Research Article
Cirrhosis and Liver Failure

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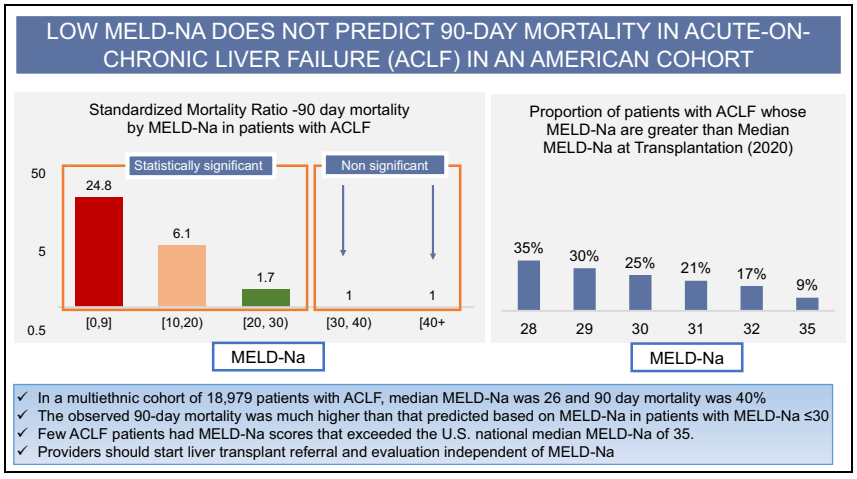
Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure

Graphical abstract



Highlights

- MELD-Na underestimates the 90-day mortality risk in patients with ACLF, particularly in those with MELD-Na less than 30.
- Compared to other ACLF studies, this study's cohort is not restricted to waitlisted patients.
- This is the first study of a large and geographically diverse population of patients with ACLF seen in routine clinical practice.
- We suggest initiating early discussions about liver transplant for patients with ACLF, regardless of their MELD-Na score.

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Lay summary

Acute-on-chronic liver failure (ACLF) is a condition marked by multiple organ failures in patients with cirrhosis and is associated with a high risk of death. Liver transplantation may be the only curative treatment for these patients. A score called model for end-stage liver disease-sodium (MELD-Na) helps guide donor liver allocation for transplantation in the United States. The higher the MELD-Na score in a patient, the more likely that a patient receives a liver transplant. Our study data showed that MELD-Na score underestimates the risk of dying at 90 days in patients with ACLF. Thus, physicians need to start liver transplant evaluation early instead of waiting for a high MELD-Na number.

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Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure

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See Editorial, pages 1316–1318

Background & Aims: It is unclear whether the model for end-stage liver disease-sodium (MELD-Na) score captures the clinical severity of acute-on-chronic liver failure (ACLF). We compared observed 90-day mortality in patients with ACLF with expected mortality based on the calculated MELD-Na and examined the consequences of underestimating clinical severity.
Methods: We identified patients with ACLF during hospitalization for cirrhosis in 127 VA hospitals between 01/01/2004 and 12/31/2014. We examined MELD-Na scores by ACLF presence and grade. We used actual and observed 90-day mortality to estimate a standardized mortality ratio (SMR) by ACLF presence and grade. We used transplant center-specific median MELD-Na at transplantation (MMaT) to estimate the proportion likely to receive priority for liver transplantation (LT) based on MELD-Na alone.
Results: Of 71,894 patients hospitalized for decompensated cirrhosis, 18,979 (26.4%) patients met the criteria for ACLF on admission. The median (P25-P75) MELD-Na on admission was 26 (22–30) for ACLF compared to 15 (12–20) for patients without ACLF; it was 24 (21–27), 27 (23–31), and 32 (26–37) for ACLF-1, 2 and 3, respectively. At 90 days, 40.0% of patients with ACLF died (30.8%, 41.6% and 68.8% with ACLF-1, 2 and 3, respectively) compared to 21.3% of patients without ACLF. Compared to the expected death rate based on MELD-Na, mortality risk was higher for patients with ACLF, SMR (95% CI): 1.52 (1.48–1.52), 1.46 (1.41–1.51), 1.50 (1.44–1.55), 1.66 (1.58–1.74) for overall ACLF, ACLF-1, -2 and -3, respectively. Only 9.1% of patients with ACLF reached the national median MELD-Na of 35 and between 17.3% to 35.1% exceeded the MMaT at any center. During index admission, 589 (0.8%) patients with ACLF were considered for LT evaluation and 16 (0.1%) were listed for LT.
Conclusions: In a US cohort of hospitalized patients with decompensated cirrhosis, MELD-Na did not capture 90-day mortality risk in patients with ACLF. Patients with ACLF are at a disadvantage in the current MELD-Na-based system.

Lay summary: Acute-on-chronic liver failure (ACLF) is a condition marked by multiple organ failures in patients with cirrhosis and is associated with a high risk of death. Liver transplantation may be the only curative treatment for these patients. A score called model for end-stage liver disease-sodium (MELD-Na) helps guide donor liver allocation for transplantation in the United States. The higher the MELD-Na score in a patient, the more likely that a patient receives a liver transplant. Our study data showed that MELD-Na score underestimates the risk of dying at 90 days in patients with ACLF. Thus, physicians need to start liver transplant evaluation early instead of waiting for a high MELD-Na number.

Introduction

Acute-on-chronic liver failure (ACLF) is characterized by the presence of organ failure(s) in the setting of decompensated cirrhosis, and is associated with high short-term mortality.[1] ACLF is estimated to be present in 1 in 4 hospitalized patients with decompensated cirrhosis;[2,3] with a 28- and 90-day mortality as high as 25% and 40%, respectively.[3] Experts have proposed that in the presence of 2 or more organ failures, patients with ACLF should be evaluated for liver transplantation (LT) or be considered for withdrawal of care if they are are ineligible for transplantation.[4] LT is associated with improved survival in patients with ACLF, with 1-year survival of 88%[5] compared with 8% without LT.[6]

The model for end-stage liver disease-sodium (MELD-Na) aims to provide distributive justice for LT by allocating organs to the sickest patients first. However, MELD-Na does not accurately reflect the prognosis of patients in certain circumstances (*e.g.*, hepatocellular carcinoma [HCC]). This may also be true for patients with ACLF. For example, data from the United Network for Organ Sharing (UNOS) suggest that mortality of patients with ACLF and 3 or more organ failures (ACLF-3) might be equivalent to the mortality of patients with acute liver failure.[7] The degree to which MELD-Na captures this extremely high risk of mortality in ACLF remains unclear.

