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ORIGINAL ARTICLE

Prospective Study

sTREM-1 as promising prognostic biomarker for acute-on-chronic liver failure and mortality in patients with acute decompensation of cirrhosis

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Abstract

BACKGROUND

Acute decompensation (AD) of cirrhosis is associated with high short-term mortality, mainly due to the development of acute-on-chronic liver failure (ACLF). Thus, there is a need for biomarkers for early and accurate identification of AD patients with high risk of development of ACLF and mortality. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is released from activated innate immune cells and correlated with various inflammatory processes.

AIM

To explore the prognostic value of sTREM-1 in patients with AD of cirrhosis.

METHODS

A multicenter prospective cohort of 442 patients with cirrhosis hospitalized for AD was divided into a study cohort (n = 309) and validation cohort (n = 133). Demographic and clinical data were collected, and serum sTREM-1 was measured at admission. All enrolled patients were followed-up for at least 1 year.

RESULTS

In patients with AD and cirrhosis, serum sTREM-1 was an independent prognosis predictor for 1-year survival and correlated with liver, coagulation, cerebral and kidney failure. A new prognostic model of AD (P-AD) incorporating sTREM-1, blood urea nitrogen (BUN), total bilirubin (TBil), international normalized ratio (INR) and hepatic encephalopathy grades was established and performed better than the model for end-stage liver disease (MELD), MELD-sodium (MELD-Na), chronic liver failure-consortium (CLIF-C) ACLF and CLIF-C AD scores. Additionally, sTREM-1 was increased in ACLF and predicted the development of ACLF during first 28-d follow-up. The ACLF risk score incorporating serum sTREM-1, BUN, INR, TBil and aspartate aminotransferase levels was established and significantly superior to MELD, MELD-Na, CLIF-C ACLF, CLIF-C AD and P-AD in predicting risk of ACLF development.

CONCLUSION

Serum sTREM-1 is a promising prognostic biomarker for ACLF development and mortality in patients with AD of cirrhosis.

Key Words: Soluble triggering receptor expressed on myeloid cell-1; Acute decompensation; Cirrhosis; Acute-on-chronic liver failure; Prognostic biomarker

Core Tip: Acute decompensation (AD) of cirrhosis is associated with high short-term mortality, mainly due to development of acute-on-chronic liver failure (ACLF). serum Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is an independent risk factor for development of ACLF and mortality in patients with AD of cirrhosis. The new prognostic model of AD (P-AD) and the ACLF risk score (ACLF-R) were established and performed better than currently available prognostic models in predicting 1-year mortality and 28-d ACLF development in patients with AD of cirrhosis. Serum sTREM-1 Level, P-AD and ACLF-R score will facilitate clinical decision-making in the management of AD of cirrhosis.

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INTRODUCTION

Acute decompensation (AD) of cirrhosis is acute deterioration of pre-existing cirrhosis[1]. As the disease progresses, a severe syndrome hallmarked by intense systemic inflammatory response, multiorgan failure and high short-term mortality is observed and defined as acute-on-chronic liver failure (ACLF)[2]. The prognosis of AD with or without ACLF is significantly different. Hence, early and accurate biomarkers are required to identify AD patients with a high risk of development of ACLF and mortality, to improve the management and outcomes. Despite extensive research, few biomarkers can satisfactorily solve these challenges[3,4]. Therefore, further investigation is warranted to find novel biomarkers for accurate risk stratification of patients with AD of cirrhosis.

Infections and sepsis contribute to poor prognosis in AD patients with or without ACLF[1,5]. Triggering receptor expressed on myeloid cells-1 (TREM-1) is a pattern recognition receptor (PRR) and member of the immunoglobulin superfamily, which is mainly expressed on the surface of immune cells. TREM-1 is a crucial mediator of bacterial infection (BI) and septic shock that acts by synergizing with other PRRs to amplify the inflammatory responses[6,7]. Soluble TREM-1 (sTREM-1), the extracellular portion of TREM-1, is cleaved by metalloproteinases and released during inflammation[8]. sTREM-1 has been explored as a biomarker for the diagnosis and prognosis of BIs and sepsis[7,9-11].

Previous studies have demonstrated that sTREM-1 has high diagnostic value for sepsis in patients with ACLF[12]. In addition, sTREM-1 Levels perform well in identifying BI and predicting 90-d mortality for patients with cirrhosis[13]. The value of sTREM-1 as a biomarker in cirrhosis has been evaluated but not extensively. The potential value of sTREM-1 in AD patients is still unknown.

Against the above background, we hypothesized that sTREM-1 has the potential to serve as a biomarker of progression and prognosis in AD of cirrhosis, reflecting the risk of ACLF development. The aim of this study was to investigate the effectiveness of sTREM-1 for the prediction of ACLF development and mortality in patients with AD of cirrhosis. Soluble CD14 subtype (sCD14-ST), another biomarker of sepsis in ACLF found in our previous study[12], was also assessed for comparison.

MATERIALS AND METHODS

Ethical approval

This study was approved by the Renji Hospital Ethics Committee of Shanghai Jiao Tong University School of Medicine, No. (2014)148k and all of the patients signed written informed consent before the study.

Study population

Patients with AD of cirrhosis were recruited from a prospective multicenter cohort study, named CATCH-LIFE (NCT02457637), conducted by the Chinese Chronic Liver Failure Consortium, which comprised 15 hospitals from January 2015 to December 2017. All 442 patients were randomly divided into a study cohort (n = 309) and a validation cohort (n = 133) using EXCEL-generated random numbers. The sample size was determined based on the calculation results of the PASS 15.0 and by reference to high-quality literature on similar studies[4]. Exclusion criteria are listed in the Supplemental Methods.

