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ORIGINAL RESEARCH

CHINAT-CD4 Score Predicts Transplant-Free Survival in Patients with Acute-on-Chronic Liver Failure

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Aim: The early prognosis evaluation of acute-on-chronic liver failure (ACLF) is important to decrease its mortality. We aimed to develop a new score to accurately predict the outcome of patients with ACLF.

Methods: A derivation set of 408 patients with hepatitis B virus-related ACLF (HBV-ACLF) based on the Asian Pacific Association for the Study of the Liver criteria is used to develop a prognostic score that was validated in 209 patients with HBV-ACLF and 195 patients with non-HBV-ACLF.

Results: Seven factors were significantly related to the 28-day mortality and constituted a new score (CHINAT-CD4 = 0.320 × ln (creatinine) + 0.668 × hepatic encephalopathy score + 0.745 × ln (international normalized ratio) + 0.476 × ln (neutrophil) + 0.251 × ln (aspartate aminotransferase) + 0.411 × ln (total bilirubin) - 0.605 × ln (CD4+ T cells count)). The C-indices of the new score for the 28-/90-day mortality (0.810/0.806) outperformed those of the other seven scores ($p \leq 0.05$). The results were confirmed in a validation set (0.798/793 for HBV-ACLF; 0.790/0.788 for non-HBV-ACLF). The novel score based on $CD4^+$ T cell count showed high predictive performance for the 28-/90-day mortality of ACLF.

Conclusion: The novel score based on $CD4^+$ T cell count can accurately predict the 28-/90-day mortality for patients with ACLF.

Keywords: liver failure, chronic liver disease, prognostic score, risk stratification, inflammatory markers

Introduction

Acute-on-chronic liver failure (ACLF) is an entity where acute hepatic decompensation occurs in patient with chronic liver disease or cirrhosis resulting in a high mortality.[1] Globally, hepatitis B reactivation remains the main cause of ACLF in the East.[2] Early evaluation of potential predictors can be helpful for managing patients with ACLF.[3] Therefore, score that enables early and accurate risk stratification is needed for the prognosis evaluation of patients with ACLF.

Disease severity scores such as MELD and MELD-Na have been used for the prognosis evaluation of patients with severe liver disease. However, MELD and MELD-Na do not take into account respiratory failures, circulatory failures, and cerebral function disorder, thus giving no priority to ACLF patients.[4] The ICU scores like SOFA, CLIF-SOFA, and CLIF-C OF have also been used for the evaluation of patients with ACLF.[5] However, the ICU scores were arbitrarily formulated and included patients with and without hepatic insults.[6] In addition, the ICU scores are predictive of mortality only in cases that extra-hepatic organ failures are included.[1]

The Chronic Liver Failure (CLIF) Consortium developed a specific prognostic score for ACLF (CLIF-C ACLFs) in alcoholic liver disease or hepatitis C virus (HCV)-related populations.[7] However, hepatitis B virus (HBV)-associated ACLF (HBV-ACLF) exhibits clinical characteristics different from those of alcoholic liver disease or HCV-related

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ACLF. Therefore, the Chinese Group on the Study of Severe Hepatitis B (COSSH) study proposed that regardless of the presence of cirrhosis, patients with chronic hepatitis B (CHB), total bilirubin (TBIL) ≥12 mg/dL and an INR ≥ 1.5 should be included in the ACLF definition.[8] Compared with the EASL-ACLF, the COSSH-ACLF identified 20% more HBV-related ACLF patients.[8] AARC score which includes grade of HE, INR, TBIL, lactate and creatinine reliably predicts the severity and clinical outcome of patients with ACLF.[1] The AARC score has been found to be superior to SOFA, CLIF-SOFA, and MELD for assessing the severity of patients with ACLF.[9]

HBV-related ACLF is a common disease in the Asia-Pacific, especially in China. A few studies have reported the prognostic scoring system for HBV-related ACLF patients.[1,8] In this study, based on 617 patients with HBV-related ACLF in China, we did a retrospective cohort study to identify powerful prognostic factors to ACLF and developed a novel prognostic score, which is meaningful for management of patients with HBV-ACLF.

