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NACSELD Acute-on-Chronic Liver Failure (NACSELD-ACLF) Score Predicts 30-Day Survival in Hospitalized Patients with Cirrhosis.

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The North American Consortium for the Study of End-Stage Liver Disease's definition of acute-on-chronic liver failure (NACSELD-ACLF) as two or more extrahepatic organ failures has been proposed as a simple bedside tool to assess the risk of mortality in hospitalized patients with cirrhosis. We validated the NACSELD-ACLF's ability to predict 30-day survival (defined as in-hospital death or hospice discharge) in a separate multicenter prospectively enrolled cohort of both infected and uninfected hospitalized patients with cirrhosis. We used the NACSELD database of 14 tertiary care hepatology centers that prospectively enrolled nonelective hospitalized patients with cirrhosis (n = 2,675). The cohort was randomly split 60%/40% into training (n = 1,605) and testing (n = 1,070) groups. Organ failures assessed were (1) shock, (2) hepatic encephalopathy (grade III/IV), (3) renal (need for dialysis), and (4) respiratory (mechanical ventilation). Patients were most commonly Caucasian (79%) men (62%) with a mean age of 57 years and a diagnosis of alcohol-induced cirrhosis (45%), and 1,079 patients had an infection during hospitalization. The mean Model for End-Stage Liver Disease score was 19, and the median Child score was 10. No demographic differences were present between the two split groups. Multivariable modeling revealed that the NACSELD-ACLF score, as determined by number of organ failures, was the strongest predictor of decreased survival after controlling for admission age, white blood cell count, serum albumin, Model for End-Stage Liver Disease score, and presence of infection. The c-statistics were 0.8073 for the training set and 0.8532 for the validation set. *Conclusion:* **Although infection status remains an important predictor of death, NACSELD-ACLF was independently validated in a separate large multinational prospective cohort as a simple, reliable bedside tool to predict 30-day survival in both infected and uninfected patients hospitalized with a diagnosis of cirrhosis. (HEPATOLOGY 2018; 00:000-000).**

Acute-on-chronic liver failure (ACLF) has emerged as a major determinant of survival in chronic liver disease. Multiple organ failures superimposed on compensated cirrhosis (type B ACLF) or on decompensated cirrhosis (type C ACLF) per World Gastroenterology Organization consensus are the most prevalent in Western countries.[1] Although numerous scoring systems to predict prognosis in ACLF[2-7] already exist, a simple bedside tool to accurately predict prognosis is essential to

Abbreviations: ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; CI, confidence interval; MELD, Model for End-Stage Liver Disease; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; OR, odds ratio; WBC, white blood cell.

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clinicians. We previously developed the infection-related ACLF score, defined as two or more extrahepatic organ failures.[2] These organ failures are easy to assess and include cardiovascular (shock), brain (grade III/IV, hepatic encephalopathy), renal (need for dialysis), and respiratory (mechanical ventilation). This simple bedside tool was developed from prospectively collected variables on 507 patients with cirrhosis hospitalized with an acute infection and included in the multinational data set from the North American Consortium for the Study of End-Stage Liver Disease (NACSELD). Although increasing numbers of extrahepatic organ failures clearly predicted increasing probability of mortality, a clear difference in 30-day mortality was seen between patients with no or one and those with two or more organ failures.[2] Such a score, once validated, may be useful to facilitate earlier transplant evaluation but, probably more importantly, earlier recognition of futility of care and subsequent institution of palliate care or hospice. However, the infection-related ACLF score was developed in patients with acute infections and needs to be validated in a larger data set of infected and uninfected patients.

We therefore sought to validate our prior simple ACLF classification criteria in a second independent prospective multinational data set of nonelectively hospitalized patient with cirrhosis, with or without acute infections. We hypothesized that this simple scoring system would be able to predict mortality in all hospitalized patients with cirrhosis regardless of infection status. This score has been renamed the "NACSELD-ACLF."

Patients and Methods

In this prospective study, following informed consent, patients from 14 centers across North America had their data collected and entered into REDCap.[8] The cohort included all nonelectively hospitalized patients with cirrhosis irrespective of the presence or absence of infection. Patients with human immunodeficiency virus, previous transplantation, or nonhepatic malignancy were excluded, as outlined.[9] The diagnosis of cirrhosis was made on biopsy or on a combination of clinical, endoscopic, or radiological evidence of portal hypertension or cirrhosis and/or signs of hepatic decompensation. Infections were also previously defined and categorized accordingly.[9] Data were collected regarding cirrhosis severity, indications for admission, medication usage, complications of cirrhosis and organ failures, second and nosocomial infections, and discharge details. Mortality was assessed both during hospital stay and post–hospital discharge.

