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The clinical courses of HBV-related acute-on-chronic liver failure and a multi-state model to predict disease evolution

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Abbreviations: ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AUROCs, areas under the receiver operating characteristic curves; CATCH-LIFE, Chinese Acute-on-chronic liver failure Consortium; COSSHs, Chinese Group on the Study of Severe Hepatitis B-ACLF score; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; K, serum potassium; LT, liver transplantation; MELDs, Model For End-Stage Liver Disease Score; MELD-Na, MELD-sodium score; Na, serum sodium; OF, organ failure; TB, total bilirubin.

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Abstract

Background and Aims: Acute-on-chronic liver failure (ACLF) is a highly dynamic syndrome. The objective of this study was to delineate the clinical course of patients with HBV-ACLF and to develop a model to estimate the temporal evolution of disease severity.

Methods: We enrolled eligible patients from 2 large, multicenter prospective cohorts. The ACLF grade, organ failures, and outcomes were assessed at multiple time points (days 1/4/7/14/21/28). Probabilities for ACLF transitions between these disease states and to death within 28 days were calculated using a multi-state model that used baseline information and updated ACLF status. The model was validated in independent patients.

Results: Among all the 445 patients with HBV-ACLF, 76 represented disease progression, 195 had a stable or fluctuating course, 8 with improvement, and the remaining 166 with resolution within 28-day follow-up. New coagulation (63.64%) or renal failure (45.45%) was frequently observed during early progression. Patients with disease progression had a higher incidence of new episodes of ascites [10 (13.16%) vs. 22 (5.96%), $p = 0.027$] and HE [13 (17.11%) vs. 21 (5.69%), $p = 0.001$], and a significant increase in white blood cell count. The multi-state model represented dynamic areas under the receiver operating characteristic curves ranging from 0.71 to 0.84 for predicting all ACLF states and death at 4, 7, 14, 21, and 28 days post-enrollment and from 0.73 to 0.94 for predicting death alone, performing better than traditional prognostic scores.

Conclusions: HBV-ACLF is a highly dynamic syndrome with reversibility. The multi-state model is a tool to estimate the temporal evolution of disease severity, which may inform clinical decisions on treatment.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a fatal syndrome caused by an acute exacerbation of underlying chronic liver diseases and presenting as multi-organ failures.[1] Ideally, preventing (AD)-ACLF transition is a "golden window" to contain disease progression.[2] However, as reported by the CANONIC study and other subsequent studies,[3–5] the majority of patients already presented ACLF upon admission to the hospital rather than developing this syndrome during hospital follow-up. Hence, the management of ACLF syndrome itself remains a major burden for health care providers.

Currently, liver transplantation (LT) is the only definite therapy to reduce ACLF mortality, but limited by donor organ shortage and high mortality on the waiting list. However, an optimal "therapeutic window" may exist in selected patients. Consequently, there is a need to understand the clinical evolution of ACLF to tailor current therapeutic options and provide guidance for designing clinical trials testing novel therapy.[6,7]

The CANONIC study stratified the differential clinical courses of disease resolution, improvement, worsening, or steady or fluctuation in patients with ACLF at enrollment.[8] As reported, half of the patients with ACLF resolved or improved, and one-fifth of them worsened during hospitalization.[8] However, HBV-ACLF represents distinct clinical phenotypes from ACLF with alcohol or HCV etiology. A remarked feature of HBV-ACLF is the particularly high incidence of liver failure,[8] which is precipitated frequently by the acute flare of hepatitis B, superimposed infection of HEV, or DILI. Besides, HBV-ACLF occurs more frequently in patients with previously compensated cirrhosis,[4] which may have a higher potential to recover than those with decompensated cirrhosis. Further, there is also a lack of bedside prediction to inform the updated status of patients and thereby guide clinical decisions.

In the study, we identified 445 patients with HBV-related ACLF from 2 large-scale prospective observational cohorts. Our aims were to describe the clinical courses in these patients, particularly the

changes in different organ functions, onset of new decompensation events, and worsening of systemic inflammation, and evaluate the potential risk factors of the worsening of ACLF and mortality. Finally, we developed and validated a time-homogeneous Markov model, which made updated predictions regarding disease progression by estimating the transition intensities of time and risk factors between ACLF grades as well as towards the absorbing state (death) during the in-hospital follow-up to predict disease progression of patients with HBV-ACLF.

METHODS

Study design and patients

We retrospectively identified patients with HBV-ACLF who were diagnosed at admission or during hospitalization from the large, multicenter, prospective, observational cohort of the Chinese Acute-on-chronic Liver Failure Consortium (CATCH-LIFE) study. The ACLF was diagnosed based on EASL-CLIF criteria.[3] The CATCH-LIFE study consecutively enrolled 2600 and 1370 patients with cirrhosis or other chronic liver diseases hospitalized for AD and/or abnormal liver function from January 2015 to December 2016 (NCT02457637) in a training cohort and a validation cohort from September 2018 to March 2019 (NCT03641872), respectively. The details of the design and patient characteristics of the CATCH-LIFE study have been reported elsewhere.[9,10] The study adhered to the Declaration of Helsinki and was approved by the Renji Hospital Ethics Committee of Shanghai Jiao Tong University School of Medicine (Approval No. (2014) 148 k and (2016) 142 k), and written consent was obtained from all the study patients or their legal representatives.