Study design

Clinical characteristics, candidate indicators and outcomes were collected to develop and validate the novel ACLF risk prediction score and prognostic score for AD of cirrhosis. Serum samples were collected at admission to measure the concentrations of C-reactive protein (CRP), procalcitonin (PCT), sTREM-1 and sCD14-ST using the Luminex 200 System (Millipore). Patients' clinical data and laboratory parameters were collected and recorded at admission (day 1) and during 28-d follow-up (on day 4, 7, 14, 21 and 28). The management of patients with AD was according to established guidelines [14]. Patients were followed-up for at least 1 year. The presence or development of ACLF was carefully evaluated at admission or during the first 28-d after enrollment.

Definitions

Cirrhosis was diagnosed based on a composite of clinical signs and findings provided by imaging examination or signs of portal hypertension on endoscopy[15]. Patients with cirrhosis who had at least one AD event, including gastrointestinal bleeding, hepatic encephalopathy (HE), ascites, BI or jaundice [total bilirubin (TBil) > 5 mg/dL], within 1 month before enrollment were diagnosed with AD[2]. The diagnostic criteria of ACLF were based on the CANONIC study[16].

Calculation of scores

The model for end-stage liver disease (MELD), MELD-sodium (MELD-Na), chronic liver failure-consortium (CLIF-C) ACLF and CLIF-C AD scores were calculated as detailed in the Supplemental Methods.

Statistical analysis

Statistical analysis was performed using SPSS 26.0, MedCalc 19.0, and R 4.1.1 (https://www.r-project.org). Categorical variables, presented as numbers (percentages) in tables, were analyzed by χ^2 or Fisher's exact test. The normality assumption of continuous variables was validated using the Kolmogorov–Smirnov test. Normally distributed variables were presented as mean ± SD and compared using Student's t test. Non-normally distributed variables were presented as

median [interquartile range (IQR)] and compared using the Mann–Whitney U test. Rank correlation was analyzed by the Spearman method.

Liver transplanted patients (11 in study cohort; 6 in validation cohort) were excluded from the mortality or ACLF development analysis. Risk factors that were significantly associated with the 1-year mortality or 28-d ACLF development in univariate analysis were selected as candidate variables for the multivariate analysis. Independent prognostic factors for AD were identified by multivariate Cox regression. The proportional hazards assumption was assessed by the Schoenfeld residual test. The prognostic model of AD (P-AD) was developed utilizing multivariate Cox regression analysis according to the stepwise forward method: Likelihood ratios, with entry and removal probabilities of 0.05 and 0.10, respectively. Independent risk factors for predicting ACLF development were identified by multivariate logistic regression. The ACLF risk score (ACLF-R) was developed utilizing multivariate logistic regression analysis according to the stepwise forward method: Likelihood ratios, with entry and removal probabilities of 0.05 and 0.10, respectively.

The goodness-of-fit of the new predictive models was evaluated using the Hosmer–Lemeshow test, calibration curve and Brier score. Harrell's C-index, area under the receiver operating curve (AUROC), and the z test (DeLong's method) were used to assess the performance of the new models. The Kaplan–Meier method and log-rank test were used to compare the cumulative survival rates. The cut-point of the "high" and "low" group was based on Youden Index. The performance of the predictive Cox model in the validation cohort was assessed using the same statistical analysis methods applied to the derivation data. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the study population

Demographic and clinical characteristics of both study and validation cohorts are listed in Supplementary Table 1. There were no significant differences in baseline characteristics between both cohorts. Most patients were male (69%) and the most common etiology was hepatitis B virus infection (63%). About half of patients (41%) had a history of previous decompensation of cirrhosis before admission. Patients had moderate to severe hepatic impairment as reflected by a mean MELD score of 14 and CLIF-C ACLF score of 35.

Relationship between sTREM-1 levels and mortality

During a 1-year follow-up period, 112 (25%) patients died and 17 (4%) were transplanted. Univariate analysis of 1-year survival in the study and validation cohort are shown in Supplementary Tables 1 and 2, respectively. As expected, nonsurvivors had significantly higher levels of TBil and international normalized ratio (INR) reflecting worse liver function. The presence of organ failure (liver, kidney, coagulation and cerebral failure) was significantly more frequent in nonsurvivors. Nonsurvivors had significantly higher frequency of BIs with higher white blood cell (WBC), CRP and PCT levels. Finally, serum sTREM-1 Levels at admission were significantly higher in nonsurvivors (Figure 1A and Supplementary Figure 1A) with (Supplementary Figure 1B) or without (Supplementary Figure 1C) BI. The cumulative survival duration for patients with low sTREM-1 Levels was significantly longer than in those with high sTREM-1 Levels (Figure 1B). However, no significant difference was found between the survivors and nonsurvivors in the serum levels of sCD14-ST (Figure 1C and Supplementary Figure 1D). The AUROC of sTREM-1 for 1-year mortality was 0.724, which was significantly higher than that of sCD14-ST and CRP (AUROC = 0.551 and 0.651 respectively, both $P < 0.05$) and tended to be higher than those of WBC and PCT (AUROC = 0.662 and 0.679, $P = 0.063$ and 0.109, respectively; Figure 1D and Supplementary Table 3).