Analyses were performed on the entire cohort and individually on the infected and uninfected groups and compared. NACSELD-ACLF was defined as two or more organ failures of the four described. Brain failure was determined to be a 3 or 4 West-Haven grade of encephalopathy.[2] Renal failure was the need for renal replacement therapy. This is different from acute kidney injury, which has recently been redefined by the International Ascites Club.[10] Respiratory failure was assessed as the need for bilevel positive airway pressure or mechanical ventilation. Shock was defined as the need for pressor support, a mean arterial pressure <60 mm Hg, or a reduction of >40 mm Hg in systolic blood pressure from baseline despite adequate fluid resuscitation.

Continuous variables are presented as either means with standard deviations or medians with interquartile ranges and analyzed using either a one-way analysis of variance or a Kruskal-Wallis H test. Categorical variables are presented as percentages and were analyzed using either a chi-squared test or Fisher's exact test. Backward elimination multivariable logistic regression

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analyzing 30-day mortality was performed on all patients, infected patients, and uninfected patients using variables that were $P < 0.1$ on univariate analysis. Interaction between variables, where appropriate, was also evaluated. We also randomly divided the group into a 60/40 split to determine the split validity of the results. Where appropriate, overall survival was used as the outcome of interest. Transplant-free survival was separately evaluated but did not change the variables of the model or the overall outcome.

Statistical significance was always defined as $P < 0.05$. Data were analyzed with SAS version 9.2.

Results

The database included 2,675 patients, 1,079 of whom had an acute infection at admission or developed an acute infection during their initial hospital stay and 1,595 of whom neither had an acute infection at admission nor developed one during their initial hospitalization at one of the 14 NACSELD sites. Demographics for the study population displayed by infection status and by training and testing cohorts are presented in Tables 1 and 2. Infected patients were more likely to be female and had higher heart rates, temperatures, white blood cell (WBC) counts, and serum creatinine values and lower systolic blood pressures, serum albumin values, and sodium values at enrollment than their uninfected counterparts. Overall illness severity as measured by both the Child score and the Model for End-Stage Liver Disease (MELD) score were higher in infected patients. The split-test cohorts (testing/training) were similar on demographics, etiology and severity of cirrhosis, and infection characteristics (Table 2) because the splitting was performed randomly. In the total cohort, 103 (4%) of patients underwent liver transplantation within 30 days of hospital discharge.

Crude survival rates were lower in patients with acute infection and those with organ failures (Fig. 1) compared to those without these conditions. Acutely infected patients with an organ failure had numerically lower survival than uninfected patients with the same organ failure. As the number of organ failures increased (Fig. 2), the rate of survival decreased; the rate of survival was inferior in patients with versus without an infection. Thirty-day survival was lowest in patients with four organ failures at 19%. Patients who met criteria for NACSELD-ACLF (two or more organ failures) had an overall 59% 30-day survival (52% 30-day survival if they were infected versus 76% if they were noninfected) versus 93% in patients without NACSELD-ACLF (Fig. 3).

We then fit a multivariable logistic regression model that mirrors the model presented previously by our group predicting 30-day survival for infected patients (Table 3) separately from uninfected patients. While not all of the covariates that were significant in the original study, including second infections,[2]

TABLE 1. Demographics Are Displayed and Compared for All Patients, Infected Patients, and Noninfected Patients

