Journal of Clinical and Translational Pathology **2022** vol. 2(4) | 117–125
DOI: 10.14218/JCTP.2022.00015

Original Article

Association of Elevated Serum Soluble Triggering Receptor Expressed on Myeloid Cells-1 with 90-day Outcomes of Patients with Acute-on-chronic Liver Failure: A Cohort Study

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Received: June 14, 2022 | **Revised:** September 14, 2022 | **Accepted:** September 20, 2022 | **Published:** September 27, 2022

Abstract

Background and objectives: Triggering receptor expressed on myeloid cells-1 (TREM-1) is an important inflammation-related biomarker. The present study aimed to determine whether this affects the short-term prognosis of patients with acute-chronic liver failure (ACLF). ***Methods:*** The serum sTREM-1 levels of 30 healthy subjects (HS), 40 chronic hepatitis patients without cirrhosis and liver failure (CH), 38 liver cirrhosis (LC) patients, and 59 ACLF patients were evaluated by enzyme-linked immunosorbent assay. The predictive accuracy of the logistic model for survival rate within 90 days in patients with ACLF was determined using the area under the receiver operating characteristic curve (AUC).Kaplan-Meier analysis and log-rank test were performed to revalidate the factors l for the 90-day survival rate of patients with ACLF. ***Results:*** Compared to the CH, LC and HS groups, the serum sTREM-1 levels of ACLF patients were significantly elevated ($p < 0.001$). In ACLF patients, the serum sTREM-1 levels further increased in non-survivors (661.51 [494.36–1,028.82] pg/mL), when compared to the survivors (440.92 [308.00–523.21] pg/mL) ($p = 0.002$). The multivariate logistic regression analysis indicated that serum sTREM-1, sodium, and the international normalized ratio (INR) were independent predictors for the 90-day mortality of patients with ACLF. The AUC value for logit (p) in predicting the 90-day prognosis of ACLF patients was 0.89 (0.78–1.00), with a sensitivity of 70%, a specificity of 89.74%. ***Conclusions:*** Serum sTREM-1 is a valuable independent factor for determining the 90-day mortality of ACLF patients. Combining the INR and sodium in the logistic regression model may improve the accuracy in predicting the prognosis.

Citation of this article: Huang Y, Cai JJ, Han T. Association of Elevated Serum Soluble Triggering Receptor Expressed on Myeloid Cells-1 with 90-day Outcomes of Patients with Acute-on-chronic Liver Failure: A Cohort Study. J Clin Transl Pathol 2022;2(4):117–125. doi: 10.14218/JCTP.2022.00015.

Introduction

Acute-on-chronic liver failure (ACLF) is the state of acute inflammatory response and cytokine burst,[1] which is accompanied by organ dysfunction and organ failure, and attended by an extremely high 28-day mortality.[2] At present, liver transplantation is the only measure for the radical treatment of ACLF, but this is restrained by the donor organ, the economy, and ethics.[3] Therefore, the early identification and prompt therapeutic intervention of patients with unfavorable prognoses are the top priority for preventing or reversing the clinical process. However, due to the lack of sensitivity and reliability for disease prognosis and monitoring, the present biomarkers used in clinical practice remain unsatisfactory. Therefore, novel potential biomarkers are urgently required.

Triggering receptor expressed on myeloid cells 1 (TREM-1) acts as a sensitive biomarker for the extent of inflammatory response in infectious and non-infectious diseases, and is expressed on the cell surface of most immune cells as an immunoglobulin receptor, which amplifies inflammatory response by stimulating the TREM-1/DAP12 pathway.[4,5] In the engagement with its ligands, TREM-1 initiates intracellular signaling cascades through synergism with pattern recognition receptors (PRR), such as Toll-like receptor (TLR) and nucleotide-binding oligomerization domain-like receptor signaling, and subsequently triggers the phosphorylation of spleen tyrosine kinase and phospholipase C, intracellular calcium (Ca^{2+}) mobilization, and the activation of transcription factors, such as nuclear factor-kappa B (NF-κB), nuclear factor of activated T cells, activator protein 1 and uridine triphosphate, which transcribe genes that encode pro-inflammatory cytokines, chemokines and cell-surface molecules.[5–8] Therefore, TREM-1 was recognized as the main participant in the

Keywords: sTREM-1; Liver failure; Prognosis; International normalized ratio.