Development and evaluation of sTREM-1 based prognostic model

Multivariate Cox regression analyses showed that sTREM-1, TBil, INR, blood urea nitrogen (BUN) and HE grades were independent prognostic factors for AD of cirrhosis (Table 1). Therefore, we developed a prognostic model [C-index: 0.796; 95%CI: 0.745–0.846], named P-AD, based on five parameters: P-AD = 0.512 × HE + 0.288 × ln [TBil (mg/dL)] + 2.145 × ln (INR) + 0.725 × ln [BUN (mmol/L)] + 0.772 × ln [sTREM-1 (μg/L)], where HE = 0 for patients without HE; HE = 1 for patients with mild HE (grades 1 and 2); and HE = 2 for patients with severe HE (grades 3 and 4).

The P-AD score for the nonsurvivor group was significantly higher in the study (Figure 2A and B) and validation (Supplementary Figure 2A and B) cohorts. This model had a good discriminatory performance in AD patients with (Figure 2C) or without (Supplementary Figure 3A) ACLF. In predicting the outcome of AD patients, the P-AD score significantly outperformed MELD, MELD-Na and CLIF-C ACLF scores in the study (Figure 2D and Supplementary Table 4) and validation (Supplementary Figure 2C-E and Supplementary Table 5) cohorts. The P-AD score also showed superiority and improvement in predictive ability in AD patients without ACLF (Supplementary Figure 3C and D and Supplementary Table 6). The calibration curves were well fitted between the predicted and observed survival rate for patients with (Figure 2E) or without (Supplementary Figure 3B) ACLF. The estimated intercept (95%CI) and slope (95%CI) for the study cohort were -0.036 (-0.190 to 0.118) and 0.993 (0.798–1.189), and for the validation cohort 0.000 (-0.227 to 0.227) and 0.966 (0.673–1.259), respectively. No significant differences from a perfect fit (intercept = 0, slope = 1) were found in either the study ($P = 0.646$ and 0.947) or the validation ($P = 1.000$ and 0.820 for intercept and slope, respectively) cohort. The Bier score for the P-AD in study and validation cohorts were 0.107 and 0.121, respectively. For patients without ACLF, the intercept and slope were -0.017 (-0.137 to 0.103) and 0.982 (0.837–1.127) in study cohort, and -0.074 (-0.359 to 0.211) and 1.018 (0.679–1.356) in validation cohort, respectively. Intercepts and slopes were not significantly different from perfect fit in both the study ($P = 0.781$ and 0.805) and the validation ($P = 0.610$ and 0.917)

Table 1 Baseline characteristics of patients from study cohort according to 365-d survival, *n* (%)

Variable	Survivors[1] (*n* = 220)	Non-survivors (*n* = 78)	*P* value	Multivariate Cox regression	
				HR (95%CI)	*P* value
Age (yr)	51 ± 12	52 ± 11	0.692		
Sex, female	68 (31)	23 (30)	0.815		
Etiology					
HBV	149 (68)	48 (62)	0.321		
HCV	17 (8)	3 (4)	0.239		
Alcohol	30 (14)	15 (19)	0.236		
Autoimmune	27 (12)	10 (13)	0.900		
Others	15 (7)	10 (13)	0.100		
ACLF	12 (6)	28 (36)	< 0.001		
Bacterial infection	64 (29)	40 (51)	< 0.001		
UGIB	40 (18)	16 (21)	0.651		
Ascites	160 (73)	64 (82)	0.101		
HE (I-II/III-IV)	18/3	12/6	0.003	1.669 (1.094-2.546)	0.017
WBC ($\times10^9$/L)	4.6 (3.1-6.0)	6.4 (4.4-9.4)	< 0.001		0.627
Hb (g/L)	111 (87-126)	106 (80-124)	0.132		
Platelets ($\times10^9$/L)	71 (45-113)	60 (45-102)	0.226		
Albumin (g/L)	30 (27-34)	29 (24-33)	0.030		0.213
ALT (U/L)	46 (27-120)	77 (35-296)	0.021		0.581
AST (U/L)	64 (38-138)	107 (62-258)	0.001		0.123
TBil (mg/dL)	3.0 (1.3-9.8)	11.7 (4.5-25.9)	< 0.001	1.333 (1.053-1.688)	0.017
INR	1.4 (1.2-1.7)	1.9 (1.5-2.6)	< 0.001	8.546 (3.850-18.968)	< 0.001
Creatinine (mg/dL)	0.8 (0.6-0.9)	0.8 (0.6-1.1)	0.112		
BUN (mmol/L)	4.7 (3.5-6.7)	6.0 (3.8-10.2)	0.003	2.065 (1.345-3.171)	0.001
Sodium (mmol/L)	138 (135-140)	135 (130-138)	< 0.001		0.529
CRP (mg/L)	3.2 (1.9-4.0)	3.9 (3.4-4.3)	< 0.001		0.070
PCT (μg/L)	0.1 (0.1-0.3)	0.3 (0.1-0.7)	< 0.001		0.403
sCD14-ST (mg/L)	1.2 (1.0-1.5)	1.3 (1.0-1.6)	0.170		
sTREM-1 (μg/L)	0.8 (0.6-1.1)	1.2 (0.9-1.6)	< 0.001	2.163 (1.295-3.614)	0.003
Organ failure					
Liver	43 (20)	39 (50)	< 0.001		
Coagulation	6 (3)	20 (26)	< 0.001		
Cerebral	3 (1)	6 (8)	0.015		
Lung	0 (0)	0 (0)	1.000		
Circulation	2 (1)	0 (0)	1.000		
Kidney	3 (1)	6 (8)	0.015		
MELD	11 (6-17)	22 (11-26)	< 0.001		
MELD-Na	11 (7-19)	24 (17-30)	< 0.001		
CLIF-C ACLF	33 ± 7	40 ± 9	< 0.001		
CLIF-C AD	44 ± 9	55 ± 12	< 0.001		
P-AD	2.6 (2.1-3.4)	4.4 (3.2-5.1)	< 0.001		

[1]Transplanted-free survivors.