Definitions of the clinical course of ACLF

As reported,[8] ACLF grading was evaluated for each patient at admission on days 4/7/14/21/28 during hospitalization or the last time point before discharge, death, or liver transplantation. Clinical course patterns were then assessed by comparing initial and final ACLF grades. The initial ACLF grade was assessed at the time of diagnosis of ACLF, either during hospitalization or during a hospital stay. The final ACLF grade was obtained at the last available assessment after diagnosis, within 28 days before death, liver transplant, or hospital discharge.

The clinical course patterns of HBV-ACLF were defined as previously reported:

- Resolution was defined by regression from any ACLF status to no ACLF.
- Improvement was defined by de-escalation of ACLF grade (ACLF-3 to ACLF-2 or 1 or ACLF-2 to 1).
- Worsening was defined by the escalation of ACLF grade.
- The steady course was defined as no change in the initial ACLF grade compared to the final grade. A steady course with variations of the ACLF grade during follow-up was defined as a fluctuating steady course.

Data collection

The data collection and follow-up schedule and standard management of HBV-ACLF patients in the CATCH-LIFE study have been reported elsewhere[11] and detailed in the Supplemental material, http://links.lww.com/HC9/A713.

Development and validation of a multi-state Markov model

To predict the transition between ACLF gradings and death during hospitalization, a time-homogeneous Markov Model was developed using a derivation cohort. The Markov model is capable of predicting disease progression with a more straightforward estimation of the SE and predicting multiple outcomes, compared to a multinomial logistic regression. Patients' ACLF gradings were evaluated on days after enrolment, as described before. Deaths occurring between intervals were recorded at the next time point, and data were aborted for the model after death. The missing data was interpolated by a multiple imputation approach. All baseline covariates were selected by a backward selection process. Those showing significant (p value < 0.05) impact on any possible transition were kept. The model discrimination was assessed by a generalized areas under the receiver operating characteristic curves (AUROC) that fits with a multi-state model.[12] And calibration was evaluated by comparing predicted and observed events. The model performance was externally tested in the validation cohort. The R package msm was used to develop the time-homogeneous multi-state Markov Model.[13]

Statistical analysis

Variables were expressed as counts (%), mean $\pm$ SD, or median (interquartile range). And data between groups were compared by Student's t test, Mann-Whitney U test, or by $\chi 2$-test or Fisher exact test. Kaplan–Meier estimate was used to estimate survival probabilities, and log-rank test was used to conduct overall or pairwise comparisons of groups. The accuracy of ACLF grades (at diagnosis and on days 4–7) in

predicting short-term outcomes was assessed by AUROCs. We performed a multivariate logistic regression analysis to investigate the risk factors for ACLF progression. A competing risk regression model (Fine and Gray) was used to explore risk factors of ACLF death independent of LT. The results were presented as subdistribution HRs and 95% CI. All the statistical analyses were conducted with R software (version 4.0.5; http://www.r-project.org/). $p < 0.05$ was considered a significant difference in all statistical analyses.

RESULTS

Differential clinical courses of HBV-ACLF

In this study, a total of 445 patients with HBV-ACLF were enrolled, of which 308 were diagnosed on admission and 137 during hospital stay (Figure 1). Among all the patients, 76 patients represented disease progression (17.08%, Table 1 red boxes), 195 with a stable course(43.82%, Table 1 uncolored boxes), and the remaining 174 had remission or improvement (39.10%, Table 1 green boxes) during the in-hospital follow-up (Figure 2). The demographic and clinical characteristics between patients with ACLF with disease progression and those who did not excerbate (including steady course, improvement, or resolution) are compared in Supplemental Table S1, http://links.lww.com/HC9/A713. As shown, resolutions were most common (56.43%) in the 101 patients with initial ACLF-1 grade, followed by a stable or fluctuating course (21.78%) and worsening (21.78%). Among 300 patients with initial ACLF-2, the most common clinical course was stable or fluctuating ACLF grade (48.33%), followed by resolution (33.67%) and deterioration (18.00%). Finally, as expected, the majority of patients with initial ACLF-3 remained stable or fluctuating (63.64%). Still, 13.64% of patients improved, and even 22.73% of these patients had a resolution of ACLF grade. The median time between the initial and final ACLF grade assessment was 14 (1–28) days. Overall, there was a correlation between the initial and final ACLF grades. With the escalation of the initial ACLF grade, improvement or resolution at the final assessment became less likely.

The relationship between initial and final ACLF grade with short-term outcome

As shown in Table 1 and Supplemental Figure S1, http://links.lww.com/HC9/A713, the 28-day (28.00%) and 90-day mortality (28.00%) were lower in the final ACLF-1, higher in the final ACLF-2 (37.32% and 71.43%), and very high in the final ACLF-3 (73.03% and 86.52%), which was not completely correlated with whether they presented with initial ACLF-1, ACLF-2, or ACLF-3. Patients with initial ACLF-1 had a 28-day and 90-day mortality of 20.83% and 36.17%, those with initial ACLF-2 had 36.53% and 59.62%, and those with initial ACLF-3 had 64.10% and 82.05%, respectively. From the perspective of clinical courses, patients with improved or subsided ACLF grade had lower 28-day (14.56%) and 90-day(31.17%) LT-free mortality, followed by stable patients (28-day:41.04%; 90-day:65.24%) and worsening patients (28-day:66.67%; 90-day:88.00%) (Supplemental Figure S2, http://links.lww.com/HC9/A713). Further, the impact of ACLF progression on short-term mortality was independent of CLIF-CONSORTIUM scores for patients with ACLFs (Supplemental Figure S3, http://links.lww.com/HC9/A713.