It is important to understand the accuracy of MELD-Na based risk prediction in patients with ACLF. Underestimation of short-term mortality in the current MELD-Na based system may

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systematically marginalize patients with ACLF who may otherwise have preserved MELD-Na scores. Basing the timing of LT evaluation (and listing) in ACLF on a risk score of limited validity, could have a substantial negative impact on patient outcomes especially under conditions of uncertainty. Studies addressing the prognostication of patients with different degrees of ACLF severity are required to quantify the possible disconnect between expected and actual mortality in this vulnerable population.

Using a large national VA cohort of patients who were hospitalized for ACLF in any of 127 VA centers, we compared the expected mortality (based on MELD-Na) with observed mortality at 90-days overall and in subgroups based on ACLF grade. We also determined the clinical consequences of the potential disconnect between expected and observed mortality by examining the association between ACLF grades and LT evaluation and listing after accounting for age, medical comorbidities, and center characteristics.

Patients and methods

Data source

We extracted data from the VA Corporate Data Warehouse (CDW) to derive the study cohort. CDW contains patient demographics, outpatient and inpatient utilization, including diagnosis (ICD-9) and current procedural terminology (CPT) codes, laboratory data, and vital status information. Vital status combines information from Medicare, VA, social security, and VA compensation and pension benefits to determine the date of death (sensitivity 98.3%; specificity 99.8% relative to National Death Index).

We also used data from the UNOS Organ Procurement and Transplantation Network (OPTN) database linked to our study cohort to identify all candidates listed for LT between November 1, 1978 and June 30, 2019 in the US.

Study population

We used the same cohort and variables defined in our previous published paper.[3] Briefly, we identified patients who had their first hospitalization with decompensated cirrhosis at any of the 127 VA hospitals between 01/01/2004 and 12/31/2014 and were hospitalized for at least 24 hours. For our primary analysis, we defined ACLF according to the CANONIC study.[2] We excluded patients who received LT (CPT or ICD codes) prior to their index hospitalization. Decompensated cirrhosis was defined as: a) at least 1 ICD-9 code for ascites, hepatic encephalopathy, HCC, varices or variceal bleeding, portal hypertension, hepatorenal syndrome or hepatopulmonary syndrome; or b) at least 1 cirrhosis ICD-9 code combined with ICD-9 codes for infection or gastrointestinal bleeding during the index hospitalization (Table S1).

We defined liver failure as serum bilirubin value ≥12 mg/dl; kidney failure as serum creatinine ≥2.0 mg/dl or use of renal replacement therapy or, end-stage renal disease (based on ICD-9 or CPT codes); cerebral failure as presence of hepatic encephalopathy[8]; coagulation failure as serum international normalized ratio (INR) ≥2.5; circulation failure as mean arterial pressure of less than 60 mmHg and/or use of intravenous epinephrine, norepinephrine, dobutamine, dopamine, vasopressin; and respiratory failure as need for mechanical ventilation (based on ICD-9 or CPT codes).

We defined ACLF as the presence of ≥1 organ failure(s) after 24 hours of hospital admission. Patients were categorized as ACLF grades 1, 2 or 3, if they had 1, 2, or ≥3 organ failures, respectively. ACLF grade 1 was defined as: a) patients with single kidney failure, b) patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level ranging between 1.5 to 1.9 mg/dl, or c) patients with single cerebral failure who had a serum creatinine level ranging between 1.5 and 1.9 mg/dl. Thus, patients could meet ACLF criteria as long as they had ≥1 defining organ failure(s) (Table S2).

Study outcome and variables

The primary outcome was overall mortality within 90 days after the date of the index hospitalization. We calculated MELD-Na using laboratory values for bilirubin, creatinine, INR and serum sodium utilizing the first value within 24 hours of index hospitalization. If several values were present within 24 hours, we took the maximum bilirubin, creatinine, INR and lowest sodium.

Demographics and medical comorbidity

We defined HCV based on a positive HCV RNA test, and alcohol-related liver disease based on ≥1 instance of an ICD-9 code for alcohol use disorders or an alcohol use disorders identification test-consumption (AUDIT-C) ≥4 or AUDIT ≥8, at any point prior to the first admission for decompensated cirrhosis. Active alcohol use was further defined when the patient had any alcohol code and/or AUDIT-C ≥4 or AUDIT ≥8 within 1 year prior to the first admission.

We also examined 2 facility level factors: whether the facility was 1 of the 6 LT centers for Veterans, and facility complexity (high, medium and low) based on the VA policy and the presence of complexity of patients, services and levels of intensive care units[9] (Table S3).

Liver transplant evaluation and listing

At the VA, for a patient to be listed for LT, they require an initial evaluation at the referring VA ("pre-VA Central Office or pre-VACO"), which is then reviewed by 1 of the 6 transplant centers. The second stage is an in-person evaluation at 1of the 6 LT centers to determine final listing status. We identified consideration of transplant evaluation using the "Text Document Titles Domain", also known as the Text Integration Utility (TIU), which contains information in the form of free text from reports or progress notes entered into the electronic medical record. Using the text search function, we searched for key words such as "transplant", "liver" restricting to liver or liver/kidney transplantation mentioned in the consult/progress notes titles (text search algorithm).

Using these criteria, a random sample of 100 nationwide patients (26 ACLF and 74 non-ACLF) were selected for in depth chart reviews. One transplant physician (RH) reviewed all charts while blinded to the findings of text search terms. Based on *a priori* considerations, we classified patients as being considered for LT if there was at least 1 instance of any evaluation for LT (*e.g.*, mental health evaluation, psychosocial evaluation, medical evaluation, *etc.*). Patients did not need to complete the full evaluation process or be referred to the second stage on in-person evaluation at the LT center to be classified as 'considered' for LT. Overall, our algorithm had a positive predictive value (PPV) of 83% to identity consideration of LT evaluation any time during or after index hospitalization (PPV 96.1% in patients with ACLF; 80% in patients without ACLF). We further linked our

cohort with data from the UNOS database to identify patients who were listed for LT.