Methods

Study Population

In the retrospective cohort study, we screened out patients with chronic liver disease or compensated cirrhosis who were hospitalized at Shanghai Public Health Clinical Center between January 1, 2014, and December 30, 2019. Patients who met the Asian Pacific Association for the Study for the Liver (APASL)-ACLF criteria were enrolled.[1] Patients with pregnant, hepatocellular carcinoma, other malignancies, severe extra-hepatic disease, or patients who receiving immunotherapy were excluded. Finally, 617 patients with HBV-related ACLF were enrolled. Among the 617 patients with HBV-ACLF, 54 patients (8.8%) combined with alcoholic liver disease, 35 patients (5.7%) combined with drug-induced liver injury, 30 patients (4.9%) combined with autoimmune liver disease, and 15 patients (2.4%) combined with hepatitis E virus or hepatitis A virus infection. The 408 patients with HBV-related ACLF admitted to hospital between January 1, 2014, and December 30, 2017, constituted the derivation set. The 209 HBV-related ACLF patients admitted to hospital between September 1, 2018, and December 30, 2019, and 195 patients with non-HBV-ACLF constituted the validation set (Figure 1). In the validation cohort, the constitute of

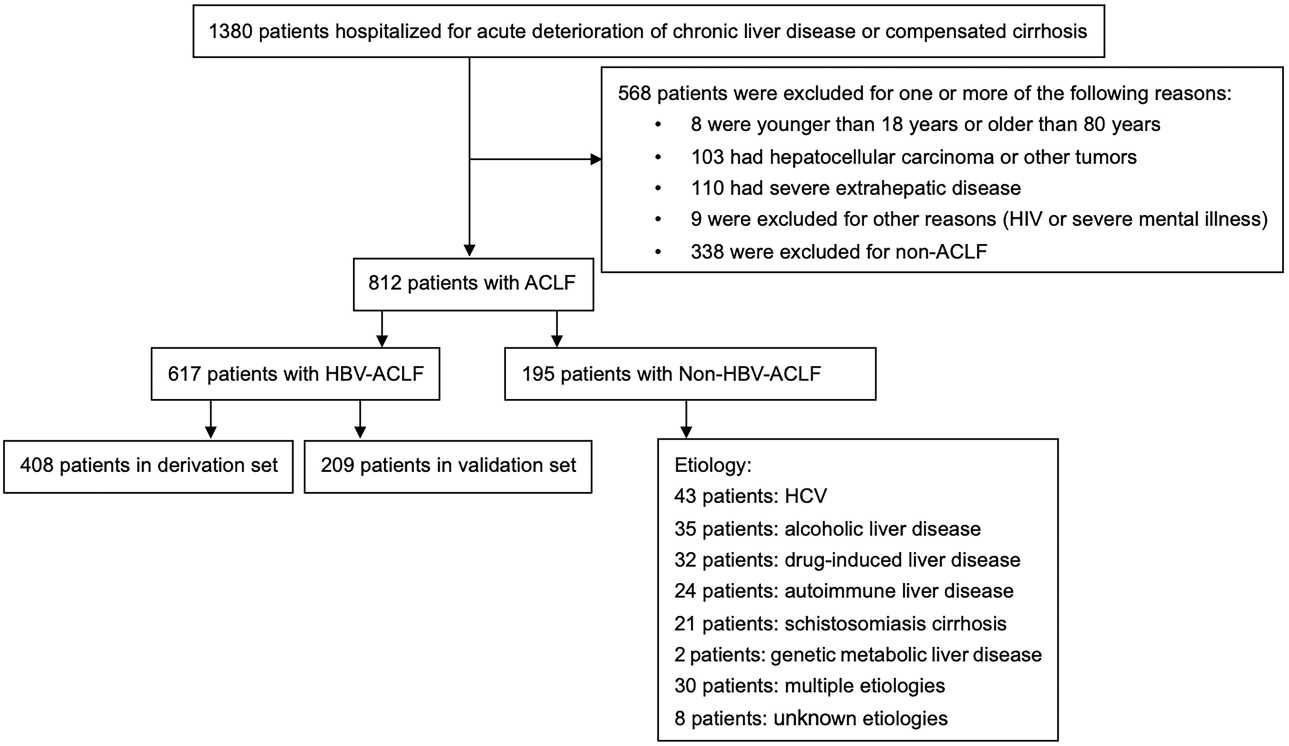

Figure 1 Screening of patients according to the APASL-ACLF criteria.
Abbreviations: ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; HBV-ACLF, HBV-related ACLF; HIV, Human Immunodeficiency Virus; HCV, hepatitis C virus.

etiologies of 195 patients with non-HBV-ACLF were as follows: (1) HCV, 43 patients (22.1%); (2) alcoholic liver disease, 35 patients (18.0%); (3) drug-induced liver injury, 32 patients (16.4%); (4) autoimmune liver disease, 24 patients (12.3%); (5) schistosomiasis cirrhosis, 21 patients (10.8%); (6) genetic metabolic liver disease, 2 patients (1.0%); (7) multiple etiologies, 30 patients (15.4%); (8) unknown etiologies, 8 patients (4.1%). Definitions related to organ failure and bacterial infection are provided in Supplementary Methods 1.