We also investigated a further impact of the resolution of liver failure on outcomes in patients with ACLF remission. As shown in Supplemental Table S2, http://links.lww.com/HC9/A713, the resolution of liver failure was associated with significantly lower 90-day, 180-day, and 365-day Lx-tree mortality, in patients with ACLF resolution, irrespectively of initial ACLF grade.

Dynamic assessment of ACLF grade during early clinical course predicts short-term outcome

Considering that prognosis correlated better with clinical course than with ACLF grade at diagnosis, a dynamic assessment of ACLF grade may improve the predictive accuracy of the short-term outcome. Notably, 71.41% of patients had already defined final ACLF grade at days 4–7. ACLF grade at days 4–7 after diagnosis (days 4–7 ACLF) predicted 28-day and 90-day outcomes more accurately than ACLF grade at diagnosis [AUROC (95% CI): 0.76 (0.71–0.81) vs. 0.65 (0.58–0.71) and 0.77 (0.72–0.81) vs. 0.62 (0.55–0.69), respectively; $p < 0.001$] (Supplemental Figure S4, http://links.lww.com/HC9/A713).

New events during the early clinical course

Organ failures

Initially, liver failure (386, 86.74%) was the most common type of OF, followed by coagulation failure (311, 69.89%) and renal failure (77, 17.30%). Coagulation failure (72.73%) was the major new OFs during ACLF-1-2 progression, followed by renal failure (36.36%). And the incidence of extrahepatic OFs, including renal (59.26%), circulatory (14.81%), respiratory (31.48%), or brain failures (50.00%), increased substantially during ACLF-2-3 transition (Table 2).

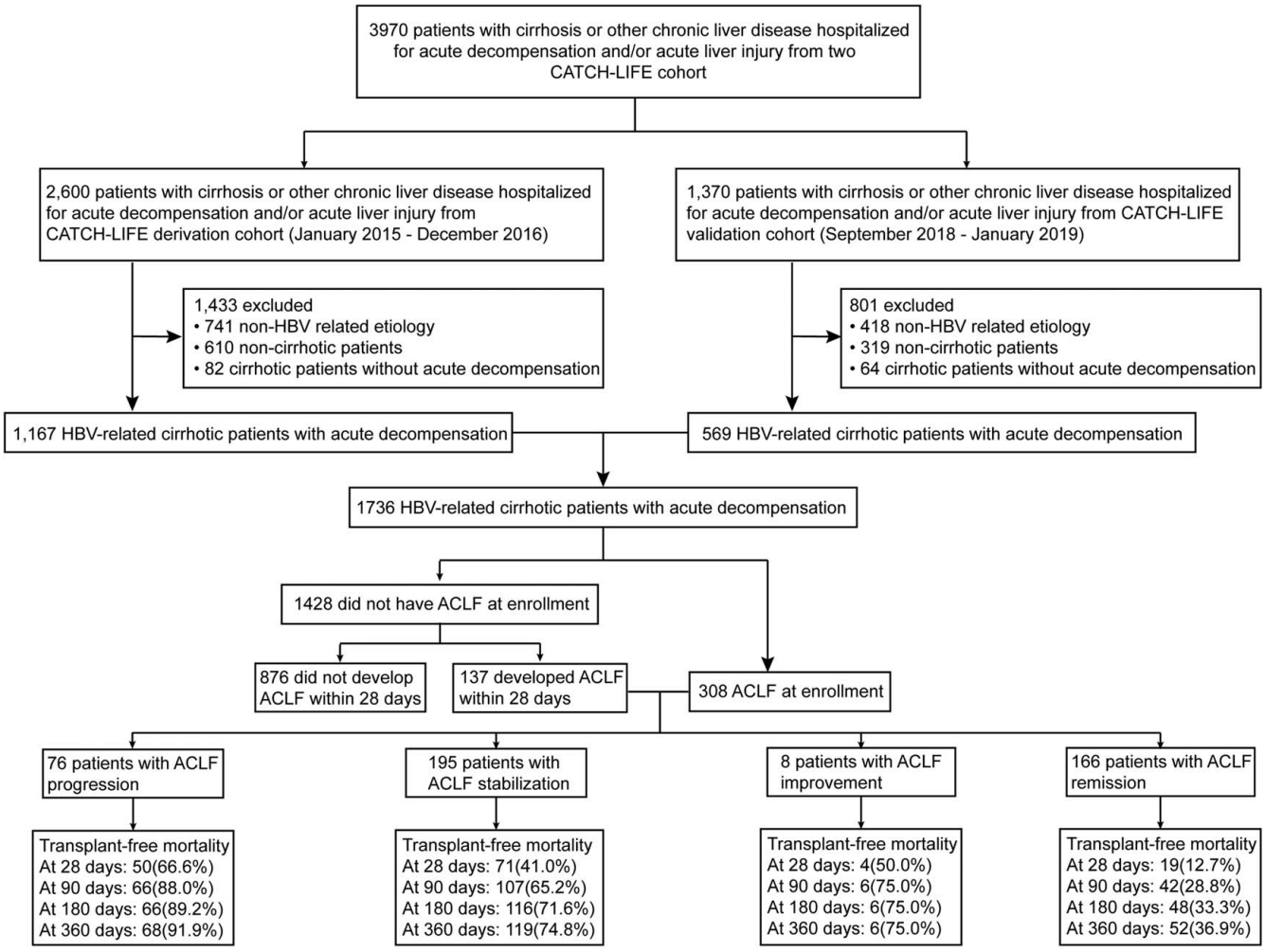

FIGURE 1 Patient screening flow chart according to the diagnosis of HBV-ACLF and the clinical courses in the derivation and validation cohort. Abbreviation: CATCH-LIFE, Chinese Acute-on-Chronic Liver Failure Consortium; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure.

