction of Inpatient Mortality in Patients with Chronic Liver Disease. Hepatology 2020.
[27]   Trieb M, Rainer F, Stadlbauer V, Douschan P, Horvath A, Binder L, et al. HDL-related biomarkers are robust predictors of survival in patients with chronic liver failure. J Hepatol 2020.
[28]   Moreau N, Wittebole X, Fleury Y, Forget P, Laterre PF, Castanares-Zapatero D. Neutrophil-to-Lymphocyte Ratio Predicts Death in Acute-on-Chronic Liver Failure Patients Admitted to the Intensive Care Unit: A Retrospective Cohort Study. Shock 2018;49:385-392.
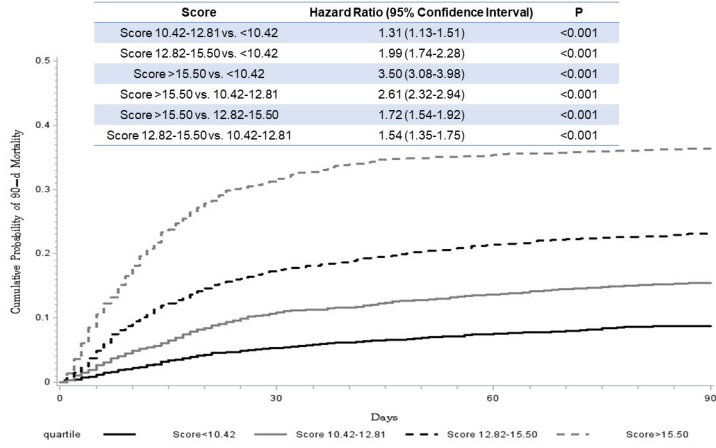
Legends to Figures

Figure 1 Attrition and study flow figure for final selection of study population (01/2002 – 06/2018) of candidates listed for liver transplantation with acute on chronic liver failure at listing in the UNOS database**.**

Figure 2 Cumulative incidence of WL mortality at 90 days from listing for liver transplant among candidates who are in acute on chronic liver failure (ACLF) at listing comparing four risk quartiles of score (quartile 1 with score <10.42: continuous black line vs. quartile 2 with score 10.41-12.81: continuous gray line vs. quartile 3 with score 12.82-15.50: dotted black line vs. quartile 4 with score >15.50: dotted gray line) in the validation cohort.
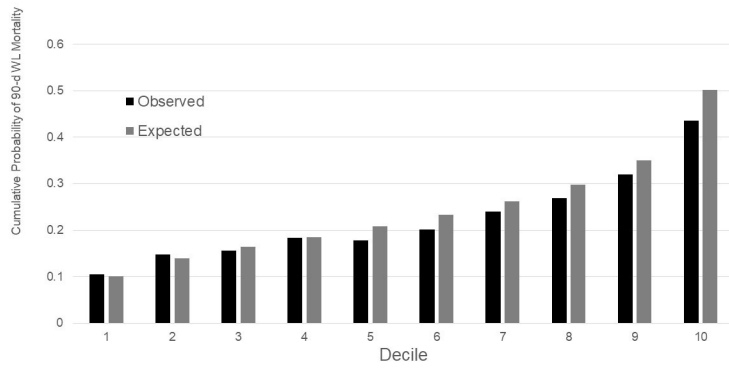
Figure 3 Calibration between observed versus expected deciles on the cumulative incidence of WL mortality at 90 days from listing for liver transplantation among candidates with acute on chronic liver failure at listing in the validation cohort.

286,082 candidates listed for liver transplant (01/1985 – 06/2018)

189,467 candidates listed for liver transplant (01/2002 – 06/2018)

176,605 adult (>18 years) candidates listed for liver transplant

141,107 adult candidates listed for liver transplant without HCC

81,862 adults candidates without HCC listed for HCV, ALD, NASH

20,083 candidates with ACLF at the time of listing

1667 missing data: 1625 KPSS 42 on MELD

18,416 candidates with ACLF at listing without missing data

ACLF-1 (N=8720)   ACLF-2 (N=5586)*   ACLF-3 (N=4110)

*N without weighting for PF 5698, 2412, and 1586 for ACLF 2, 3a, 3b respectively

ACLF-3a
3 OF (N=2232)*

ACLF-3b
4-6 OF (N=1878)*

Score	Hazard Ratio (95% Confidence Interval)	P
Score 10.42-12.81 vs. <10.42	1.31 (1.13-1.51)	<0.001
Score 12.82-15.50 vs. <10.42	1.99 (1.74-2.28)	<0.001
Score >15.50 vs. <10.42	3.50 (3.08-3.98)	<0.001
Score >15.50 vs. 10.42-12.81	2.61 (2.32-2.94)	<0.001
Score >15.50 vs. 12.82-15.50	1.72 (1.54-1.92)	<0.001
Score 12.82-15.50 vs. 10.42-12.81	1.54 (1.35-1.75)	<0.001

- Among candidates listed for liver transplantation with acute on chronic liver failure at listing, MELD score and ACLF interact in predicting cumulative risk of 90-d waitlist mortality.

- The impact of ACLF grade on 90-d waitlist mortality is much higher at lower listing MELD score, especially below 25.

- A validated novel score using MELD score and ACLF grade at listing provides estimate of 90-d WL mortality.