Statistical analyses

We compared baseline demographic and clinical features, as well as observed 90-day mortality after index admission, in patients with decompensated cirrhosis, with and without ACLF. We used chi-square tests for categorical variables and parametric and non-parametric tests for continuous variables when appropriate. We estimated patients' expected 90-day mortality based on their MELD-Na score as published by Kim *et al.*[10] Then, we compared the observed mortality against the mortality expected based on patients' MELD-Na by calculating the standardized mortality ratio (SMR ratio >1 is suggestive of increased observed *vs.* expected mortality).

We also examined the impact of potential underestimation of mortality by MELD-Na. First, in the descriptive analysis, we examined the proportion of patients who were below the median MELD-Na at transplantation (MMaT) cut-offs. The MMaT scores are calculated every 180 days, and are based on a 365-day cohort of transplant recipients excluding status 1A, living donors, cardiac death donors, and donors from outside the region of the recipient transplant hospital (national shares).[11] We calculated the crude proportions of patients with ACLF in our cohort whose MELD-Na were higher than the MMaT for all different VA transplant centers. Second, we calculated the proportion of patients with ACLF (overall and each ACLF grade) who had any mention of consideration of LT evaluation in the national VA during index admission and at 30 and 180 days. Lastly, because some patients may be listed for LT in centers outside the VA, we examined the proportion of patients with ACLF who were listed for LT during index admission and 180 days. We repeated these descriptive analyses in groups stratified by MMaT cut-off at VA transplant centers. Finally, we used logistic regression (univariate and multivariate) to understand independent predictors of LT evaluation initiation, including clinically important factors. All analyses were conducted using SAS version 9.4 (SAS Institute Inc. Cary, North Carolina).

Sensitivity and subgroup analysis

Because access to LT might influence LT-related decisions in patients with ACLF, we restricted our overall cohort to patients who were seen in VA LT centers. For the primary analysis, ACLF was defined according to the CANONIC study.[2] In sensitivity analyses, we used 2 additional ACLF definitions. First, we defined our ACLF cohort based on the North American Consortium for the Study of End-Stage Liver Disease's definition (NACSELD-ACLF) which proposed a simple bedside tool to assess the risk of mortality using ≥2 extrahepatic organ failures to rule in ACLF (brain, respiratory, circulatory or kidney failures).[12] Second, we adapted the Asian Pacific Association for the Study of the Liver (APASL) definition of ACLF by restricting the ACLF cohort to patients with total bilirubin ≥5 mg/dl and INR ≥1.5.[13] The purpose of these analyses was to examine the extent to which ACLF definition had a major effect on our results and inferences.

Results

Of 71,894 patients hospitalized with decompensated cirrhosis, 18,979 (26.4%) patients met the criteria for ACLF on admission; 12.8% had 1, 10.1% had 2, and 3.5% had 3 or more organ failures. The mean age was 61 years in the non-ACLF group and 62 years in the ACLF group; the majority of patients were men (98.1%). In total, 60.2% had ascites, 36.0% hepatic encephalopathy, 17.4% had varices and/or variceal bleeding and 14% had HCC (Table 1). Alcohol or HCV was the main underlying cause of cirrhosis, whereas gastrointestinal bleeding, infection or alcohol abuse were the likely precipitating events in 41.6% of patients with ACLF, with excessive alcohol use in the last year being the most common precipitating event (28.7%). Kidney failure (71.9%) and cerebral failure (36.0%) were the most common organ failures. Similar results were also observed in analyses stratified by ACLF grades in terms of hepatic decompensation or causes of cirrhosis; however, compared to ACLF-1, patients with ACLF-2 and 3 had greater prevalence of bacterial infection (10.5% for ACLF-1 compared to 16.4% and 23.38% for ACLF-2 and 3, respectively) and alcoholism (22.9% for ACLF-1, compared to 33.2% and 36.8 for ACLF-2 and 3, respectively). The median (P25-P75) MELD-Na on admission was 26 (22–30) for ACLF compared to 15 (12–20) for patients without ACLF; it was 24 (21–27), 27 (23–31), and 32 (26–37) for ACLF-1, 2 and 3 patients, respectively.

At 90 days, 40.0% of patients in the ACLF group died compared to 21.3% of patients without ACLF. The risk of 90-day mortality increased with worsening grade of ACLF; with 90-day mortality rates of 30.8%, 41.6% and 68.8% in patients with ACLF-1, 2 and 3, respectively.

MELD-Na underestimated mortality in patients hospitalized with ACLF

The observed (actual) 90-day mortality in ACLF was consistently higher than the mortality expected based on MELD-Na. For example, 14.5% of patients with ACLF had MELD-Na scores that fell between 10 and 20. The SMR for this group was 6.1 (95% CI 5.7–6.5), showing that a patient with ACLF with MELD-Na score between 10 and 20 was approximately 6 times more likely to die than what would be expected based on MELD-Na alone (Table 2, Fig. 1). This difference was seen across all ACLF grades and most MELD-Na scores. MELD-Na accurately captured the observed risk of death in patients with MELD-Na ≥30 (MELD-Na 30–40: SMR 1.1; MELD-Na >40: SMR 1.0).

We found similar SMR estimates when we restricted the analysis to patients seen in LT centers (Table S4). Using the NACSELD-ACLF criteria to define ACLF, the SMR inferences did not change and were consistent with those in our primary analysis that used CANONIC criteria to classify patients with ACLF (Table S5). Specifically, using NACSELD-ACLF, the 90-day mortality in patients with ACLF was significantly higher than expected based on MELD-Na scores (overall SMR 1.7; 95% CI 1.6–1.7). The disparity was largest for MELD-Na [0–9]: SMR (24.8; 95% CI 9.4–40.2); compared to MELD-Na [10–19] and [20–29] which had SMRs of 7.9 (95% CI 7.2–8.5) and 2.1 (95% CI 2.0–2.2), respectively. Limiting our primary cohort to patients with bilirubin ≥5 mg/dl and INR ≥1.5 did not change our inference either.[13] The 90-day mortality in patients with ACLF was significantly higher than expected based on MELD-Na scores (overall SMR 1.6; 95% CI 1.5–1.6). This disparity was more significant in patients with MELD-Na [10–19] and [20–29] who SMRs of 3.8 (95% CI 2.2–5.5) and 2.4 (95% CI 2.2–2.4), respectively (Table S6).