The data are expressed as mean ± SD, medians (interquartile range) or number of patients (%). Student's *t*-test or Mann-Whitney U test was used for continuous variables and χ^2 test or Fisher exact test for categorical variables.

ACLF: Acute-on-chronic liver failure; UGIB: Upper gastrointestinal bleeding; BUN: Blood urea nitrogen; TBil: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio; HE: Hepatic encephalopathy; CRP: C-reactive protein; PCT: Procalcitonin; sCD14-ST: Soluble CD14 subtype; sTREM-1: Soluble triggering receptor expressed on myeloid cell-1; MELD: Model for end-stage liver disease; MELD-Na: Model for end-stage liver disease-sodium; CLIF-C ACLF: Chronic liver failure-consortium acute-on-chronic liver failure score; CLIF-C AD: Chronic liver failure-consortium acute decompensation score; P-AD: Prognostic model of acute decompensation; HR: Hazard ratio.

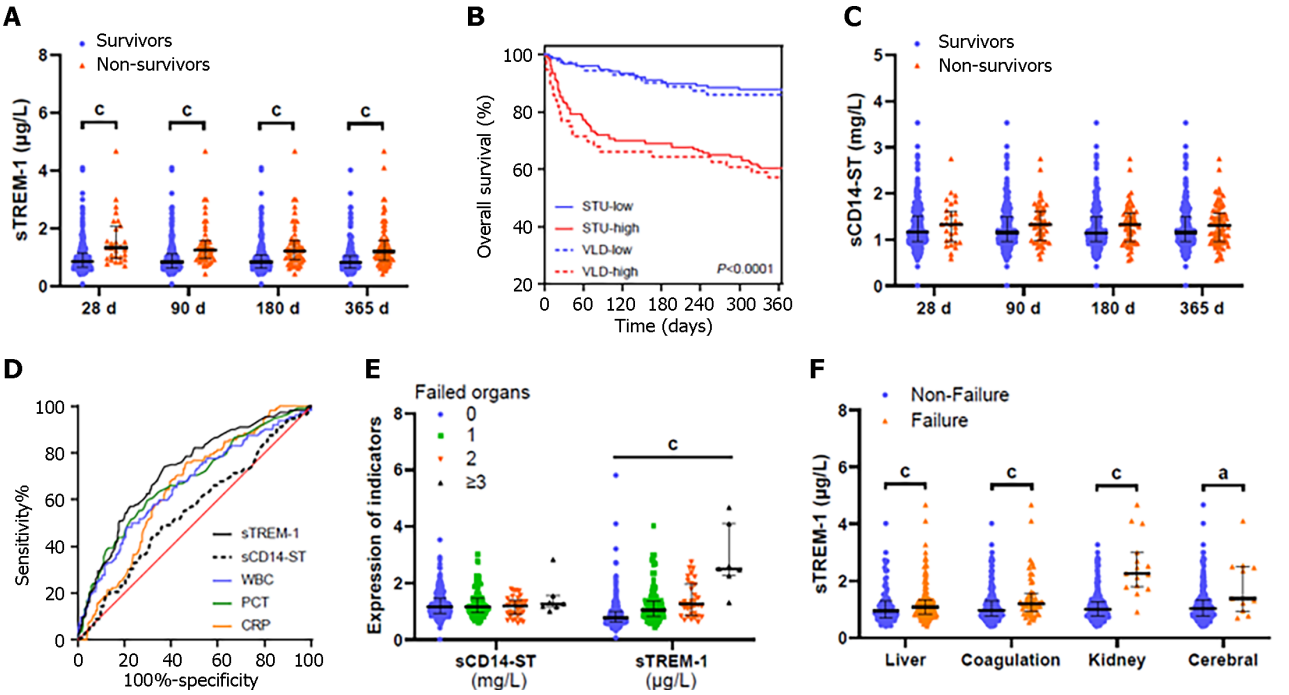

Figure 1 Association of soluble triggering receptor expressed on myeloid cell-1 at admission with prognosis and organ failure in patients with acute decompensation of cirrhosis. A: Soluble triggering receptor expressed on myeloid cell-1 (sTREM-1) distribution in study cohort (median with interquartile range); B: Survival rates after 1-year (365-d) of patients in the "high" and "low" sTREM-1 groups in the study and validation cohorts; C: Soluble CD14 subtype (sCD14-ST) distribution in study cohort (median with interquartile range); D: Prediction of 1-year mortality according to sTREM-1, sCD14-ST, white blood cell, C-reactive protein and procalcitonin; E: sCD14-ST or sTREM-1 Levels according to the numbers of failed organs; F: sTREM-1 distribution of patients with and without liver, coagulation, kidney, or cerebral failure. $^aP < 0.05$, $^cP < 0.001$. ACLF: Acute-on-chronic liver failure; CRP: C-reactive protein; PCT: Procalcitonin; sCD14-ST: Soluble CD14 subtype; sTREM-1: Soluble triggering receptor expressed on myeloid cell-1; STU: Study; VLD: Validation; WBC: White blood cell.

cohorts. The Bier scores were 0.108 and 0.097 in study and validation cohorts, respectively.