Variable	Total (N = 2,675)	No Infection (n = 1,596)	Infection (n = 1,079)	*P*
Age, years	57.22 (10.82)	57.37 (10.48)	56.99 (11.32)	0.38
Male gender	62% (1,659/2,671)	64% (1015/1,593)	60% (644/1,078)	0.04
Caucasian	79% (2,113/2,669)	80% (1269/1,592)	78% (844/1,077)	0.40
Alcohol etiology	45% (1,186/2,654)	45% (715/1,581)	44% (471/1,073)	0.50
Diabetes	34% (907/2,636)	34% (541/1,575)	35% (366/1,061)	0.94
NACSELD-ACLF	10% (264/2,671)	5% (78/1,596)	17% (186/1,075)	<0.0001
Testing set	40% (1,070/2,675)	40% (643/1,596)	40% (427/1,079)	0.71
Heart rate, mean (SD)	85.22 (17.05)	84.36 (17.13)	86.50 (17.57)	0.003
Systolic blood pressure	121.50 (21.48)	122.63 (16.64)	119.83 (20.96)	0.0009
Diastolic blood pressure	68.18 (13.50)	68.59 (21.76)	67.57 (13.81)	0.054
Temperature	98.04 (1.54)	97.95 (1.74)	98.17 (1.17)	0.0001
WBC count	5.2 (6.7)	4.8 (6.5)	5.7 (7.0)	0.002
Creatinine, mean (SD)	1.43 (1.71)	1.39 (1.96)	1.48 (1.25)	<0.0001
Serum albumin	2.84 (0.67)	2.91 (0.65)	2.75 (0.69)	<0.0001
Serum sodium	134.25 (7.00)	134.71 (6.85)	133.57 (7.18)	<0.0001
Child score, median (IQR)	10.0 (8.0-11.0)	9.0 (8.0-11.0)	10.0 (9.0-12.0)	<0.0001
MELD score, median (IQR)	19.0 (14.0-24.0)	17.0 (13.0-23.0)	20.0 (15.0-26.0)	<0.0001
30-day survival	90% (2,394/2,675)	93% (1,490/1,596)	84% (904/1,079)	<0.0001

Abbreviations: IQR, interquartile range; SD, standard deviation.

TABLE 2. Demographics Are Displayed and Compared for All Patients and for the Training and Testing Cohorts

Variable	Total (N = 2,675)	Training Set (n = 1,605)	Testing Set (n = 1,070)	*P*
Age, years	57.22 (10.82)	57.51 (10.68)	56.78 (11.03)	0.09
Male gender	62% (1,659/2,671)	62% (991/1,601)	62% (668/1,070)	0.78
Caucasian	79% (2,113/2,669)	78% (1,257/1,603)	80% (856/1,066)	0.24
Alcohol etiology	45% (1,186/2,654)	46% (726/1,590)	43% (460/1,064)	0.22
Diabetes	34% (907/2,636)	35% (554/1,578)	33% (353/1,058)	0.36
Admitted with infection	27% (699/2,633)	26% (415/1,580)	27% (284/1,053)	0.68
Second infection	7% (197/2,638)	7% (113/1,585)	8% (84/1,053)	0.42
Had infection	40% (1,079/2,675)	41% (652/1,605)	40% (427/1,070)	0.71
NACSELD-ACLF	10% (264/2,671)	10% (164/1,604)	9% (100/1,067)	0.47
Heart rate, mean (SD)	85.22 (17.05)	85.59 (17.13)	84.68 (16.93)	0.18
Systolic blood pressure	121.50 (21.48)	122.08 (21.98)	120.64 (20.70)	0.09
Diastolic blood pressure	68.18 (13.50)	68.47 (13.66)	67.75 (13.26)	0.18
Temperature	98.04 (1.54)	98.06 (1.82)	98.02 (0.97)	0.49
WBC count	5.2 (6.7)	5.3 (7.2)	5.0 (5.9)	0.33
Creatinine, mean (SD)	1.43 (1.71)	1.44 (1.98)	1.41 (1.22)	0.72
Serum albumin	2.84 (0.67)	2.83 (0.67)	2.86 (0.67)	0.41
Serum sodium	134.25 (7.00)	134.33 (6.81)	134.13 (7.29)	0.49
Child score, median (IQR)	10.0 (8.0-11.0)	9.50 (8.0-11.0)	10.0 (8.0-11.0)	0.22
MELD score, median (IQR)	19.0 (14.0-24.0)	18.0 (14.0-24.0)	19.0 (14.0-24.0)	0.15
30-day survival	90% (2,394/2,675)	90% (1,444/1,605)	89% (950/1,070)	0.33

Abbreviations: IQR, interquartile range; SD, standard deviation.