TABLE 1 Clinical course patterns and types in those patients with ACLF studied

	Final grade			
Initial grade	**No ACLF (n = 166)**	**ACLF-1 (n = 25)**	**ACLF-2 (n = 161)**	**ACLF-3 (n = 93)**
ACLF-1 (%)				
Prevalence (n = 101)	57 (56.43)	22 (21.78)	11 (10.89)	11 (10.89)
28-day mortality (n = 96)	1/53 (1.89)	6/22 (27.27)	4/10 (40.00)	9/11 (81.82)
90-day mortality (n = 94)	9/51 (17.65)	6/22 (27.27)	10/10 (100.00)	9/11 (81.82)
ACLF-2 (%)				
Prevalence (n = 300)	99 (33.00)	2 (0.67)	145 (48.33)	54 (18.00)
28-day mortality (n = 271)	15/88 (17.05)	1/2 (50.00)	46/127 (36.22)	37/54 (68.52)
90-day mortality (n = 260)	27/86 (31.40)	1/2 (50.00)	80/118 (67.80)	47/54 (87.04)
ACLF-3 (%)				
Prevalence (n = 44)	10 (22.73)	1 (2.27)	5 (11.36)	28 (63.64)
28-day mortality (n = 39)	3/9 (33.33)	0 (0.00)	3/5 (60.00)	19/24 (79.17)
90-day mortality (n = 39)	6/9 (66.67)	0 (0.00)	5/5 (100.00)	21/24 (87.50)

Note: ACLF: resolution or improvement (green boxes); steady or fluctuating course with unchanged final ACLF grade (uncolored boxes); and worsening (red boxes).
Abbreviation: ACLF, acute-on-chronic liver failure.

FIGURE 2 The Sankey chart represents the evolution of ACLF grades. The left column represented the initial ACLF grade and the right column represented the final ACLF grade. The connecting curves between columns indicated the evolutionary trajectory, and the curve thickness indicated the number of patients. Abbreviation: ACLF, acute-on-chronic liver failure.

New onset of decompensations/bacterial infections

As shown in Supplemental Table S3, http://links.lww.com/HC9/A713, the prevalence of new episodes of decompensation events, including ascites [10 (13.16%) vs. 22 (5.96%), $p = 0.027$] and HE [13 (17.11%) vs. 21 (5.69%), $p = 0.001$] were significantly higher among patients with progression than among those without. The incidence of new bacterial infections was also higher [9 (11.84%) vs. 29 (7.86%), $p = 0.258$], although it did not achieve statistical significance ($p = 0.258$).

Evolution of systemic inflammation

As shown in Supplemental Table S4, http://links.lww.com/HC9/A713, the white blood cell count [at diagnosis: 7.41 (3.32) vs. 6.49(4.78), $p = 0.013$; 4–7 days after diagnosis: 8.32 (8.56) vs. 5.81 (4.73), $p < 0.001$] and neutrophil-to-lymphocyte ratio [at diagnosis: 5.7 (4.2) vs. 4.3 (4.7), $p = 0.020$; 4–7 days after diagnosis: 6.00 (5.22) vs. 3.30(3.67), $p < 0.001$] were significantly higher at enrollment in patients with ACLF progression than in patients without at either enrollment or 4–7 days after enrollment. We also compared the levels of

TABLE 2 The evolution of organ failures in patients with initial ACLF-1/2 who experienced disease progression

	Initial ACLF-1 (n = 23)		Initial ACLF-2 (n = 54)	
	Total (n = 22), n (%)	ACLF-1 to ACLF-2 (n = 11) , n (%)	ACLF-1 to ACLF-3 (n = 11) , n (%)	ACLF-2 to ACLF-3 (n = 54) , n (%)
Organ failures at the initial assessment				
Cardiovascular failure	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.85)
Respiratory failure	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.70)
Brain failure	1 (4.55)	0 (0.00)	1 (9.09)	2 (3.70)
Renal failure	1 (4.55)	1 (9.09)	0 (0.00)	6 (11.1)
Coagulation failure	1 (4.55)	0 (0.00)	1 (9.09)	45 (83.33)
Liver failure	19 (86.36)	10 (90.91)	9 (81.82)	52 (96.30)
Organ failures at the last assessment				
Cardiovascular failure	4 (18.18)	0 (0.00)	4 (36.36)	8 (14.81)
Respiratory failure	8 (36.36)	0 (0.00)	8 (72.73)	17 (31.48)
Brain failure	7 (31.82)	0 (0.00)	7 (63.64)	27 (50.00)
Renal failure	10 (45.45)	4 (36.36)	6 (54.55)	32 (59.26)
Coagulation failure	14 (63.64)	8 (72.73)	6 (54.55)	48 (88.89)
Liver failure	20 (90.91)	10 (90.91)	10 (90.91)	54 (100.00)

Abbreviation: ACLF, acute-on-chronic liver failure.

surrogate markers of systemic inflammation measured at enrollment versus those measured 4–7 days after enrollment (Supplemental Table S4, http://links.lww.com/HC9/A713). As shown, there was a close relationship between the clinical course and changes in inflammatory markers. Patients without ACLF progression represented a significant reduction in neutrophil-to-lymphocyte ratio and white blood cell count, but those with ACLF progression had a significant increase in white blood cell count.