Patients Management

We managed these patients following the ACLF consensus recommendations of the APASL[1] and the practice guideline for liver transplantation in China.[10] Based on the guidelines,[1,10] every patient with ACLF would be assessed for disease severity score, presence of SIRS with or without sepsis, HE and number of organ failure at admission. The baseline MELD > 28, AARC > 10, advanced HE in the absence of overt sepsis or multi-organ failure would be considered for early liver transplant. In the absence of liver transplant, patients would be offered early bridge therapies in the form of therapeutic plasma exchange and liver dialysis. Nucleos(t)ide analogs such as tenofovir, tenofovir alafenamide or entecavir would be started immediately in all HBV-infected patients.

Calculation of Prognostic Assessment Models

1. COSSH- ACLFs II = 1.649×ln (INR)+0.457×HE score +0.425×ln (neutrophil)+0.396×ln (TBIL) +0.576×ln (serum urea) +0.033×age).
2. COSSH-ACLF = (0.741×INR+0.523×HBV SOFA+0.026×age+0.003×TBIL).
3. CLIF- C ACLFs = 10 × (0.33×CLIF-C OFs+0.04×age+0.63×ln (WBC)–2).
4. MELD = 96 ×Ln creatinine + 3.8 × Ln bilirubin + 11.2 ×Ln (INR) + 6.4 × etiology (1 for viral hepatitis, and 0 for non-viral liver disease).
5. MELD-Na = MELD − Na − (0.025 × MELD × (140 − Na)) +140; the serum sodium concentration was between 125 and 140 mmol/L.
6. HINT = 1.48 × HE + 3.92 × ln (INR) + 0.73 × ln (neutrophil) −0.46 × ln (TSH) −5.78. HE = 0 for without HE, 1 for mild HE (grade 1-2), and 2 for severe HE (grade 3-4).
7. AARC = TBIL + HE grade + PT-INR + Lactate + Creatinine. 1 for Total bilirubin <15, 2 for Total bilirubin ≥15 and ≤25, and 3 for total bilirubin >25. 1 for without HE, 2 for mild HE (grade 1-2), and 3 for severe HE (grade 3-4). 1 for PT-INR<1.8, 2 for PT-INR≥1.8 and ≤2.5, and 3 for PT-INR>2.5. 1 for lactate <1.5, 2 for lactate ≥0.5 and ≤2.5, and 3 for lactate >2.5. 1 for creatinine<0.7, 2 for creatinine≤0.7 and ≤1.5, and 3 for creatinine > 1.5.

Statistical Analysis

Variance inflation factors (VIFs) were calculated to test collinearity. Variables with VIF greater than 10 were dropped (Supplementary Table 1). The significant baseline factors were prefiltered in univariate Cox proportional hazard models to identify risk factors related with the 28-day mortality of patients with ACLF. The least absolute shrinkage and selection operator (LASSO) was used to the model.[11] Multivariate Cox PH models were fitted with a both stepwise selection method using variables selected for the PH-LASSO model. The performance of the new score was compared with seven other common scores. The C-index was reported to assess discriminative ability. The optimal cut-off value for low-risk, intermediate-risk and high-risk of death were determined by X-tile software (version 3.6.1; Yale University, New Haven, CTA). The X-tile software identified the optimal thresholds by selecting the largest $\chi 2$ value.[12] All tests were two-tailed, and statistically significant was defined as $p < 0.05$. The data were processed in IBM SPSS Statistics, version 23 (IBM Corp, North Castle, NY), and R software, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Other statistical analysis methods are described in Supplementary Methods 1.

Results

Clinical Characteristics

In the derivation set, the characteristics associated with the 28-day mortality were alanine aminotransferase (ALT), AST, TBIL, albumin, globulin, WBC, neutrophils, lymphocytes, INR, CD3+ T cell count, CD8+ T cell count, CD4+ T cell count, and CD45+ T cell count (Table 1). No significant difference was found in baseline characteristics between the derivation set and the validation set (Supplementary Table 2). The acute insults of 408 patients with HBV-related ACLF in the derivation set are are shown in Table 1: (1) HBV reactivation, 278 patients (68.1%); (2) acute drinking, 39 patients (9.6%); (3) hepatotoxic drugs, 22 patients (5.4%); (4) autoimmune liver disease activation, 19 patients (4.7%); (5) bacterial infections, 8 patients (2.0%); (6) superimposed HEV infection, 7 patients (1.7%); (7) superimposed HAV infection, 3 patients (0.7%); (8) unknown insults, 32 patients (7.8%). The organ failures of 408 patients with HBV-related ACLF in the derivation set are shown in Table 1: (1) liver, 278 patients (68.1%); (2) coagulation system, 166 patients (40.7%); (3) cerebral, 71 patients (17.4%); (4) kidney, 24 patients (5.9%); (5) circulation, 3 patients (0.7%); (6) lung, 2 patients (0.5%).