Relationship between sTREM-1 Levels and ACLF

We investigated association between serum levels of sTREM-1 or sCD14-ST at admission and the presence of ACLF. Patients with ACLF had significantly higher sTREM-1 baseline levels than those without ACLF in both BI and non-BI groups (Figure 3A). sTREM-1 Levels increased with numbers of failed organs. In contrast, there was no significant difference in sCD14-ST levels whether grouped by the presence of ACLF (Supplementary Figure 3E) or by the number of failed organs (Figure 1E). Patients with liver, coagulation, kidney or cerebral failure had significantly higher sTREM-1 Levels than those without (Figure 1F). In contrast, there was no correlation between sCD14-ST and any of the aforementioned organ failures (Supplementary Figure 1E). To investigate the potential of sTREM-1 as a biomarker for ACLF development, univariate analysis of 28-d ACLF development was performed (Table 2). Patients who developed ACLF during the first 28-d follow-up had significantly higher sTREM-1 Levels at admission.

Development and evaluation of sTREM-1-based ACLF prediction model

The multivariate analysis showed that aspartate aminotransferase (AST), TBil, INR, BUN and sTREM-1 Levels were independent factors in the occurrence of ACLF during 28-d follow-up (Table 2). Therefore, we developed an ACLF risk prediction model (Hosmer-Lemeshow test, $P = 0.811$), named ACLF-R, based on: ACLF-R = 1.210 × ln [TBil (mg/dL)] + 0.565 × ln [AST (U/L)] + 3.132 × ln (INR) + 1.131 × ln [BUN (mmol/L)] + 1.237 × ln [sTREM-1 (μg/L)].

The ACLF-R score for patients who developed ACLF during 28-d follow-up was significantly higher than those who did not (Table 2). The ACLF-R score showed greater predictive power for AD patients' 28-d ACLF development than the MELD, MELD-Na, CLIF-C ACLF, CLIF-C AD and P-AD scores (Figure 3B and Table 3). The calibration curve had a good

Table 2 Baseline characteristics of patients according to the development of acute-on-chronic liver failure during 28-d follow-up, *n* (%)

Variable	No ACLF during[1] Follow-up (*n* = 340)	ACLF during Follow-up (*n* = 36)	*P* value	Multivariate logistic regression	
				RR (95%CI)	*P* value
Age (yr)	51 ± 12	51 ± 12	0.959		
Sex, female	120 (35%)	8 (22%)	0.115		
Etiology					
HBV	204 (60%)	27 (75%)	0.079		
HCV	28 (8%)	1 (3%)	0.402		
Alcohol	54 (16%)	5 (14%)	0.755		
Autoimmune	48 (14%)	3 (8%)	0.479		
Others	29 (9%)	3 (8%)	0.968		
Bacterial infection	105 (31%)	21 (58%)	0.001		
UGIB	71 (21%)	4 (11%)	0.240		
Ascites	240 (71%)	33 (92%)	0.012		0.057
HE (I-II/III-IV)	25/6	0/0	0.167		
WBC ($\times10^9$/L)	4.5 (3.0-6.1)	6.3 (4.8-8.1)	< 0.001		0.991
Hb (g/L)	108 (87-124)	116 (102-126)	0.165		
Platelets ($\times10^9$/L)	69 (47-111)	63 (45-91)	0.247		
Albumin (g/L)	30 (27-34)	30 (26-33)	0.744		
ALT (U/L)	46 (26-118)	132 (67-321)	< 0.001		0.236
AST (U/L)	63 (38-136)	183 (107-326)	< 0.001	1.971 (1.228-3.163)	0.005
TBil (mg/dL)	3.1 (1.4-8.9)	16.1 (10.0-26.8)	< 0.001	3.151 (1.717-5.782)	< 0.001
INR	1.4 (1.2-1.7)	1.9 (1.6-2.2)	< 0.001	13.841 (2.021-94.767)	0.007
Creatinine (mg/dL)	0.7 (0.6-0.9)	0.8 (0.6-1.0)	0.297		0.929
BUN (mmol/L)	4.6 (3.5-6.7)	5.6 (3.5-8.2)	0.219	3.302 (1.352-8.067)	0.009
Sodium (mmol/L)	138 (135-140)	136 (132-139)	0.016		0.962
CRP (mg/L)	3.2 (1.6-4.0)	3.7 (3.3-4.1)	0.006		0.339
PCT (μg/L)	0.1 (0.1-0.3)	0.4 (0.2-0.6)	< 0.001		0.709
sCD14-ST (mg/L)	1.2 (1.0-1.5)	1.2 (1.0-1.6)	0.226		
sTREM-1 (μg/L)	0.8 (0.6-1.0)	1.2 (1.0-1.3)	< 0.001	3.023 (1.053-8.677)	0.040
Organ failure					
Liver	58 (17%)	21 (58%)	< 0.001		
Coagulation	5 (2%)	5 (14%)	< 0.001		
Cerebral	6 (2%)	0 (0%)	1.000		
Lung	0 (0%)	0 (0%)	1.000		
Circulation	1 (0%)	0 (0%)	1.000		
Kidney	0 (0%)	0 (0%)	1.000		
MELD	11 ± 7	20 ± 5	< 0.001		
MELD-Na	12 (7-18)	24 (20-29)	< 0.001		
CLIF-C ACLF	33 (28-38)	39 (35-42)	< 0.001		
CLIF-C AD	44 ± 8	53 ± 8	< 0.001		
P-AD	2.6 (2.1-3.3)	4.1 (3.5-4.5)	< 0.001		
ACLF-R	6.6 (5.0-8.4)	10.5 (9.7-11.3)	< 0.001		