Factors associated with HBV-ACLF progression

We next explored the risk factors of ACLF progression by a logistic multivariate analysis (Table 3). The multivariate regression revealed that infection (OR 1.94; 95% CI 1.09–3.45; $p = 0.025$), alanine aminotransferase (ALT) (OR 1.00; 95% CI 1.00–1.00; $p = 0.005$), and total bilirubin (TB) at enrollment (OR 1.00; 95% CI 1.00–1.00; $p = 0.013$) were independently associated with ACLF progression in model 1. And model 2 showed that in addition to infection, ALT, and TB at enrollment, new onset of HE (OR 3.53; 95% CI 1.54–8.10; $p = 0.003$) and infection (OR 4.01; 95% CI 1.41–11.46; $p = 0.009$) were all risk factors of progression.

Additionally, we evaluated the impact of the timing of antiviral therapy on HBV-ACLF progression. All the patients received antiviral NUCs at diagnosis of HBV-ACLF. As shown in Supplemental Table S5, http://links.lww.com/HC9/A713, most patients (273, 61.35%) did not receive any antiviral treatment prior to enrolment. In all, 139 patients had a history of NUC treatment over 6 months before enrolment and the rest 33 patients had a history of NUC treatment less than 6 months. There were no significant differences between groups in the progression of HBV-ACLF ($p > 0.05$). Also, a stratification by baseline HBV DNA showed that a higher viral load at enrolment was not associated with HBV-ACLF progression ($p > 0.05$). In addition, we further evaluated the relationship between HBV viral load and short-term mortality, and there was no significant difference.

Factors associated with HBV-ACLF short-term death

We also explored the risk factors of death in HBV-ACLF patients while using LT as a competing event (Table 4). When the baseline variables were exclusively analyzed in model 1, age, HE, Na, ALT, TB, and international normalized ratio (only in 90 days) were identified as independent predictors of 28-day or 90-day LT-free mortality. When new onsets of decompensation events were added to model 1, age, infection (only in 90-day), HE, platelet count (only in 90-day), Na, ALT, TB, and international normalized ratio (only in 90-day) at enrollment remained statistically significant prognostic factors. In addition, new episodes of HE and new onset of infection (only in 90 days) were found to be other significant risk factors for short-term death.

Development and validation of a multi-state Markov model to predict the clinical trajectory of HBV-ACLF

A multi-state Markov model (Supplemental Figure S5, http://links.lww.com/HC9/A713) incorporating 8 independent covariates (age, sex, ALT, neutrophil-to-lymphocyte ratio, international normalized ratio, liver failure, hepatic insults, and extrahepatic insults) was established to predict the probability of ACLF transition and death. The

TABLE 3 Multivariate analysis of risk factors of ACLF progression

	Model 1		Model 2	
	OR (95% CI)	p	OR (95% CI)	p
HE at enrollment	—	—	2.02 (1.09–3.74)	0.026
Infection at enrollment	1.94 (1.09–3.45)	0.025	2.81 (1.37–5.78)	0.005
ALT(U/L) at enrollment	1.00 (1.00–1.00)	0.005	1.00 (1.00–1.00)	0.030
Total bilirubin(mol/L) at enrollment	1.00 (1.00–1.00)	0.013	1.00 (1.00–1.00)	0.023
New onset of hepatic encephalopathy	—	—	3.53 (1.54–8.10)	0.003
New onset of infection	—	—	4.01 (1.41–11.46)	0.009

Note: Statistical analysis was performed by using the logistic regression analysis.
Model 1: The variables entered into the multivariate analysis were age, sex, HE at enrollment, GIH at enrollment, ascites at enrollment, infection at enrollment, ALT at enrollment, Na at enrollment, PLT at enrollment, NLR at enrollment, bilirubin at enrollment, Cr at enrollment, and INR at enrollment.
Model 2: The variables entered into the multivariate analysis were age, gender, hepatic encephalopathy at enrollment, GIH at enrollment, ascites at enrollment, infection at enrollment, ALT at enrollment, Na at enrollment, PLT at enrollment, NLR at enrollment, bilirubin at enrollment, Cr at enrollment, INR at enrollment, new onset of ascites, new onset of HE, and new onset of infection.
Abbreviations: ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; Cr, creatinine; GIH, gastrointestinal haemorrhage; INR, international normalized ratio; Na, serum sodium; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet count.