Table 1 Clinical Characteristics of Patients with HBV-ACLF in the Derivation Set

Characteristic	Overall (n=408)	Deceased† (n=155)	Alive† (n=253)	*p* value
Male, n (%)	347 (85.0%)	131 (84.5%)	216 (85.4%)	0.813
Age, (years)	48 (39, 58)	49 (40, 60)	47 (38, 55)	0.113
Precipitating events, n (%)				0.312
HBV reactivation	278 (68.1%)	101 (65.2%)	177 (70.0%)	
Active drinking	39 (9.6%)	15 (9.7%)	24 (9.5%)	
Hepatotoxic drugs	22 (5.4%)	11 (7.1%)	11 (4.3%)	
ALD activation	19 (4.7%)	8 (5.2%)	11 (4.3%)	
Bacterial infection	8 (2.0%)	6 (3.9%)	2 (0.8%)	
Superimposed HEV	7 (1.72%)	2 (1.29%)	5 (1.98%)	
Superimposed HAV	3 (0.74%)	1 (0.64%)	2 (0.79%)	
Unknown	32 (7.8%)	10 (6.5%)	22 (8.7%)	
Organ failure, n (%)				<0.001
Liver	278 (68.1%)	135 (87.1%)	143 (56.5%)	
Coagulation	166 (40.7%)	94 (60.6%)	72 (28.5%)	
Cerebral	71 (17.4%)	56 (36.1%)	15 (5.9%)	
Kidney	24 (5.9%)	20 (12.9%)	4 (1.6%)	
Circulation	3 (0.7%)	3 (1.9%)	0	
Lung	2 (0.5%)	2 (1.3%)	0	
ALT, (IU/L)	145 (54, 601)	255 (81, 924)	101 (48, 392)	<0.001
AST, (IU/L)	143 (78, 426)	193 (100, 623)	123 (64, 279)	<0.001
TBIL, (μ mol/L)	310 (155, 481)	397 (256, 563)	238 (105, 419)	<0.001
ALB, (g/L)	33 (29, 36)	31 (28, 35)	33 (30, 37)	0.005
GLB, (g/L)	27 (23, 32)	27 (22, 32)	28 (23, 32)	0.049
Cr, (μmol/L)	65 (54, 81)	66 (53, 93)	64 (54, 78)	0.147
WBC, (10^9/L)	6.3 (4.5, 9.3)	6.5 (3.7, 10.1)	5.7 (4.1, 7.9)	<0.001
Neutrophils, (10^9/L)	4.3 (2.7, 7.1)	4.4 (2.8, 6.5)	3.7 (2.4, 5.6)	<0.001
Lymphocytes, (10^9/L)	1.1 (0.7, 1.6)	1.0 (0.7, 1.4)	1.2 (0.8, 1.6)	0.014
INR	2.3 (1.9, 3.2)	2.8 (2.2, 4.1)	2.1 (1.7, 2.6)	<0.001
PCT (ng/mL)	0.8 (0.4, 1.8)	0.9 (0.5, 1.8)	0.6 (0.3, 1.6)	0.007
Lymphocyte subsets (cells/ul)				
CD3+ T cells	817 (499, 1114)	681 (436, 983)	881 (555, 1164)	0.001
CD8+ T cells	288 (163, 446)	245 (143, 434)	306 (172, 455)	0.031
CD4+ T cells	439 (267, 640)	360 (254, 529)	475 (297, 681)	<0.001
CD45+ T cells	1166 (795, 1588)	1009 (695, 1472)	1271 (866, 1679)	0.001

Note: †28-day Transplant-Free Survival.

Abbreviations: HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; HBV, hepatitis B virus; ALD, autoimmune liver disease; HEV, hepatitis E virus; HAV, hepatitis A virus; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; ALB, Albumin; GLB, Globulin; Cr, Creatinine; WBC, white blood cell count; INR, international normalized ratio; PCT procalcitonin.