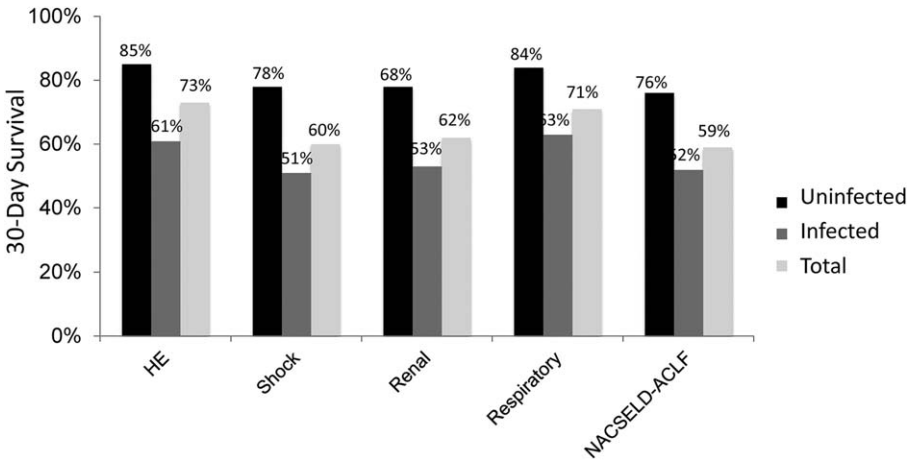

FIG. 1. Crude survival rates with individual organ failures are presented for the entire cohort, infected patients, and noninfected patients. Abbreviation: HE, hepatic encephalopathy.

admission MELD, WBC count, and serum albumin, remain significant predictors of 30-day survival, the single strongest predictor of 30-day survival remains NACSELD-ACLF for infected patients (odds ratio [OR], 0.16; confidence interval [CI], 0.11-0.32) and uninfected patients (OR, 0.29; CI 0.15-0.56). This remained significant even after controlling for MELD score, WBC count, and admission serum albumin in both models.

We also separately evaluated NACSELD-ACLF diagnosed at admission compared to >48 hours after admission. In addition, we further subdivided patients with and without an admission infection. Although there was a trend for worse survival in patients with admission NACSELD-ACLF, neither this factor nor infection status reached statistical significance (Supporting Table S1).

Because both infected and uninfected patients had the same predictors of survival in backward elimination multivariable modeling, the groups were combined for a final model (Table 3). NACSELD-ACLF, as expected, was the greatest predictor of impaired survival (OR, 0.176; CI 0.121-0.254). Of note, infection status (P = 0.016) was a significant predictor of

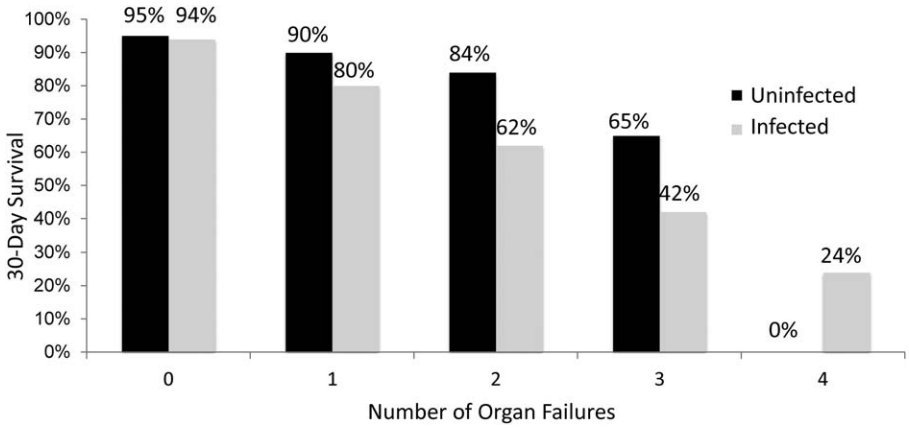

FIG. 2. Thirty-day survival for infected and noninfected patients by number of organ failures. $P < 0.0001$ for differences between the organ failures in infected and uninfected patients.

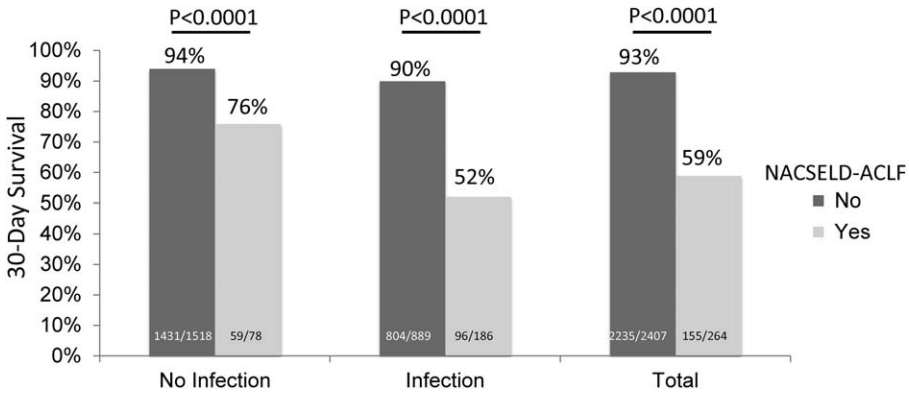

FIG. 3. Thirty-day survival for infected and noninfected patients by NACSELD-ACLF (two or more organ failures).