Abbreviations: ACLF, acute-on-chronic liver failure; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CH, chronic hepatitis without cirrhosis and failure; LC, liver cirrhosis; HS, health subjects; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; TBIL, total bilirubin; ALB, albumin; Cr, creatinine; WBC, white blood cell count; PLT, platelet count; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NMR, blood neutrophil-to-monocyte ratio; PWR, platelet-to-white blood cell ratio.

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pathophysiology of inflammatory reaction-related diseases.

Soluble TREM-1 (sTREM-1) is another expression type of TREM-1 that possesses the extracellular domain, but lacks the transmembrane and intracellular domain, when compared to TREM-1, and this can be directly detected in body fluids.[5] The hypothesis on the origin of sTREM-1: produced by splicing the version of TREM-1 mRNA or proteolytic cleavage of TREM-1 anchored to the surface of mature cells by matrix metalloproteinases.[9,10] Increasing researchers have recognized that elevated sTREM-1 levels are associated with the diagnosis and clinical outcomes of inflammatory response-related diseases, such as sepsis,[11] sepsis-related acute renal injury,[12] acute pancreatitis,[13] and acute myocardial infarction.[14] At present, a related study revealed that the level of sTREM-1 in ascites is one of the diagnostically significant markers of spontaneous bacterial peritonitis.[15] However, the ability of sTREM-1 for the prognosis of ACLF patients remains limited. The present study aimed to analyze the main characteristics of serum sTREM-1 in patients with liver disease, and determine whether this affects the short-term prognosis of patients with ACLF.

Materials and methods

Patient selection

The present cohort study was conducted based the natural history of the development of liver disease. The subjects enrolled for the present study included healthy subjects (HS), chronic hepatitis without cirrhosis and failure (CH) patients, liver cirrhosis (LC, Child-Pugh A) patients, and ALCF patients. That is, the following subjects were included for the present study: 59 ACLF patients, 38 LC patients, 40 CH patients (34 patients with hepatitis B virus [HBV] and six patients with steatohepatitis), and 30 HS. The selected population comprised of patients who attended the Department of Hepatology, Tianjin Third Central Hospital, from January 2017 to June 2019. Patients with ACLF met the following criteria of the Asian Pacific Association for the Study of the Liver: (1) acute hepatic insult manifesting as jaundice (TBIL ≥5 mg/dL, 85 mmol/L); (2) coagulopathy (INR ≥1.5 or PTA <40%); (3) patients with complications of ascites or hepatic encephalopathy within four weeks, with the basis or manifestations of chronic liver disease.[1] Exclusion criteria: coexistent history of carcinoma, HIV infection, <18 years old or >80 years old, patients with a history of immunotherapy at least at the preceding six months, or patients with severe chronic cardiopulmonary, renal, or other basic diseases. Once admitted, patients with the outcome variable ACLF survived or died during the 90-day follow-up period.

The study protocol was approved by the Ethics Committee of the Third Central Hospital of Tianjin (No. SZX-IRB-SOP-016[F]-002-01). All subjects provided a written informed consent. The present study was conducted in accordance with the Declaration of Helsinki, was registered in the Chinese clinical trials registry (with registration identification number: ChiCTR1900021539), and complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Lab methods

Blood samples were collected from fasting patients through the median cubital vein in the morning. Then, the samples were centrifuged (3,000 r/min) at 4°C, and the serum was stored in a refrigerator at −80 °C. Aftewards, the serum sTREM-1 was tested using the Quantikine Human TREM-1 Immunoassay (DTRM10C, R&D Systems, USA), and manipulated strictly according to the instructions. The sequence for the sTREM-1 test in each patient was randomized, and the tests were averaged twice to reduce bias. Next, the increase in sTREM-1 level was compared to the normal values recommended by the test for sTREM-1 levels in a healthy population and its specifications, and the cut-off value for the prognosis was determined by the subsequent statistical methods. All patient demographics, clinical parameters, laboratory values, and fundamental data of liver diseases were collected from computer-based patient records. The Model for End-Stage Liver Disease (MELD) score and MELD-Na score were calculated according to the patient's condition on the day of admission.[16] The development of patients with ACLF was assessed based on the laboratory tests and medical records, and the recommendations of relevant guidelines during hospitalization.