Development of the CHINAT-CD4 Score

Univariate cox analysis indicated that age, AST, TBIL, globulin, creatinine, serum urea, sodium, WBC, neutrophil, INR, lactate, procalcitonin, CD3+ T cell count, CD4+ T cell count, CD8+ T cell count, and CD45+ T cell count, total cholesterol, LDL-C, HE, cirrhosis and GI haemorrhage were significantly associated with the 28-day mortality (Supplementary Table 3). Penalized variable selection for the PH model with LASSO analysis selected 11 independent risk factors (age, AST, TBIL, creatinine, neutrophil, INR, CD4+ T cells, total cholesterol, lactate, HE, GI haemorrhage) that were significantly associated with 28-day mortality (Supplementary Table 4). Multivariate Cox analysis selected seven independent risk factors (AST, TBIL, creatinine, neutrophils, INR, CD4+ T cells, and HE) that were significantly associated with the 28-day mortality (Table 2). The new prognostic score was fitted by multivariate Cox analysis: CHINAT-CD4= 0.320 × ln (Cr) (umol/L) + 0.668 × HE score + 0.745 × ln (INR) + 0.476 × ln (neutrophil) (10^9/L) + 0.251 × ln (AST) (IU/L) + 0.411 × ln (TBIL) (umol/L) - 0.605 × ln (CD4+ T cell count) (cells/ul). HE score=1 for without HE, 2 for mild HE (grade 1-2), and 3 for severe HE (grade 3-4).

Discrimination of the CHINAT-CD4 Score

The discrimination of the CHINAT-CD4 score was measured by the C-index. The C-index values of the CHINAT-CD4 score for the 28-/90-day mortality (0.810/0.806) were significantly higher than those of the seven other scores (COSSH-ACLFs II: 0.778/0.774, p=0.005/p=0.005; COSSH-ACLFs: 0.764/0.761, p<0.001/p<0.001; CLIF-C ACLFs: 0.753/0.746, p<0.001/p<0.001; MELD: 0.729/0.727, p<0.001/p<0.001; MELD-Na: 0.721/0.720, p<0.001/p<0.001; HINT: 0.769/0.764, p<0.001/p<0.001; AARC: 0.761/762, p<0.001/p<0.001) (Table 3).

Risk Stratification

The two optimal cutoff values (4.2 and 5.5) of the CHINAT-CD4 score to separate patients with HBV-ACLF into low-risk (<4.2), intermediate-risk (4.2–5.5), and high-risk (≥5.5) groups of the 28-/90-day mortality. The 28-/90-day mortality ratios of each group were significantly different (low-risk, 20.7%/26.6%; intermediate-risk, 57.3%/67.4%; high-risk, 100%/100%, p<0.001) (Figure 2A and B).

Validation of the CHINAT-CD4 Score

The 209 patients with HBV-related ACLF and 195 patients with non-HBV-ACLF were used to validate the CHINAT-CD4 score. The baseline characteristics of patients with non-HBV-ACLF are shown in Supplementary Table 5. The C-index values of the CHINAT-CD4 score for the 28-/90-day mortality (0.798/0.793) were obvious higher than those of COSSH-ACLFs II (0.740/0.736, p=0.006/p=0.005), COSSH-ACLFs (0.742/0.737, p=0.003/p=0.003), CLIF-C ACLFs (0.733/0.730, p=0.010/p=0.011), MELD (0.720/0.713, p<0.001/p<0.001), MELD-Na (0.719/0.713, p<0.001/p<0.001, HINT (0.758/0.754, p = 0.040/p = 0.047) and AARC (0.755/0.749, p = 0.019/ p = 0.016) (Table 4). In the validation set of 195 non-HBV-ACLF patients, the performance of the CHINAT-CD4 score is similar to that of COSSH-ACLFs II,

Table 2 Seven Risk Factors Associated with the 28-Day Mortality in Patients with HBV-ACLF

Variables	HR [95% CI]	*p* value
Ln (AST)	1.286 (1.101–1.502)	0.002
Ln (TBIL)	1.509 (1.176–1.935)	0.001
Ln (Cr)	1.377 (1.047–1.811)	0.022
Ln (Neutrophil)	1.609 (1.253–2.067)	<0.001
Ln (INR)	2.107 (1.635–2.715)	<0.001
Ln (CD4+ T cells)	0.546 (0.425–0.701)	<0.001
HE	1.951 (1.600–2.378)	<0.001

Abbreviations: HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; HR, hazard ratio; CI, confidence interval; AST, Aspartate aminotransferase; TBIL, Total bilirubin; Cr, Creatinine; INR, international normalized ratio; HE, hepatic encephalopathy.