TABLE 4 Multivariate analysis of risk factors of 28-day/90-day mortality in those patients with ACLF of diagnosis based on Fine-Gray test

	28-day				90-day			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.04 (1.03–1.06)	< 0.001	1.04 (1.03–1.06)	< 0.001	1.04 (1.02–1.05)	< 0.001	1.04 (1.02–1.05)	< 0.001
Infection at enrollment	—	—	—	—	—	—	1.46 (1.02–2.07)	0.037
HE at enrollment	1.78 (1.20–2.65)	< 0.001	2.02 (1.34–3.05)	< 0.001	1.59 (1.14–2.20)	0.006	1.76 (1.26–2.46)	0.001
PLT(*10E9/L)	—	—	—	—	—	—	1.00 (0.99–1.00)	0.035
Serum sodium (mmol/L)	0.95 (0.92–0.98)	< 0.001	0.95 (0.92–0.98)	< 0.001	0.95 (0.92–0.97)	< 0.001	0.95 (0.93–0.97)	< 0.001
ALT (U/L)	1.00 (1.00–1.00)	< 0.001	1.00 (1.00–1.00)	< 0.001	1.00 (1.00–1.00)	< 0.001	1.00 (1.00–1.00)	< 0.001
Total bilirubin (mol/L)	1.00 (1.00–1.00)	< 0.001	1.00 (1.00–1.00)	< 0.001	1.00 (1.00–1.00)	0.002	1.00 (1.00–1.00)	0.001
INR	—	—	—	—	1.11 (1.00–1.23)	0.049	1.12 (1.01–1.24)	0.027
New onset of HE	—	—	2.68 (1.64–4.38)	< 0.001	—	—	2.55 (1.63–3.98)	< 0.001
New onset of infection	—	—	—	—	—	—	1.76 (1.02–3.04)	0.043

Notes: Model 1: age, sex, presence of HE at enrollment, GIH at enrollment, ascites at enrollment, infection at enrollment, ALT at enrollment, Serum sodium at enrollment, PLT at enrollment, NLR at enrollment, bilirubin at enrollment, Cr at enrollment, and INR at enrollment.
Model 2: age, sex, presence of HE at enrollment, GIH at enrollment, ascites at enrollment, infection at enrollment, ALT at enrollment, Serum sodium at enrollment, PLT at enrollment, NLR at enrollment, bilirubin at enrollment, Cr at enrollment, INR at enrollment, new onset of ascites, new onset of HE, and new onset of infection.
Abbreviations: ALT, alanine aminotransferase; Cr, creatinine; GIH, gastrointestinal haemorrhage; INR, international normalized ratio; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet count; PLT, platelet count.

details of covariates are in Supplemental Table S6, http://links.lww.com/HC9/A713.

When predicting all states, the AUROC of the Markov model was 0.706 on day 21, following an increase to 0.74 on day 28 (Supplemental Figure S6A, http://links.lww.com/HC9/A713). All AUROCs improved when predicting only death, for example, to 0.92 from 0.75 on day 7 based on day 1. (Supplemental Figure S6A, http://links.lww.com/HC9/A713). All exact AUROCs can be found in Supplemental Table S7, http://links.lww.com/HC9/A713 and Supplemental Table S8, http://links.lww.com/HC9/A713. Compared to the traditional prognostic scores (MELDs, MELD-sodium score, CLIF-CONSORTIUM scores for patients with ACLFs, Sequential Organ Failure Assessments, Chinese Group on the Study of Severe Hepatitis B-ACLF score (COSSH-ACLFs), and COSSH-ACLF IIs), the Markov model showed the best discriminative performance(Supplemental Figure S6B, http://links.lww.com/HC9/A713). It was shown that there was a good fitness between the predicted and actual probabilities at each state in the derivation cohort by the χ2-test (Supplemental Table S9, http://links.lww.com/HC9/A713).

In the validation cohort (Supplemental Figure S7, http://links.lww.com/HC9/A713, Supplemental Table S10, 11, and 12, http://links.lww.com/HC9/A713), the AUROC of the Markov Model performed similarly to that in the derivation cohort. In particular, the AUROC reached 0.83 when predicting only death, significantly higher than all the traditional prognostic scores (MELDs, MELD-sodium score, CLIF-CONSORTIUM scores for patients with ACLFs, Sequential Organ Failure Assessments, COSSH-ACLFs, and COSSH-ACLF IIs).

Utility of the Markov model to predict individual risk of disease progression

With the model, a graph to predict the risk of disease progression at the individual level can be plotted (Figure 3). We randomly chose a case classified as ACLF-2 at admission to delineate the utility of this model. Based on day-1 status (Figure 3A), the probability of being in the state of non-ACLF was 44.64%, and death was 24.94% on day 28. When the patient's status worsened suddenly and progressed to ACLF-3 on day 7, the prediction was updated with the new information. Thus, the patient was predicted to have a much higher risk of 65.00% dying on day 28 (Figure 3B). And the patient died at the time point of day 14 (Figure 3C). Nevertheless, if the patient were able to