Association between MELD-Na and LT-related care in patients with ACLF

Table 3 displays the MMaT for each of the 6 LT centers within the VA during the study timeframe. Between 17.3% and 35.1% of

Table 1. Baseline characteristics of 71,894 Veterans with decompensated cirrhosis (2004–2014).

	No ACLF	ACLF all grades	*p* value	ACLF grade 1	ACLF grade 2	ACLF grade 3	*p* value
Sample, N (%)	52,915 (73.6)	18,979 (26.4)		9,191 (12.8)	7,254 (10.1)	2,534 (3.5)	
Age (years), median (P25-P75)	60.9 (55.7–67.0)	62.3 (56.9–69.8)	<0.0001	63.6 (58.0–72.8)	61.2 (56.0–67.2)	61.1 (55.8–67.1)	<0.0001
Male sex	51,614 (97.6)	18,616 (98.1)	<0.0001	9,039 (98.4)	7,105 (98.0)	2,472 (97.6)	0.022
Race/ethnicity, n (%)			<0.0001				<0.0001
African American	9,057 (17.1)	4,586 (24.2)		2,596 (28.3)	1,445 (19.9)	545 (21.5)	
White	38,567 (72.9)	12,456 (65.6)		5,743 (62.5)	5,021 (69.2)	1,692 (66.8)	
Other	1,453 (2.8)	501 (2.6)		245 (2.7)	197 (2.7)	59 (2.3)	
Missing or unknown	3,838 (7.3)	1,436 (7.6)		607 (6.6)	591 (8.2)	238 (9.4)	
Cirrhosis etiology, N (%)			<0.0001				<0.0001
No Alcohol or HCV	17,850 (33.7)*	8,334 (43.9)*		4,488 (48.8)	2,804 (38.7)	1,042 (41.1)	
Alcohol	16,278 (30.8)	5,346 (28.2)		2,097 (22.8)	2,314 (31.9)	935 (36.9)	
HCV	7,658 (14.5)	2,442 (12.9)		1,253 (13.6)	977 (13.5)	212 (8.4)	
Alcohol & HCV	11,129 (21.0)	2,857 (15.1)		1,353 (14.7)	1,159 (16.0)	345 (13.6)	
Cirrhosis complications, N (%)							
Ascites	26,636 (50.3)	11,417 (60.2)	<0.0001	5,477 (59.6)	4,577 (63.1)	1,363 (53.8)	<0.0001
Hepatic encephalopathy	10,410 (19.7)	6,832 (36.0)	<0.0001	1,090 (11.9)	4,282 (59.0)	1,460 (57.6)	<0.0001
Hepatocellular carcinoma	8,769 (16.6)	1,639 (8.6)	<0.0001	880 (9.6)	624 (8.6)	135 (5.3)	<0.0001
Varices	11,136 (21.1)	3,297 (17.4)	<0.0001	1,248 (13.6)	1,682 (23.2)	367 (14.5)	<0.0001
Potential precipitating events of ACLF							
Bacterial infection	5,551 (10.5)	2,748 (14.5)	<0.0001	969 (10.5)	1,187 (16.4)	592 (23.4)	<0.0001
Gastrointestinal hemorrhage	4,565 (8.6)	1,623 (8.6)	0.750	546 (5.9)	746 (10.3)	331 (13.1)	<0.0001
Alcoholism one year prior to cirrhosis index date	19,196 (36.3)	5,433 (28.6)	<0.0001	2,103 (22.9)	2,411 (33.2)	919 (36.3)	<0.0001
Infection or GIB or Alcohol	25,015 (47.3)	7,888 (41.6)	<0.0001	3,070 (33.4)	3,452 (47.6)	1,366 (53.9)	<0.0001
Organ failures							
Liver	1,134 (2.1)	2,325 (12.3)	<0.0001	156 (1.7)	1,272 (17.5)	897 (35.4)	<0.0001
Kidney	0 (0.0)	13,648 (71.9)	<0.0001	7,259 (79.0)	4,474 (61.7)	1,915 (75.6)	<0.0001
Cerebral	10,410 (19.7)	6,832 (36.0)	<0.0001	1,090 (11.9)	4,282 (59.0)	1,460 (57.6)	<0.0001
Coagulation	1,301 (2.5)	2,630 (13.9)	<0.0001	366 (4.0)	1,337 (18.4)	927 (36.6)	<0.0001
Circulation	597 (1.1)	3,338 (17.6)	<0.0001	174 (1.9)	1,565 (21.6)	1,599 (63.1)	<0.0001
Lungs	916 (1.7)	3,217 (17.0)	<0.0001	146 (1.6)	1,578 (21.8)	1,493 (58.9)	<0.0001
Arterial pressure (mmHg), median (P25-P75)	93.2 (84.3–102.3)	87.2 (77.0–98.5)	<0.0001	89.2 (78.7–101.0)	87.0 (77.0–97.3)	81.0 (70.7–92.0)	<0.0001
MELD-Na score	15.3 (12.2–19.5)	25.6 (22.2–30.0)	<0.0001	24.0 (21.3–27.2)	26.9 (22.7–31.1)	32.2 (26.3–37.4)	<0.0001
Healthcare system factors, N (%)							
Facility complexity model score			<0.0001				0.064
Low	1,797 (3.4)	475 (2.5)		234 (2.6)	192 (2.7)	49 (1.9)	
Median	4,320 (8.2)	1,456 (7.7)		737 (8.0)	547 (7.5)	172 (6.8)	
High	46,798 (88.4)	17,048 (89.8)		8,220 (89.4)	6,515 (89.8)	2,313 (91.3)	
Liver transplant center	5,140 (9.7)	1,791 (9.4)	0.267	848 (9.2)	685 (9.4)	258 (10.2)	0.346

ACLF, acute-on-chronic liver failure; GIB, gastrointestinal bleeding; MELD-Na, model for end-stage liver disease-sodium.