Table 3 The C-Index of Prognostic Scores for Predicting the 28-/90-Day Mortality in the Derivation Set

Mortality	CHINAT-CD4	COSSH-ACLF IIs	COSSH-ACLFs	CLIF-C ACLFs	MELD	MELD-Na	HINT	AARC
28-day	0.810 (0.778–0.843)	0.778 (0.742–0.815)	0.764 (0.727–0.801)	0.753 (0.716–0.790)	0.729 (0.690–0.768)	0.721 (0.683–0.760)	0.769 (0.729–0.809)	0.761 (0.726–0.796)
*p value		0.005	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
90-day	0.806 (0.774–0.838)	0.774 (0.739–0.810)	0.761 (0.725–0.797)	0.746 (0.710–0.783)	0.727 (0.690–0.765)	0.720 (0.683–0.757)	0.764 (0.725–0.803)	0.762 (0.728–0.796)
*p value		0.005	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: *p value for comparisons between the CHINAT-CD4 score and the other scores.

Abbreviations: COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B-ACLF score; CLIF-C ACLFs, CLIF-Consortium Acute-on-Chronic Liver Failure score; MELD, Model for End-Stage Liver Disease score; MELD-Na, MELD-sodium score; HINT, HINT score; AARC score, APASL ACLF research consortium liver failure score which includes total bilirubin, INR, grade of HE, plasma lactate and serum creatinine reliably predicts the disease severity and outcome.

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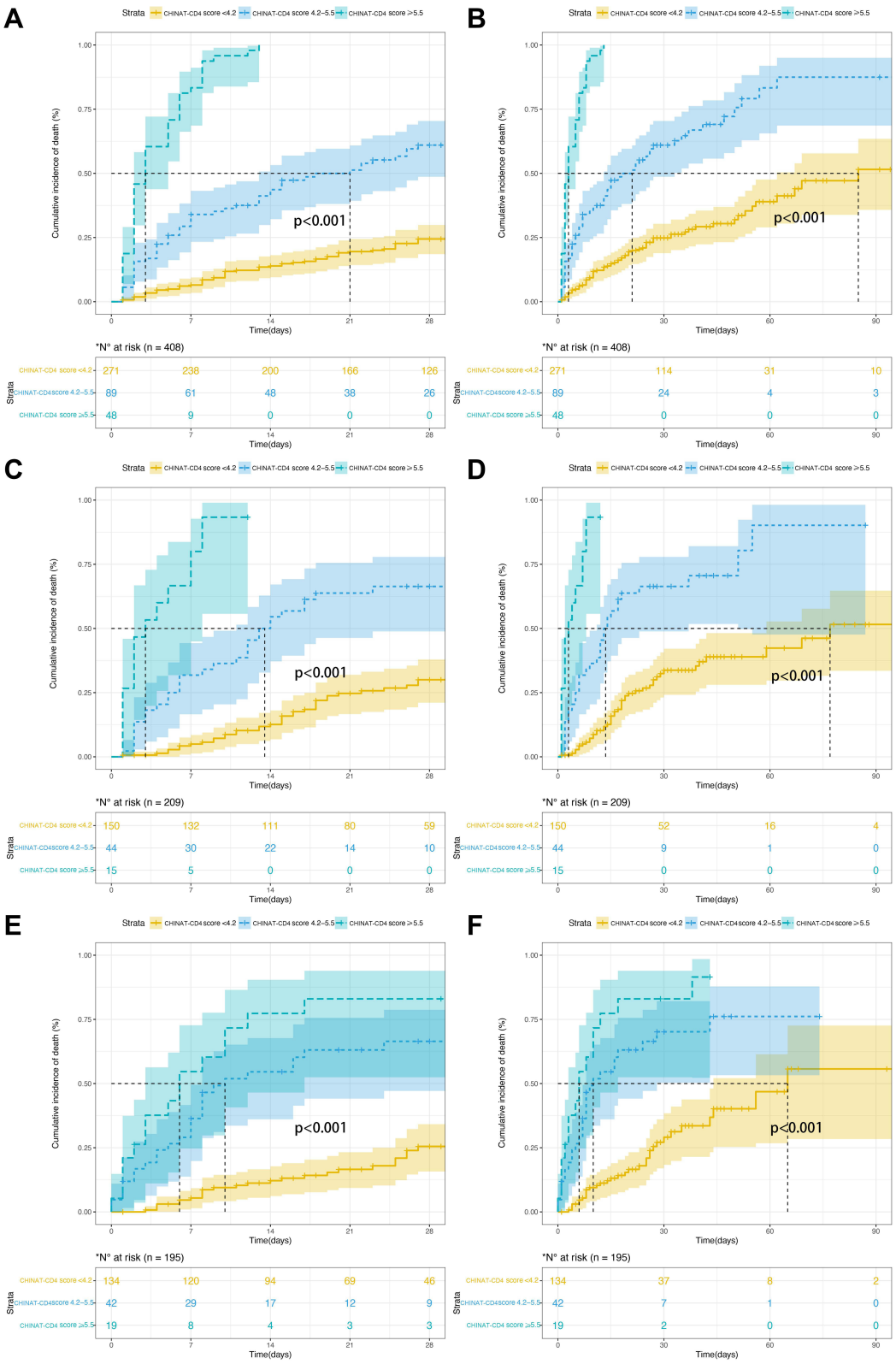