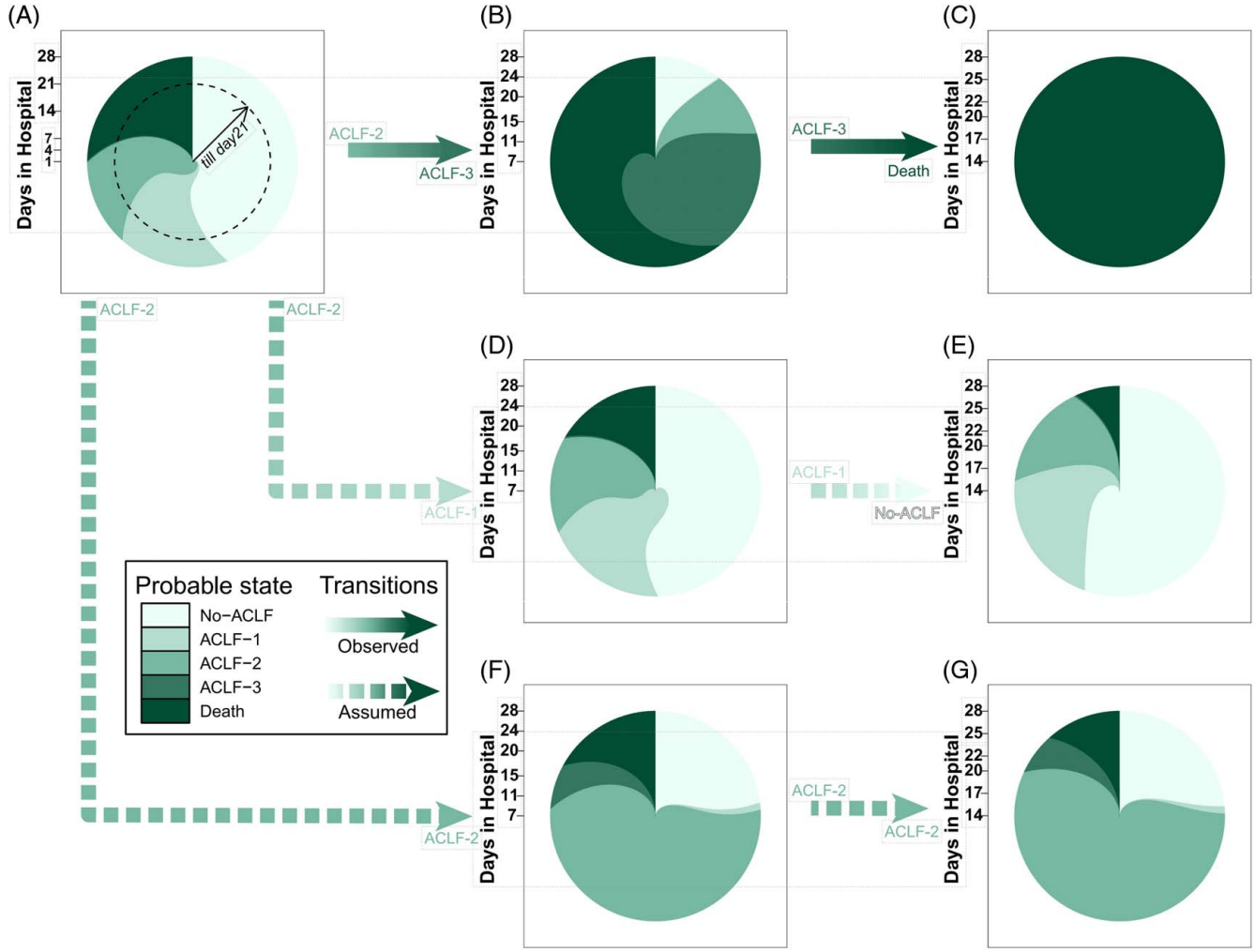

FIGURE 3 The dynamic outcome probability plot of a random patient generated from the Marcov model. To read this plot for day *t*, draw a circular line $x = t$, the length truncated by this line for each area was the patient's probability of being in this state. (A), (B), and (C) were the actual state and its corresponding prediction. (D–G) represented predicted states on the assumptions.

recover to ACLF-1 on day 7 (Figure 3D), the probability of ACLF resolution would be as high as 49.60%. Or, if keeping ACLF-2 on day 7 or day 14, the clinical trajectory within 28 days would most likely be a steady course (Figure 3F and G). For the convenience of clinical use, we developed a website application to visualize the individual risk. The website is as follows: http://101.42.177.184:3838/Markov/.

DISCUSSION

The present study revealed the differential clinical courses of HBV-ACLF by using a longitudinal prospective, multicenter cohort. Similar to ACLF with other aetiologies, HBV-ACLF is a highly dynamic syndrome, and the clinical course was associated with short-term outcomes of patients with HBV-ACLF. An assessment at day 4–7 better predict short-term outcome than the initial ACLF grade. Patients with ACLF progression had higher levels of systemic inflammation and a higher incidence of new onset of decompensation events. Based on the predictors of ACLF progression and death, we developed a Marcov model to predict dynamic changes in disease severity in patients with HBV-ACLF. The model estimates probabilities of the stabilization, progression, improvement, or resolution of ACLF for individual patients and can be used to predict the absolute risks of short-term mortality as well.

Reversibility is recognized as a hallmark of an "acute-on-chronic" condition in contrast to a chronic "end-stage" irreversible disease. As reported by the CANONIC study,[8] resolution occurred in 42.5% of overall patients with ACLF, respectively. And even patients with ACLF grade 3 represented a considerable rate of remission at 16.00%. In our study, a comparable rate of resolution was observed in patients with HBV-ACLF. Considering that patients with HBV-ACLF had more compensated cirrhosis than those in

the CANONIC study and each patient received etiology-specific anti-HBV therapy, it was surprising to see no higher reversibility in HBV-ACLF than ACLF with alcohol or HCV-related cirrhosis. The result may be biased by the discrepancy in the period between the initial and final assessment of ACLF grade between the 2 studies, though it was unlikely as the evolution of ACLF occurred very rapidly, as indicated by the CANONIC study and our study. Rather, it can be offset by an extraordinarily high rate of liver failure in patients with HBV-ACLF, which has been identified as an independent risk factor of ACLF progression in both our and the CANONIC study.[8] Actually, in our study, liver failure is generally the starting OF during disease progression, and the resolution of liver failure was associated with improved outcome even in patients with ACLF remission. Collectively, these findings validated the presence of reversibility, with a comparable degree to that reported in the CANONIC study, in HBV-ACLF under the EASL-CLIF definition.