*Fewer than 2% of patients had cholestatic liver diseases (primary biliary cholangitis, primary sclerosing cholangitis); less than 0.4% of patients had hemochromatosis/iron metabolism disorders or autoimmune hepatitis. 45% of patients had BMI ≥30 kg/m^2 (44% and 50.1% in the non-ACLF and ACLF group, respectively), suggesting that most probably had non-alcoholic fatty liver disease. Non-parametric and chi-square tests, as appropriate were used.

Table 2. Standardized mortality ratios at 90 days overall and stratified by MELD-Na score; expected deaths derived using data by Kim *et al.*[10]

	Observed event	Expected event	Crude Rate				
	n	n	Observed	Expected	Standardized mortality ratio*	95% CI	
ACLF any (N = 18,979)							
Overall	7,594	5,026	0.4	0.2	1.5	1.5	1.6
MELD-Na							
[0–9]	10	0.4	0.4	0.0	24.8	9.4	40.2
[10–19]	1,000	165.1	0.4	0.1	6.1	5.7	6.4
[20–29]	3,912	2,239.7	0.3	0.2	1.7	1.7	1.8
[30–39]	2,272	2,218.9	0.5	0.5	1.0	1.0	1.1
40+	400	402.0	0.7	0.7	1.0	0.9	1.1
ACLF-1 (n = 8,759)							
Overall	2,835	1,922	0.3	0.2	1.5	1.4	1.5
MELD-Na							
[0–9]	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
[10–19]	432	66.2	0.4	0.1	6.5	5.9	7.1
[20–29]	1,886	1,288.6	0.3	0.2	1.5	1.4	1.5
[30–39]	509	558	0.5	0.5	0.9	0.8	1.0
40+	8	9.6	0.6	0.7	0.8	0.3	1.4
ACLF 2 (n = 7,254)							
Overall	3,014	2,021	0.4	0.2	1.5	1.4	1.5
MELD-Na							
[0–9]	10	0.4	0.4	0.0	27.0	10.2	43.7
[10–19]	481	64.3	0.4	0.1	7.5	6.8	8.1
[20–29]	1,467	781.1	0.4	0.2	1.9	1.8	1.9
[30–39]	954	1,054.5	0.5	0.5	0.9	0.8	1.0
40+	102	120.9	0.6	0.4	0.8	0.7	1.0
ALCF 3 (n = 2,534)							
Overall	1,752	1,056	0.69	0.2	1.66	1.58	1.74
MELD-Na							
[0–9]	0	0	n.a.	0.0	0	n.a.	n.a.
[10–19]	87	8.6	0.6	0.1	10.1	8	12.2
[20–29]	559	170	0.6	0.2	3.3	3	3.6
[30–39]	809	606.3	0.7	0.5	1.3	1.2	1.4
40+	290	271.5	0.8	0.7	1.1	0.9	1.2

MELD-Na, model for end-stage liver disease-sodium.
*Observed events/expected events.

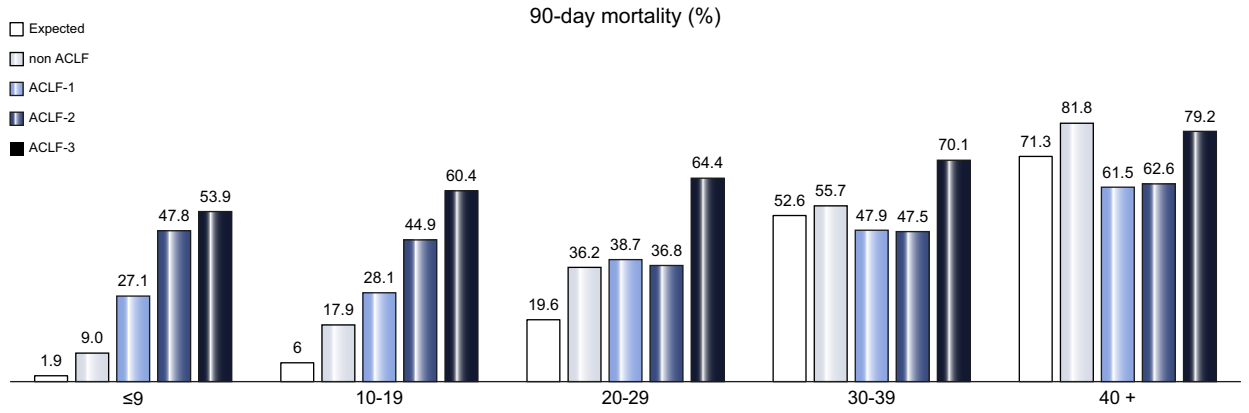

Fig. 1. Expected *vs.* observed 90-day mortality by model for end-stage liver disease-sodium score in patients with and without ACLF of several grades. Expected mortality was based on Kim *et al.*[10] ACLF, acute-on-chronic liver failure.

patients with ACLF would exceed the MMaT based on the LT center. This estimate dropped to 9.1% when using the national MMaT of 35 (as well as the Share-35 that would have allowed the patients to receive priority for LT regardless of regional or geographic boundaries) (Table 3).

The underestimation of liver disease severity (and prognosis) in patients with ACLF might have downstream negative consequences on patient care. We examined the proportion of patients whose providers formally started LT evaluation during or within 180 days after index hospitalization. During index admission, 62 (0.7%) patients with ACLF-1, 136 (1.9%) with ACLF-2 and 69 (2.7%) with ACLF-3 were considered for LT evaluation; these proportions were 3.5%, 7.3% and 4.2% at 180 days (Table 4). Most patients who were considered (59.9%) or waitlisted for LT at admission (75.1%) had MELD-Na scores >30. In a subgroup analysis of 2,534 patients with ACLF-3 (observed 90-day

Table 3. Proportion of ACLF patients whose MELD-Na was greater than 6 benchmark cut-offs based on LT centers and national median.