TABLE 3. Multivariable Logistic Regression Analysis Predicting 30-Day Survival of Admitted Patients With Cirrhosis and an Infection, Without an Infection, and All Together

Effect	Estimate	SE	*P*	OR (95% CI)
Infected patients				
NACSELD-ACLF	−1.8435	0.2297	<0.0001	0.16 (0.10-0.25)
MELD	−0.0508	0.014	0.0003	0.95 (0.93-0.98)
WBC	−0.6561	0.1282	<0.0001	0.52 (0.40-0.67)
Albumin	0.2168	0.1561	0.165	1.24 (0.92-1.69)
Uninfected patients				
NACSELD-ACLF	−1.2258	0.3281	0.0002	0.29 (0.15-0.56)
MELD	−0.0971	0.0146	<0.0001	0.91 (0.88-0.93)
WBC	−0.4146	0.1181	0.0004	0.66 (0.52-0.83)
Albumin	0.2707	0.1761	0.1243	1.31 (0.93-1.85)
All patients				
NACSELD-ACLF	−1.739	0.189	<0.0001	0.176 (0.121-0.254)
Age	−0.048	0.008	<0.0001	0.954 (0.938-0.969)
WBC	−0.555	0.083	<0.0001	0.574 (0.488-0.676)
Albumin	0.306	0.118	0.0096	1.357 (1.077-1.710)
MELD	−0.085	0.011	<0.0001	0.918 (0.900-0.938)
Had infection	−0.402	0.166	0.0156	0.669 (0.483-0.927)

Abbreviation: SE, standard error.

mortality independent of age, MELD, WBC count, and admission serum albumin. The final model c-statistic was 0.8073 in the training cohort, which increased to 0.8532 in the testing cohort. The sensitivity of this final measure was 84%, with a specificity of 70%.

Lastly, we compared the ability of the NACSLED-ACLF model and the Asian Pacific Association for the Study of the Liver (APASL) model[11] to predict patient survival. To accomplish this, the cohorts had to be modified. The cohort used to assess the NACSELD-ACLF model was modified by eliminating (1) patients admitted with infections (n = 741) and (2) patients without an admission infection who developed NACSELD-ACLF within 48 hours of admission (n = 59), which left 1,875 who were assessed. The cohort used to evaluate the APASL model was modified by eliminating (1) patients admitted with infections (n = 741) and (2) patients with

admission serum bilirubin >5.0 mg/dL and/or an international normalized ratio >1.5 (n = 681), which left 1,253 who were assessed. Thirty-day survival was markedly affected when patients met either the NACSELD-ACLF criteria (93% [1,647/1,770] $ACLF^-$ versus 55% [58/105] $ACLF^+$) or the APASL criteria for ACLF (95% [906/950] $ACLF^-$ versus 87% [264/303] $ACLF^+$; $P < 0.001$). The area under the curve of the NACSELD-ACLF model was numerically higher (0.8240; 95% CI, 0.7868-0.8559) than the area under the curve of the APASL model (0.7783; 95% CI, 0.7174-0.8292) but not statistically significantly different. We were not able to compare NACSELD-ACLF to the chronic liver failure-sequential organ failure assessment score because our database does not contain partial pressure of arterial oxygen/fractional inspired oxygen data.

Discussion

The number of organ failures is the greatest single determinant of mortality in hospitalized patients with cirrhosis.[2] Although several scoring systems have been proposed to facilitate prognosis determination,[3-7,11,12] none of them is both derived and validated in a multinational prospective cohort, nor are any as simple to apply. The NACSELD-ACLF score is a simple bedside tool for clinicians to use that has now been validated not only in an independent multinational prospective data set but also in both infected and uninfected individuals with cirrhosis. It has also been compared to the APASL model and had a numerically higher area under the curve but was not statistically significantly different in its ability to predict patient survival. The NACSLED-ACLF score will be available soon as a downloadable app to make it even easier to use at a patient's bedside, sponsored by the American Association for the Study of Liver Disease's innovation fund.