Figure 2 Risk stratification of the CHINAT-CD4 score. (**A**) The derivation set for 28-day mortality, (**B**) The derivation set for 90-day mortality, (**C**) The validation set of HBV-ACLF for 28-day mortality, (**D**) The validation set of HBV-ACLF for 90-day mortality, (**E**) The validation set of non-HBV-ACLF for 28-day mortality, (**F**) The validation set of non-HBV-ACLF for 90-day mortality. *Number of liver transplant-free patients.

Table 4 The C-Index of Prognostic Scores for Predicting the 28-/90-Day Mortality in the Validation Set

Mortality	CHINAT-CD4	COSSH-ACLF IIs	COSSH-ACLFs	CLIF-C ACLFs	MELD	MELD-Na	HINT	AARC
Validation set of HBV-ACLF								
28-day	0.798 (0.751–0.845)	0.740 (0.686–0.795)	0.742 (0.687–0.796)	0.733 (0.680–0.785)	0.720 (0.664–0.777)	0.719 (0.665–0.773)	0.758 (0.704–0.811)	0.755 (0.704–0.806)
*p value		0.006	0.003	0.010	<0.001	<0.001	0.040	0.019
90-day	0.793 (0.747–0.839)	0.736 (0.683–0.789)	0.737 (0.684–0.790)	0.730 (0.678–0.781)	0.713 (0.659–0.768)	0.713 (0.660–0.766)	0.754 (0.701–0.807)	0.749 (0.699–0.800)
*p value		0.005	0.003	0.011	<0.001	<0.001	0.047	0.016
Validation set of Non-HBV-ACLF								
28-day	0.790 (0.738–0.842)	0.780 (0.725–0.834)	0.783 (0.730–0.835)	0.745 (0.682–0.808)	0.764 (0.708–0.820)	0.749 (0.688–0.810)	0.754 (0.695–0.814)	0.795 (0.743–0.847)
*p value		0.628	0.673	0.092	0.288	0.152	0.037	0.639
90-day	0.788 (0.737–0.839)	0.779 (0.727–0.832)	0.781 (0.730–0.833)	0.743 (0.683–0.804)	0.760 (0.706–0.815)	0.742 (0.682–0.801)	0.755 (0.697–0.813)	0.794 (0.743–0.846)
*p value		0.668	0.699	0.081	0.251	0.092	0.053	0.682

Note: *p value for comparisons between the CHINAT-CD4 score and the other scores.

Abbreviations: HBV-ACLF, HBV-related acute-on-chronic liver failure; COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B-ACLF score; CLIF-C ACLFs, CLIF-Consortium Acute-on-Chronic Liver Failure score; MELD, Model for End-Stage Liver Disease score; MELD-Na, MELD-sodium score; HINT, HINT score; AARC score, APASL ACLF research consortium liver failure score which includes total bilirubin, INR, grade of HE, plasma lactate and serum creatinine reliably predicts the disease severity and outcome.

COSSH-ACLFs, CLIF-C ACLFs, MELD, MELD-Na, HINT and AARC for the prediction of the 28-day mortality ($p>0.05$) and the 90-day mortality ($p>0.05$) (Table 4). The risk stratification also showed the simpler predictive performance (Figure 2C–F).

Discussion

The aim of this study was to develop an appropriate prognostic score for HBV-related ACLF based on the APASL criteria. Our results showed that the CHINAT-CD4 score, which includes the INR, creatinine levels, HE score, neutrophil counts, AST levels, total bilirubin levels, and CD4+ T cells counts had the highest prognostic value for predicting the 28/90 days mortalities of patients with HBV-related ACLF among the eight scoring systems. Among these factors, ALT, TBIL, Cr, INR and HE are associated with liver, kidney failure, coagulation and cerebral dysfunction, respectively. Although the difference of baseline Cr might be not significant at admission between survivors and non-survivors (Table 1). In the present study, the prevalence of kidney failure is higher in survivors than that in non-survivors (12.9% vs 1.6%, $p<0.001$) (Table 1), which supported that kidney failure is one of vital extrahepatic failed organs.