MELD-Na cut-off based	Patients with MELD-Na greater than cut-off, n (N = 18,979)	Proportion
28	6,694	35.3%
29	5,682	29.9%
30	4,765	25.1%
31	4,011	21.1%
32	3,303	17.4%
35	1,746	9.2%

ACLF, acute-on-chronic liver failure; LT, liver transplantation; MELD-Na, model for end-stage-liver disease-sodium; VA, Veterans Affairs.

mortality 68.8%), LT was considered in 2.3% of patients with MELD ≥30 (n = 59/2,534) compared with 0.4% of patients with MELD score <30 (10/2,534). In the 1,791 patients seen in LT centers, at 180 days from ACLF diagnosis, 8.9% were considered for LT evaluation, 3.0% were waitlisted and 1.2% received LT. These proportions were higher than those for patients seen in non-LT centers, where 4.7% were considered for LT evaluation, 1.0% were listed and 0.5% were transplanted. The use of NASCLED or APASL criteria did not significantly change these results. Only 7.0% and 8.7% of patients classified with ACLF by NASCELD and APASL were considered for LT at 180 days, respectively.

Table 5 presents results from the multivariable regression analysis. MELD score had the strongest association with consideration for LT evaluation. During index hospitalization, compared to patients with an MELD ≤9, the adjusted odds ratios (ORs) of being considered for LT were 2.1 (95% CI 1.1–4.0), 4.3 (95% CI 2.1–8.6) and 7.3 (95% CI 3.2–16.6) for patients with MELD 20–29, 30–39, and 40+, respectively. The presence of ACLF had a positive albeit weaker association with consideration of LT. Compared to patients without ACLF, patients with ACLF-2 and 3 had 1.9- and 2.3-fold higher odds of being considered for LT evaluation after adjusting for demographic, clinical and center factors (Table 5).

We also found that presence of HCC and being treated at a designated VA LT center were associated with consideration of LT. The associations between MELD-Na and consideration of LT persisted in the analysis that extended the timeframe to 180 days. Compared to patients with MELD ≤9, the adjusted ORs of being considered for LT within 180 days of index hospitalization were 2.3 (95% CI 1.7–3.1), 4.1 (95% CI 2.9–5.7) and 4.2 (95% CI 2.6–6.9) for patients with MELD 20–29, 30–39 and 40+, respectively. The association between ACLF and consideration for LT was attenuated for patients with ACLF-2 (adjusted OR 1.7; 95% CI 1.5–1.9) and no longer significant for patients with ACLF-3 (adjusted OR 0.9; 95% CI 0.9–1.0) (Table 5). Only 16 (0.1%) patients were listed for LT during index hospitalization; this number increased to 61 (1.2%) patients at 180 days (Table S7).

Last, and as a *post-hoc* analysis, we examined why patients with ACLF and relatively preserved liver function (MELD-Na <20) had higher than expected 90-day mortality. We found that these "low MELD" patients with ACLF were more likely to be white and older compared to those with MELD-Na ≥20 (Table S8). Patients with low MELD-Na were less likely to have HCV or alcohol as the underlying cause of liver disease and were more likely to have hepatic encephalopathy at baseline than patients who had higher MELD-Na. We did not find any statistically significant differences in the triggers (precipitating events) but there were differences in the types of organ failures between the 2 groups. Patients with MELD-Na <20 had a higher prevalence of brain, circulatory and lung failure compared to those with MELD-Na ≥20 (Table S8).

Discussion

Our analyses of a geographically diverse cohort of patients with ACLF showed 3 major findings. First, ACLF was associated with a high short-term mortality and MELD-Na did not capture the severity of underlying liver disease, especially in patients who presented with 1 or 2 organ failures. Second, the MELD-Na score reached the threshold for LT in only a small minority of patients with ACLF. Specifically, only 35.3% met or exceeded the MMaT at any of the VA LT centers. Fewer than 5% of patients were evaluated for LT within 180-days of index hospitalization and less than 1% were listed for transplantation in the same timeframe. Third, patient's MELD-Na was the main determinant of consideration and listing for LT, even among patients with ACLF-3 who have the highest risk of short-term mortality. Notably, 65% of patients with ACLF had MELD-Na <30, suggesting that these patients (with high mortality yet disproportionately low MELD-Na) are majorly disadvantaged by the current MELD-based system.

Our data show that MELD-Na does not fully capture underlying disease severity in ACLF. This is likely due to the effect of extrahepatic organ failures on patient outcomes, which are not

Table 4. Frequencies and proportions of liver transplant consideration at index admission and 180 days from diagnosis of ACLF, n (%, columns).

	No-ACLF	ACLF	ACLF-1	ACLF-2	ACLF-3
MELD-Na	**52,915**	**18,979**	**9,191**	**7,254**	**2,534**
Consideration at admission					
n (%)	322 (0.6)	267 (1.4)	62 (0.7)	136 (1.9)	69 (2.7)
[0–9]	9 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
[10–19]	211 (65.5)	9 (3.4)	3 (4.8)	6 (4.4)	0 (0.0)
[20–29]	96 (29.8)	122 (45.7)	46 (74.2)	66 (48.5)	10 (14.5)
[30–39]	6 (1.9)	109 (40.8)	13 (21.0)	60 (44.1)	36 (52.2)
40+	0 (0.0)	27 (10.1)	0 (0.0)	4 (2.9)	23 (33.3)
Consideration 180 days					
n (%)	1,743 (3.3)	958 (5.0)	322 (3.5)	530 (7.3)	106 (4.2)
[0–9]	46 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
[10–19]	1,190 (68.3)	51 (5.3)	34 (10.6)	16 (3.0)	1 (0.9)
[20–29]	489 (28.1)	539 (56.3)	226 (70.2)	301 (56.8)	12 (11.3)
[30–39]	18 (1.0)	334 (34.9)	62 (19.3)	209 (39.4)	63 (59.4)
40+	0 (0.0)	34 (3.6)	0 (0.0)	4 (0.8)	30 (28.3)

ACLF, acute-on-chronic liver failure; MELD-Na, model for end-stage-liver disease-sodium.

Table 5. Logistic regression for association of being considered for LT with Na-MELD and ACLF score during admission and extended to 180 days after discharge.