[1]No liver transplantation and acute-on-chronic liver failure score development during 28-d follow-up.
The data are expressed as mean ± SD, medians (interquartile range) or number of patients (%). Student's *t*-test or Mann-Whitney U test was used for continuous variables and χ^2 test or Fisher exact test for categorical variables.
ACLF: Acute-on-chronic liver failure score; UGIB: Upper gastrointestinal bleeding; BUN: Blood urea nitrogen; TBil: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio; HE: Hepatic encephalopathy; CRP: C-reactive protein; PCT: Procalcitonin; sCD14-ST: Soluble CD14 subtype; sTREM-1: Soluble triggering receptor expressed on myeloid cell-1; MELD: Model for end-stage liver disease; MELD-Na: Model for end-stage liver disease -sodium; CLIF-C ACLF: Chronic liver failure-consortium acute-on-chronic liver failure score score. CLIF-C AD: Chronic liver failure-consortium acute decompensation score; P-AD: Prognostic model of acute decompensation; ACLF-R: Acute-on-chronic liver failure score risk score; RR: Relative risk.

Table 3 Efficiency of prognostic scores to predict development of acute-on-chronic liver failure during 28-d follow-up

Score	AUROC	95% CI	*P* value[1]	*P* value[2]
ACLF-R	0.91	0.88-0.94		
P-AD	0.87	0.83-0.90		0.012
MELD	0.84	0.80-0.88	0.397	0.013
MELD-Na	0.83	0.79-0.87	0.225	0.004
CLIF-C AD	0.80	0.75-0.84	0.029	0.003
CLIF-C ACLF	0.78	0.74-0.82	0.006	< 0.001

[1]Prognostic model of acute decompensation area under the receiver operating curve (AUROC) *vs* prognostic score AUROC.
[2]Acute-on-chronic liver failure risk score AUROC *vs* prognostic score AUROC.
ACLF-R: Acute-on-chronic liver failure risk score; P-AD: Prognostic model of acute decompensation; MELD: Model for end-stage liver disease; MELD-Na: Model for end-stage liver disease-sodium; CLIF-C ACLF: Chronic liver failure-consortium acute-on-chronic liver failure risk score; CLIF-C AD: Chronic liver failure-consortium acute decompensation score; AUROC: Area under the receiver operating curve.

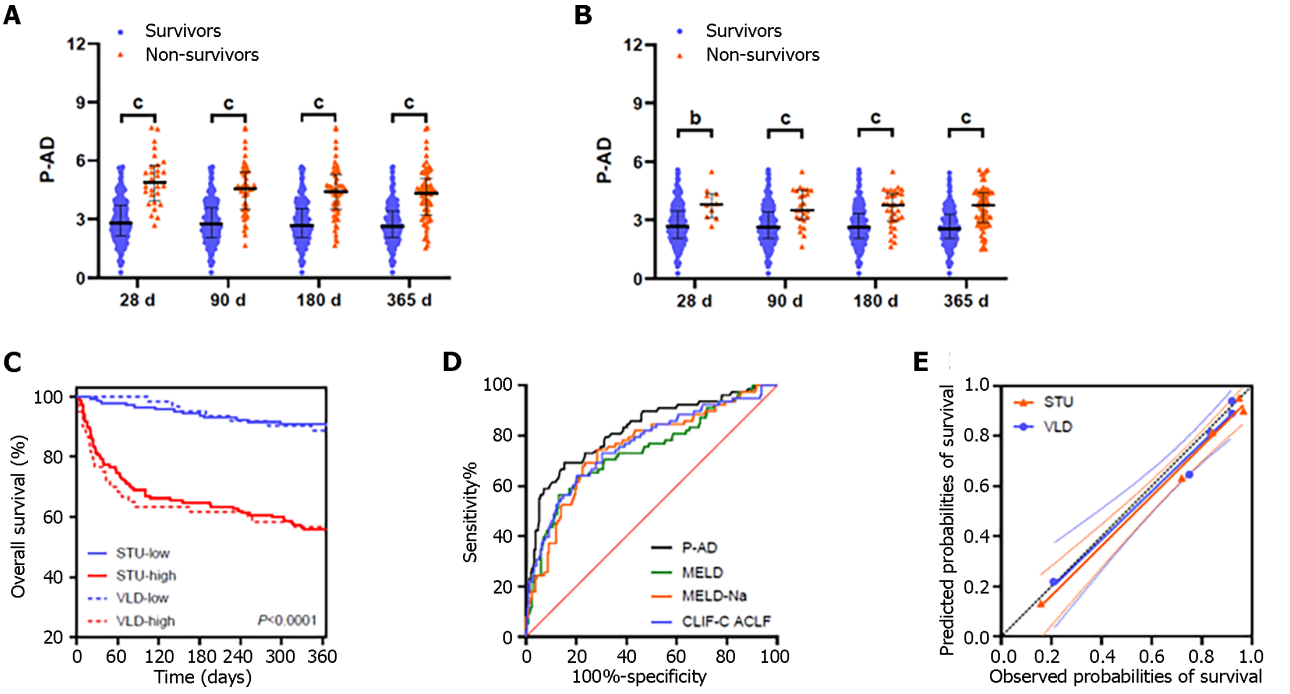

Figure 2 Prognostic model of acute decompensation score associated with prognosis of cirrhosis with acute decompensation. A: Prognostic model of acute decompensation (P-AD) score distribution for acute decompensation (AD) patients with acute-on-chronic liver failure (ACLF) in the study cohort (median with interquartile range); B: P-AD score distribution for AD patients without ACLF in the study cohort (median with interquartile range); C: 1-year (365-d) survival rates of AD patients belonging "high" and "low" P-AD groups in both cohorts; D: Prediction of 1-year mortality for patients according to P-AD and other scores in study cohort; E: Calibration plot comparing the observed and predicted probabilities of survival from the Kaplan-Meier and P-AD model in AD patients. $^{b}P < 0.01$, $^{c}P < 0.001$. STU: Study; VLD: Validation; P-AD: Prognostic model of acute decompensation; MELD: Model for end-stage liver disease; CLIF-C ACLF: Chronic liver failure-consortium acute-on-chronic liver failure score.