In this study, a retrospective cohort further validated the prognostic value of the new CHINAT-CD4 score for 209 patients with HBV-related ACLF and 195 non-HBV-ACLF patients. In the validation set of 209 HBV-related ACLF patients, the prognostic performance of the CHINAT-CD4 score had the highest prognostic value for predicting the 28/90 days mortalities ($p<0.05$). In the validation set of 195 non-HBV-ACLF patients, the prognostic value of the CHINAT-CD4 score is similar to that of other seven scores for predicting the 28-day and the 90-day mortality ($p>0.05$). Although no statistical significance was observed between the new CHINAT-CD4 score and the other scores ($p>0.05$), the CHINAT-CD4 score provides an accurate prognosis for predicting the 28-day mortality (C-index, 0.790) and the 90-day mortality (C-index, 0.788), and also may help predict the severity of patients with non-HBV-related ACLF.

In this study, the numbers of CD4+ T cells was significantly associated with the mortality. Similar to severe sepsis, there exists a degree of cellular immune depression in patients with HBV-related ACLF, which might contribute to the increased morbidity.[13] The typical evidence of "sepsis-like" immune paralysis was the functional inactivation of circulating monocytes.[14–18] A reduction in CD4+T cells, mainly CD4+CD25$^{-/+}$T cells, constitutes important characteristics of immune dysfunction of patients with HBV-related ACLF.[19] Using a prospective study of 45 patients with HBV-related ACLF, Li et al found that proportions of CD200R+CD4+T cells exhibited significant differences between the survival group and the non-survival group.[20] Additionally, previous studies demonstrated CD4+CD25+ T-regulatory cells were independent risk factors for patients with ACLF.[21,22]

Some previous studies also investigated the relationship between CD4+ T cells count and HBV-ACLF outcomes. Wang et al reported that patients with HBV-related ACLF had dysfunction of immune system, and the T cells can predict the prognosis in HBV-related ACLF patients.[22] Zhai et al found that the ratio of Th-17 to Treg cells was associated negatively with the survival of ACLF patients.[23] The possible pathological mechanism how the CD4(+) T cells affect the prognosis of ACLF has also been reported. Du et al reported that naïve CD4$^+$ T cells differentiate into Tfh cells in the presence of HBV-ACLF patients' serum rich in IL-12/21, which can be blocked by neutralizing IL-12/21 antibodies.[24] Xu et al reported that TLR2 expression in peripheral CD4+ T Cells promotes Th17 response and is associated with disease aggravation of HBV-related ACLF.[25] Zhang et al found that IL-17-producing CD4(+) T cells increase with severity of liver damage in patients with HBV-related ACLF.[26]

The new CHINAT-CD4 score, which includes the INR, creatinine levels, HE score, neutrophil counts, AST levels, total bilirubin levels, and CD4+ T cells counts, might be modified by specific treatment of ACLF such as antiviral treatment, plasma exchange and liver dialysis. Antiviral therapy may improve AST levels and thus modify the score. Plasma exchange and liver dialysis may improve total bilirubin levels and the INR, and then modify the score. Therefore, in this study, the baseline CHINAT-CD4 score rather than any dynamic CHINAT-CD4 score is suggested to predict the 28-day mortality and the 90-day mortality of patients with ACLF.

In conclusion, this study demonstrated that the CHINAT-CD4 score can accurately predict the short-term mortality not only in patients with HBV-ACLF but also in patients with non-HBV-ACLF. It may be used to help liver transplantation decision-making and guide patient management, However, the CHINAT-CD4 score needs to be validated in prospective studies or multi-center big-sample studies.

Abbreviations

ACLF, acute-on-chronic liver failure; HCV, hepatitis C virus; CLIF-C, Chronic Liver Failure Consortium; COSSH, Chinese Group on the Study of Severe Hepatitis B; HBV-ACLF, hepatitis B virus-related ACLF; Cr, creatinine; HE, hepatic encephalopathy; INR, international normalized ratio; AST, aspartate aminotransferase; TB, total bilirubin; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; PH, proportional hazard; HR, hazard ratio; VIF, variance inflation factor; SD, standard deviation; IQR, interquartile range; ALT, alanine aminotransferase; WBC, white blood cell count.

Ethical Statement

The study protocol was approved by the clinical research ethics committee of the Shanghai Public Health Clinical Center. All patients signed the informed consents. The procedures were performed in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association. Written informed consents were obtained from all patients.

Consent for Publication

All authors read and approved the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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