	During index hospitalization		Within 180 days of hospitalization	
Consideration of LT	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
MELD-Na (ref: ≤9)				
(0–9)	1.0 (0.5–2.0)	1.0 (0.5–2.0)	1.2 (0.9–1.6)	1.3 (0.9–1.7)
(10–19)	1.9 (1.0–3.6)	2.1 (1.1–4.0)	1.9 (1.4–2.5)	2.3 (1.7–3.1)
(20–29)	5.0 (2.6–9.7)	4.3 (2.1–8.6)	3.2 (2.3–4.4)	4.1 (2.9–5.7)
(30–39)	10.3 (4.9–21.6)	7.3 (3.2–16.6)	2.6 (1.7–4.1)	4.2 (2.6–6.9)
ACLF (ref: no ACLF)				
ACLF-1	1.1 (0.9–1.5)	0.9 (0.7–1.2)	1.1 (0.9–1.2)	0.9 (0.8–1.1)
ACLF-2	3.1 (2.6–3.8)	1.9 (1.5–2.5)	2.3 (2.1–2.6)	1.7 (1.5–1.9)
ACLF-3	4.6 (3.5–6.0)	2.3 (1.6–3.3)	1.3 (1.1–1.6)	0.9 (0.7–1.1)
Age	0.9 (0.9–1.0)	0.9 (0.9–0.9)	0.9 (0.9–1.0)	0.9 (0.9–1.0)
Male	0.7 (0.5–1.2)	0.9 (0.6–1.5)	0.9 (0.7–1.1)	1.0 (0.7–1.2)
Race (ref: White)				
African American	0.8 (0.7–1.0)	0.6 (0.5–0.7)	0.8 (0.7–0.9)	0.6 (0.5–0.6)
Other	1.2 (0.7–1.8)	1.0 (0.7–1.7)	1.0 (0.8–1.3)	0.8 (0.7–1.1)
Missing or unknown	0.9 (0.6–1.2)	0.7 (0.5–0.9)	0.7 (0.5–0.8)	0.6 (0.5–0.7)
Cirrhosis etiology (ref: HCV)				
No alcohol or HCV	0.3 (0.3–0.4)	0.5 (0.4–0.6)	0.2 (0.2–0.2)	0.3 (0.3–0.4)
Alcohol	0.2 (0.1–0.2)	0.2 (0.1–0.3)	0.2 (0.1–0.2)	0.2 (0.2–0.2)
Alcohol & HCV	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.5 (0.4–0.5)	0.4 (0.4–0.5)
Ascites	1.2 (1.0–1.4)		1.7 (1.6–1.9)	
HCC	3.0 (2.5–3.6)	3.0 (2.5–3.6)	3.2 (3.0–3.5)	3.0 (2.7–3.3)
Varices	1.8 (1.5–2.1)		2.8 (2.6–3.1)	
GIB or infection or alcohol	0.7 (0.6–0.8)		0.7 (0.7–0.8)	
Facility complexity model score (ref: high)				
Low complexity	0.3 (0.2–0.7)	0.6 (0.3–1.3)	0.6 (0.4–0.7)	0.7 (0.5–1.0)
Median complexity	0.6 (0.4–0.8)	1.0 (0.7–1.5)	0.7 (0.6–0.8)	1.0 (0.8–1.1)
Liver transplant center	6.6 (5.6–7.8)	5.9 (5.0–7.0)	2.4 (2.2–2.7)	2.1 (1.9–2.4)

ACLF, acute-on-chronic liver failure; GIB, gastrointestinal bleeding; MELD-Na, model for end-stage liver disease-sodium.
Odds ratio (95% CI).

considered in calculating MELD-Na. Other scores based on organ failure may be more appropriate to predict prognosis in patients with ACLF than MELD-Na. Jalan *et al.*[14] showed that the CLIF Consortium Organ Failure score (CLIF-C OFs) had a higher AUROC to predict 90-mortality in ACLF of 0.76 (95% CI 0.70–83) *vs.* 0.67 (95% CI 0.60–0.74) for the MELD-Na score. For example, using a virtual 66-year-old patient with decompensated cirrhosis and sepsis on antibiotics, creatinine of 2.6 mg/dl, sodium 138 mmol/L, INR 1.5, total bilirubin 2.1 mg/dl, median arterial blood pressure of 60 mmHg, room air saturation of 100% and West Haven hepatic encephalopathy grade 3; the MELD-Na would be 23 with an expected 90-day mortality of 13%. However, considering he has ACLF-2, using the CLIF-C ACLF score his expected 90-day and 6-month mortality would be 61% and 66%. These data are also consistent with recent analysis of the UNOS database (2004–2016) that found that ACLF, particularly ACLF-3, was associated with high mortality among waitlisted patients, including patients with lower MELD-Na scores.[15] The authors further showed that patients with ACLF-3 at the time of listing have a higher 14-day mortality than those listed as status 1A, independent of MELD-Na score.[7] The UNOS database analyses are important but limited to patients who are evaluated and listed for LT (that is, all met the minimal listing criteria including the accepted MELD-Na cut-offs for LT). We believe our results extend these data to the larger population of patients with ACLF. In general, our results are similar to those reported by Sundaram, Jalan *et al.*,[15] providing convergent validity to our findings. Our data, however, not only underscore the limitations of MELD-Na as a prognostic marker in patients with ACLF, but they also highlight the fact that these patients (with ACLF) are at a disadvantage in the current system. For example, 36% (26,866) of patients who met ACLF criteria had a MELD-Na <15, *i.e.,* below the recommended threshold for LT evaluation[16,17] and most patients with ACLF (90%) had MELD-Na scores that were below the cut-offs beyond which patients can benefit from broader organ sharing (MELD-Na 35). These proportions did not change much in our sensitivity analyses that defined ACLF based on NASCELD or APASL criteria.