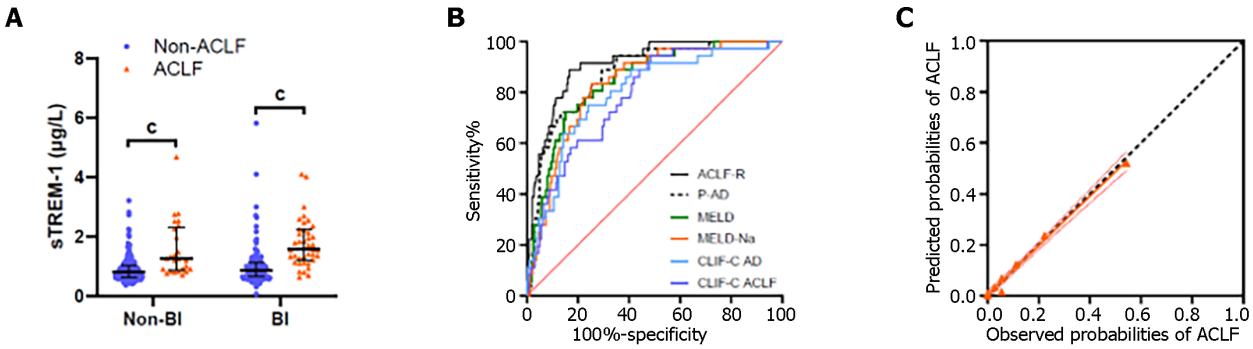

Figure 3 Acute-on-chronic liver failure risk score associated with acute-on-chronic liver failure development in cirrhosis with acute decompensation. A: In bacterial infections (BI) or non-BI group, Soluble triggering receptor expressed on myeloid cell-1 Levels at admission were higher in patients with acute-on-chronic liver failure (ACLF) than those without; B: Prediction development of ACLF during 28-d follow-up for patients with acute decompensation according to ACLF risk score (ACLF-R) and other models; C: Calibration plot comparing the observed and predicted probabilities of ACLF from the Kaplan-Meier and ACLF-R. °P < 0.001. sTREM-1: Soluble triggering receptor expressed on myeloid cell-1; ACLF: Acute-on-chronic liver failure score; BI: Bacterial infections; ACLF-R: Acute-on-chronic liver failure risk score; P-AD: Prognostic model of acute decompensation; MELD: Model for end-stage liver disease; CLIF-C: Chronic liver failure-consortium; CLIF-C AD: Chronic liver failure-consortium acute decompensation score; CLIF-C ACLF: Chronic liver failure-consortium acute-on-chronic liver failure score.

fit between the predicted and observed probabilities of ACLF development (Figure 3C). The estimated intercept (95%CI) and slope (95%CI) were 0.003 (-0.012 to 0.018) and 0.968 (0.889–1.046), and no significant difference from a perfect fit was found (P = 0.672 and 0.418 for intercept and slope, respectively). The Bier score for the ACLF-R was 0.062.

DISCUSSION

The development of simple and accurate predictive models permitting the early recognition of individuals with high risk of development of ACLF and mortality could enhance the triage, management, and prognosis of AD patients. In this study, we assessed the performance of sTREM-1 as a disease progression and prognostic biomarker in AD patients and further constructed P-AD and ACLF-R score based on sTREM-1 and four other clinical parameters. Serum sTREM-1 Levels at admission were independently associated with 1-year mortality and 28-d ACLF development in patients with AD of cirrhosis. P-AD and ACLF-R scores outperformed the MELD, MELD-Na, CLIF-C ACLF and CLIF-C AD scores in a multicenter prospective cohort.

Because the pathogenic mechanism of AD, especially ACLF, is complex and involves multiple systems[1,2], a comprehensive prognostic model with indicators reflecting multiple pathological processes is required to forecast the prognosis of AD. The MELD score is an accurate predictor of survival in patients with advanced liver disease and used in organ allocation for liver transplantation[17]. MELD-Na, a model incorporating serum sodium into MELD, has been demonstrated to provide more accurate mortality prediction than MELD[18]. Therefore, MELD-Na is the most widely used model for organ allocation in patients listed for liver transplantation. Recent studies showed that patients with cirrhosis with persistently low MELD-Na scores still experienced high rates of liver-related mortality[19]. Patients with ACLF are at a mortality disadvantage in the current MELD-Na based system because MELD-Na does not capture 90-d mortality risk in ACLF[20]. Organ failure based scores such as CLIF-C ACLF perform better than MELD based assessment in predicting waiting list mortality among ACLF patients[16,21]. The CLIF-C AD score was developed for AD patients without ACLF[1]. A recent study showed that even in the low-risk group (CLIF-C ADs ≤ 45), the 90-d mortality was as high as 10%[22]. Therefore, it is necessary to enhance prognosis stratification in patients with AD. The present study demonstrated that serum sTREM-1 Levels could act as independent predictor of 1-year mortality in patients with AD of cirrhosis.