The current scoring system takes into account relevant clinical variables such as age, MELD score, WBC count, and serum albumin on admission and infection status along with NACSELD-ACLF. These are variables that are easily available in clinical practice, consistent across centers, and likely difficult to modify. The prevention of infections, whether nosocomial or health care–associated, should therefore be a major focus of clinical research and cirrhosis-management programs. This is because infected patients have a uniformly worse crude prognosis compared to uninfected patients, which continues to be significant on multivariable analysis. Our findings are in contrast to the study by Moreau et al., in which infected and uninfected patients had similar outcomes,[3] although their database was significantly smaller than the current one and possibly underpowered to find this important determinant of outcome. We also found a lower admission WBC count to be predictive of greater survival. This discrepancy between the North American and European experiences could be due to any one of the following: (1) we had few patients with active alcohol misuse in our population compared to the European cohort, which can also modulate the WBC count regardless of infection; (2) WBC count may just be another marker of infection status, with uninfected patients having a superior outcome; and/or (3) patients with ACLF have increased numbers of regulatory immune cells, and those with increased stimulated monocyte and polymorphonuclear burst have an increased risk for sepsis and ACLF.[13,14]

The greatest contribution of this survival analysis may be to help determine futility of continued aggressive care in these hospitalized patients with cirrhosis. Health care expenditures may be reduced if fewer resources are used in patients with four organ failures, in whom survival is unlikely.[2,7] The NACSELD-ACLF score may also potentially modulate transplant-listing practices in ACLF, which are inconsistent across centers. Infected patients are often inactivated on the transplant list, but in the absence of multiple organ failures, posttransplant survival in ACLF patients remains good.[15] The challenge will be to dovetail these findings into criteria followed by transplant programs to optimize outcomes and minimize cost.

When considering individual organ failures, recent data show that hospitalized patients with cirrhosis who are not liver transplant candidates but undergo dialysis have as high as a 91% 90-day mortality.[16] As a result, it seems prudent to be highly selective in offering this type of life support to patients who are not transplant candidates.[17,18] In most cases, dialysis in patients with ACLF is likely futile if they have relative or absolute contraindications to transplant. This may decrease suffering among these patients and result in significant cost savings. Of note, NACSELD-ACLF mortality is independent of MELD even with the heavy weighting of creatinine in the MELD scoring system.

Age continues to be a critical determinant of prognosis as younger individuals show improved outcomes compared to their older counterparts. Increasing age

also negatively impacts survival in post-surgery ACLF.[19] However, there are factors other than age, such as sarcopenia and functional status, that likely play an additional role in determining prognosis.[20] We previously showed that hepatic encephalopathy independently impairs prognosis[21]; however, more work needs to be done to determine the interaction between age, ACLF, and short-term and long-term outcomes. In addition, it would have been ideal to reevaluate patients for ACLF 3-5 days after diagnosis to determine if this better predicted mortality, as some have shown previously; however, these data were not available.[7,22]

Although cost-saving is important, a cost-effective intervention to treat ACLF is still sadly lacking. Of note, a higher serum albumin was the single independent factor associated with improved outcome. However, intravenous administration of albumin has not thus far been demonstrated to reduce mortality in ACLF despite its ability to stabilize endothelium, relieve oxidative stress, and function as an immunomodulatory agent.[23] Current data do not support parenteral albumin use outside well-accepted indications (such as during spontaneous bacterial peritonitis or acute kidney injury and after paracentesis), although it is still worth investigating the option in ACLF patients.[24,25]

The greatest opportunity for modulation in ACLF lies within the immune system. WBC count remains a critical marker of prognosis; greater inflammation, as evidenced by a higher WBC count, is associated with worse outcomes. Current data have documented that an excessive immunologic response is part of ACLF initiation.[26,27] However, the innate and adaptive immune response in the infected versus uninfected patient with ACLF needs further exploration. In addition, understanding the evolution of these responses over time and their role in predisposing patients to second infections requires urgent evaluation to develop intervention strategies that will improve outcomes.[9,28-31]

Despite the robust recent research in ACLF, the number and cost of hospitalizations in patients with cirrhosis have doubled and, over the last decade, more than tripled in those with ACLF.[32] As a result, it is even more critical now than in the past to have a simple validated bedside tool to predict prognosis in admitted patients with cirrhosis. The tool should facilitate appropriate patient and family discussions regarding continued aggressive care. The NACSELD-ACLF score may be used to determine whether to proceed with transplant (two or fewer organ failures) versus palliative care (more than two organ failures) and, if used appropriately, may save resources.[7,29,33] The high c-statistic for our validated model (0.8532) confirms its marked accuracy, thereby engendering confidence in its prognostication ability and therefore clinical applicability.

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