Our findings also show the potential (negative) impact of underappreciation of patients' liver disease severity on patient outcomes. We found that, overall, fewer than 5% of patients were evaluated for LT within 180 days of the index hospitalization; this proportion increased to 7.2% in patients with ACLF-2, and was 4.2% in ACLF-3. Clinicians often rely on availability in deciding the probability of mortality based on information they can retrieve. In the current MELD-Na based system, clinicians' strongly associate the risk of death with patients' MELD-Na scores. It is plausible that this availability heuristic (*i.e.*, deciding the probability of mortality based on information they can easily retrieve) might have led the clinicians to classify patients with ACLF and low MELD-Na scores as unlikely to need or benefit from LT. Our data point towards the need for physician education so that they recognize the high mortality risk in ACLF. They also call for a re-evaluation of the current organ allocation system for patients with ACLF-2 and ACLF-3. In May 2019, OPTN established the implementation of the MMaT to decrease MELD-inflation in patients with standardized exception points. Using the most current cut-offs for each VA transplant center, only 17.3 to 35.1% of patients with ACLF would meet that center-specific median cut-off (without removing the recommended 3 points).

Under such an approach, patients with ACLF would still not benefit from such standardized exceptions either. Further, in the absence of specific policies (and criteria) for transplant evaluation, ACLF may continue to be under-appreciated as being associated with high short-term mortality.

A few specific points are important for the practicing clinician. We found that 14.6% of patients with ACLF could have MELD-Na <20. Most of these patients had brain, circulatory and lung failures. In fact, these data are consistent with those from Sundaram *et al.* where the authors found that respiratory and circulatory failures had the worst impact on 1-year post-transplant survival.[15] A more recent study suggested a reduction in mortality in those patients who were successfully removed from mechanical ventilation or who experienced a recovery from circulatory or brain failure,[5] suggesting that such patients might benefit from LT. Collectively, our data show that in patients with cirrhosis, the presence of multiple organ failures should alert treating clinicians to the high risk of short-term mortality, regardless of patients' MELD-Na score. The results from our sensitivity analyses are also important for clinicians. For example, NACSELD proposed an ACLF definition that uses extrahepatic organ failures to predict 30-day survival. While the score is easy to calculate, it does not include 2 important organ failures (liver and coagulation failures).[12] Consequently, NACSELD-ACLF criteria may miss up to 63% of patients meeting CANONIC ACLF criteria and hence may falsely reassure the clinician that a patient with a clinical syndrome consistent with ACLF who does not meet NACSELD-ACLF criteria and has low MELD-Na does not warrant LT evaluation. We recognize that LT in ACLF is as much art as science and incorporates both preconceived notions of prediction and treatment, the nature of organ failure (brain, respiratory failure)[15] and the dynamic changes in organ failure severity.[4,5] While not all patients with ACLF may be candidates for LT, our data show that an effort should be made to establish protocols on how to assess the critical needs of these patients independently of MELD-Na.[18] Future research should also focus on developing and validating prognostic scores that incorporate dynamic changes in patients clinical course and novel biomarkers to identify the highest risk patients,[19–21] as well as the golden window of time[13] when application of liver-directed therapies might improve patient outcomes, treatments and prognosis while they are being evaluated for LT.[22,23]

Our work has several limitations. First, we did not capture longitudinal changes of ACLF scores over time, so patients who were ACLF-3 could experience improvement over time. Secondly, whereas our results are mainly derived from male populations seen in the VA, we believe the biological processes and clinician heuristics are likely similar in veterans and non-veterans; both groups are also subjected to similar organ allocation criteria; hence our results may be generalizable to patients outside the VA. Third, we used the CANONIC definition to identify patients with ACLF. This definition was initially developed and validated in a European cohort, but was subsequently validated by us[3] and others in the VA population.[24] Furthermore, using NACSELD-ACLF and APASL criteria did not result in any clinically meaningful change in our results (Table S5 and S6). Fourth, we included patients who were managed in over 120 centers in the US. We recognize that there might have been center-level differences in the use of vasopressors and/or ventilator support – criteria used to define organ failure in our cohort. However, we found the use of mechanical ventilation or circulatory support among these patients was not different across the 127 VA centers (data not shown), suggesting that center practices were relatively similar. Last, our study was not designed to identify the full range of possible causes for the low rates of LT consideration. Future studies should examine the role of factors beyond those related to the disconnect between actual and perceived risk of mortality in ACLF.

In conclusion, MELD-Na does not capture short-term mortality risk in ACLF. Clinicians should seek timely input from LT centers and national review boards for patients who meet criteria for ACLF-2 or ACLF-3 yet have low MELD-Na scores. Efforts are needed to rethink severity assessment and organ allocation schemes for patients with ACLF.

Abbreviations

ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; AUDIT(-C), alcohol use disorders identification test (– consumption); CDW, corporate data warehouse; CPT, current procedural terminology; EASL-CLIF, European Association for the Study of the Liver-chronic liver failure; HCC, hepatocellular carcinoma; INR, international normalized ratio; LT, liver transplantation; MELD-Na, model for end-stage liver disease-sodium; MMaT, median MELD at transplantation; NACSELD, the North American Consortium for the Study of End-Stage Liver Disease; OR, odds ratio; SMR, standardized mortality ratio; UNOS, United Network for Organ Sharing; VA, Veterans Affairs.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Ruben Hernaez (RH), Yan Liu (YL), Jennifer R. Kramer (JRK), Abbas Rana (AR), Hashem B. El-Serag (HBE), Fasiha Kanwal (FK) participated in the stages of the manuscript. Specifically, study concept and design(ALL); acquisition of data (YL); analysis and interpretation of data (RH, YL, JRK, HBE, FK); drafting of the manuscript (RH, YL, JRK, HBE, FK); critical revision of the manuscript for important intellectual content (RH, YL, JRK, HBE, FK); statistical analysis (RH, YL, FK); obtained funding (AR); administrative, technical, or material support (RH, YL, FK); study supervision (RH, FK). (a) substantial contributions to the conception and design; or the acquisition, analysis, or interpretation of the data: RH, YL, JRK, AR, HBE, FK. (b) the drafting of the article or critical revision for important intellectual content: RH, YL, JRK, AR, HBE, FK. (c) final approval of the version to be published: RH, YL, JRK, AR, HBE, FK. (d) agreement to be

accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved. RH, YL, JRK, AR, HBE, FK.

Supplementary data

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Author names in bold designate shared co-first authorship

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