sTREM-1 is increased in ACLF patients with sepsis[12] and cirrhotic patients with BI[13]. sTREM-1 is also increased and involved in noninfectious inflammatory diseases such as relapsing polychondritis[23] and adult-onset Still's disease [24]. Infections and sepsis contribute to poor prognosis in AD patients with or without ACLF[1,5]. Systemic circulatory dysfunction and systemic inflammation are typical pathologies of AD and further exacerbated in ACLF[25]. Therefore, it can be speculated that there are two major theories supporting sTREM-1 as a prognostic biomarker in AD. First, sTREM-1 Levels may reflect BIs and/or sepsis in patients with AD of cirrhosis. Second, sTREM-1 Levels may reflect the severity of systemic inflammatory in AD. Moreover, we developed and validated the P-AD score, based on sTREM-1 and four other parameters (TBil, INR, BUN and HE grade). P-AD score had a better prognostic capability than MELD, MELD-Na, CLIF-C ACLF, and CLIF-C AD scores. Therefore, the P-AD score enables decision-making regarding the allocation of intensive care resources and priorities of liver transplantation for patients with AD of cirrhosis.

TREM-1 pathways contribute to the pathology of infectious diseases[6-11] and noninfectious inflammatory diseases[23, 24]. sTREM-1 is a specific biomarker of TREM-1 pathway activation[26]. BI is one of the most common triggers for inflammation promoting ACLF development[2,27]. It can induce inflammation *via* two classes of molecules: Pathogen-associated molecular patterns and virulence factors. Both molecules are recognized by PRRs and result in the production

of inflammatory molecules. The inflammatory response to bacteria can be excessive and cause tissue damage, releasing damage-associated molecular patterns (DAMPs). DAMP recognition by PRRs accentuates inflammation and leads to ACLF *via* a storm of inflammatory cytokines[28]. These findings suggest that systemic inflammation can drive ACLF. sTREM-1, a PRR that amplifies inflammatory responses by synergizing with other PRRs, could help define signatures to improve our understanding of inflammation in ACLF and inform preventative strategies. Our findings are consistent with these results and support the hypothesis that increased sTREM-1 Levels may be involved in and reflect the activation of inflammatory pathways occurring in ACLF.

So far, there is a paucity of commonly accepted and verified biomarkers or models to assess the probability of ACLF development. This study revealed that sTREM-1 is significantly increased in ACLF and correlated with failure of critical organs, including liver, brain and kidney, as well as coagulation. Further results revealed that for AD patients without ACLF at admission, sTREM-1 could be a useful biomarker to assess the risk of ACLF development. We developed and validated the ACLF-R score, based on sTREM-1 and four other parameters (TBil, AST, INR and BUN), which have better predictive capability in ACLF developing than MELD, MELD-Na, CLIF-C ACLF, CLIF-C AD, and P-AD scores.

There were some strengths and limitations to the present study. First, this investigation was based on a large multicenter prospective cohort of patients with cirrhosis hospitalized for AD. Second, results obtained from the study cohort were validated by the validation cohort. However, since the number of AD patients who progressed to ACLF during the 28-d follow-up was limited, our results for sTREM-1 and ACLF-R predicting ACLF development need to be validated in another independent multicenter prospective cohort. Finally, the design of this investigation did not involve a mechanistic demonstration about the role of sTREM-1 in the pathophysiology of ACLF. Therefore, the mechanistic hypothesis suggested by current results needs to be investigated in future studies.

CONCLUSION

Serum sTREM-1 is a promising biomarker to predict development of ACLF and mortality in patients with AD of cirrhosis. The P-AD and ACLF-R score were superior to currently available prognostic models in predicting mortality and development of ACLF.

ARTICLE HIGHLIGHTS

Research background

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is a biomarker of inflammatory diseases such as liver injury, and is released from activated innate immune cells.

Research motivation

Acute decompensation (AD) of cirrhosis is associated with high short-term mortality, mainly due to the development of acute-on-chronic liver failure (ACLF). Thus, accurate biomarkers are required to identify AD patients with high risk of ACLF development and mortality.

Research objectives

This study aimed to explore the prognostic value of sTREM-1 in patients with AD of cirrhosis, and to construct more effective prognostic models for improving patient clinical management and prognosis.

Research methods

We collected data and samples from 442 hospitalized patients with AD of cirrhosis from a multicenter prospective cohort including 15 liver units in 10 provinces of China. Prognostic model of AD (P-AD) and ACLF risk score (ACLF-R) were established based on independent factors associated with mortality or ACLF development, and compared with widely used scores, such as model for end-stage liver disease (MELD), MELD-sodium (MELD-Na), chronic liver failure-consortium (CLIF-C) ACLF and CLIF-C AD.

Research results

Serum sTREM-1 Level was associated with 1-year mortality and correlated with organ failure, including liver, coagulation, kidney, and cerebral failures, in patients with AD of cirrhosis. Serum sTREM-1 was related to the development of ACLF during 28-d follow-up. P-AD and ACLF-R scores were significantly superior to MELD, MELD-Na, CLIF-C ACLF and CLIF-C AD.

Research conclusions

Serum sTREM-1 Level, P-AD and ACLF-R score will facilitate clinical decision-making in the management of patients with AD of cirrhosis.

Research perspectives

A new approach to early diagnosis and treatment of patients with AD of cirrhosis.

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FOOTNOTES

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Informed consent statement: All of the patients signed written informed consent before the study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The original datasets generated in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author at drhyan@163.com.

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