A key issue was whether the reversibility within the short period of follow-up translated into the survival benefit. It was cleared by our findings that patients with ACLF resolution or improvement had a better short-term outcome than those with severe clinical course. However, the survival benefit was visible in patients with initial HBV-ACLF grades 1 and 2 but less significant in patients with initial ACLF grade 3 especially when the follow-up was expanded to the 90-day. It raised the concern that the standard care may prolong the course but could not reverse the final outcome when the state of ACLF fell into the very advanced stage, which suggested that patients with initial HBV-ACLF grade 3 should still consider the possibility for LT even showing an early resolution. On the other hand, although early LT improved 1-year and 3-year survival of HBV-ACLF grade 3, those patients had a higher post-LT mortality risk.[14]

Future multicenter, prospective, and large-scale studies were warranted to define the balance between the benefit and risk of transplantation in HBV-ACLF-3 grade, as well as specific priority strategies for those patients.

In line with recent studies,[15–18] our findings supported the central role of systemic inflammation in driving ACLF progression. The origin of systemic inflammation is believed to arise from bacterial infections or sterile inflammation caused by hepatic necrosis. Infections are frequent in ACLF and have been shown to be associated with intense systemic inflammation and poor clinical course.[19,20] In consistency, infections, either at enrollment or during the hospital stay, were identified as a key driver of HBV-ACLF progression in our study. Also, high ALT was identified as another independent risk factor of ACLF progression, which reflects liver injury and the associated sterile inflammation. Actually, both infection-related and sterile inflammation have been demonstrated to be potential therapeutic targets for ACLF progression or death. In addition, HE at enrollment or a new episode of HE was highlighted as a strong predictor of both HBV-ACLF progression and death. This finding was consistent with prior studies that showed prognosis was extremely poor in the patients with ACLF with HE, and the impact of HE on outcome was independent of other extrahepatic OFs.[21]

We developed a multi-state Markov Model to predict temporal changes in disease severity in patients with HBV-ACLF. The model estimates probabilities of progression, improvement, stabilization, or resolution of ACLF for individual patients and can be updated by status of ACLF at multiple time points. The model can also be used to predict the absolute risks of short-term death. Although our multi-state model showed only moderate overall discrimination, of which AUROC (day 1–day 28) was 0.66 in the validation dataset, it is worth noting that the commonly recognized AUROC, which is only used to predict dichotomized outcomes, should not be directly compared with our measure. Our AUROC of 0.66 is the discrimination for predicting 5 individual outcomes, so it is merely an “averaged” number. For instance, as already compared to all traditional diagnostic scores in our article, our model showed the most favorable accuracy when predicting only death, yet its discriminative ability fairly decreased when predicting ACLF-2. Of course, our study was unable to answer whether the Markov Model predicted disease progression or death in non-HBV cohort, and it should be further validated.

CONCLUSION

In summary, HBV-ACLF is a highly dynamic syndrome with preserving reversibility, particularly in the early stage. A progressive clinical course correlates better with a poor outcome than the initial ACLF grade, and prognosis can be more accurately predicted at 4–7 days after diagnosis by ACLF grade than initial ACLF grade. Coagulation failure was the major new OFs during ACLF early progression, followed by renal failure. HBV-ACLF progression was accompanied by a higher incidence of new ascites and HE, as well as worsening of systemic inflammation. Infection, high ALT and serum bilirubin at enrollment, and new onset of HE or infection were associated with disease progression. A Markov model updating ACLF status information predicted disease progression or death. Our findings may provide a rational basis for the understanding of the natural history of HBV-ACLF and a useful tool for management and identified drivers of ACLF exacerbation that may be therapeutic targets.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

AUTHOR CONTRIBUTIONS

Xia Yu, Xinxin Liu, Shan Yin, Wenyi Gu, Wenting Tan, Yi Zhou, Yixin Hou, Qun Zhang, Shue Xiong, Jing Liu, Ruochan Chen, Liyuan Long, Beiling Li, Xiuhua Jiang, Sen Luo, Yuanyuan Chen, Chang Jiang, Jinming Zhao, Liujuan Ji, Xue Mei, Jing Li, Tao Li, Rongjiong Zheng, Xinyi Zhou, and Haotang Ren collected and analysed the data; Yu Shi, Hai Li, Jifang Sheng, Guohong Deng, Xiaomei Xiang, Xianbo Wang, Xin Zheng, Yan Huang, Jinjun Chen, Zhongji Meng, Yanhang Gao, Zhiping Qian, Feng Liu, Xiaobo Lu, Jia Shang, Shaoyang Wang, Huadong Yan, Yubao Zheng, and Weituo Zhang designed the research study; Xia Yu and Xinxin Liu wrote the paper, Yu Shi, Hai Li, and Jifang Sheng critically reviewed the manuscript. All authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Renji Hospital Ethics Committee of Shanghai Jiao Tong University School of Medicine (NCT02457637 and NCT03641872). The patients/participants provided their written informed consent to participate in this study.

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