Statistical analysis

The diagnosis of the included patients and the collected clinical data were verified by two experienced physicians based on the guidelines, thereby reducing errors in the diagnosis and entry. Patients with missing important data were excluded, and non-important missing data were treated as null values. All data were statistically analyzed using the SPSS 22.0 software (SPSS Inc, Chicago, IL, USA). Normallly distributed data were expressed as mean ± standard deviation, while skewed distributed data were presented in median (p25-p75). *T*-test, one-way ANOVA, or nonparametric test was used to compare the quantitative variables. The prediction model was constructed by logistic regression analysis: all variables were selected for the univariate logistic regression analysis, and the statistically significant factors (except for the MELD score and MELD-Na score) were selected for the forward stepwise multivariate logistic regression analysis, in order to construct the prediction model. The model was tested using the likelihood ratio test and Hosmer-Lemeshow test. The predictive accuracy of the logistic regression model for mortality within 90 days in ACLF patients was determined using the area under the receiver operating characteristic curve (AUC), positive predictive value (PPV), and negative predictive value (NPV). Kaplan-Meier analysis and log-rank test were used to revalidate the relevant independent influencing factors and logistic regression model for the 90-day mortality of ACLF patients. A p-value of <0.05 was considered statistically significant.

Results

Participant characteristics

The basic clinical data of the recruited subjects are presented in Table 1. There was no gender predilection among the four groups. Furthermore, the ALT, AST, TBIL, sTREM-1, neutrophil-to-lymphocyte ratio (NLR) and alpha-fetoprotein (AFP) levels were significantly higher in ACLF patients, when compared to the trio-groups, while the ALB level was the opposite ($p < 0.05$). The complications for ACLF during hospitalization included the following: hepatic encephalopathy (12 of 59 patients, 20.3%), ascites (39 of 59 patients, 66.1%), hepatorenal syndrome (7 of 59 patients, 11.9%), gastroesophageal variceal bleeding (9 of 59 patients, 15.3%), and bacterial infections (30 of 59 patients, 50.1%).

Serum sTREM-1 levels among the different groups

The sTREM-1 level was highest in ACLF patients (474.62 [365.21–638.16] pg/mL), followed by the levels for CH patients (198.89 [124.00–282.18] pg/mL), LC patients (186.75

Table 1. Clinical characteristics of all recruited subjects

Variables	ACLF (*n* = 59)	LC (*n* = 38)	CH (*n* = 40)	HS (*n* = 30)	*p*-value
Age (years)[a]	55.12 ± 11.7	58.75 ± 9.62	43.18 ± 12.51	51.87 ± 9.61	<0.001
Male (*n*, %)[a]	44/74.58	22/57.89	29/72.50	17/56.67	0.135
HBV (*n*, %)[b]	30/50.85	23/60.53	34/85.00	-	0.002
ALT (U/L)[a]	188.00 (51.00–398.00)	26.00 (18.00–39.00)	55.00 (35.50–120.25	17.00 (13.00–23.25)	<0.001
AST (U/L)[a]	112.00 (69.00–227.00)	35.00 (23.00–48.00)	37.50 (23.50–65.50)	16.50 (15.00–21.25)	<0.001
TBIL (μmol/L)	213.40 (283.70–3,703.00)	27.00 (17.00–38.00)	18.10 (12.78–21.80)	9.85 (8.70–13.63)	<0.001
ALB (g/L)[a]	30.47 ± 4.20	41.17 ± 6.69	47.46 ± 3.53	47.54 ± 5.90	<0.001
Cr (μmol/L)[a]	72.00 (54.00–102.00)	66.00 (58.00–71.00)	69.00 (55.75–82.00)	70.50 (60.75–82.50)	0.709
WBC ($\times 10^9$/L)[a]	6.74 ± 3.47	4.23 ± 1.71	5.90 ± 1.81	6.12 ± 1.63	0.148
PLT ($\times 10^9$/L)[a]	97.17 ± 58.17	85.42 ± 38.23	211.77 ± 61.13	245.57 ± 55.24	<0.001
PLR[a]	88.71 (63.25–150.30)	74.56 (54.44–117.50)	110.59 (90.34–137.68)	109.20 (89.13–134.30)	0.004
NLR[a]	6.70 ± 6.12	3.04 ± 2.63	2.34 ± 2.76	1.67 ± 0.67	<0.001
PWR[a]	17.25 ± 13.18	21.10 ± 7.51	36.65 ± 8.06	42.80 ± 15.49	<0.001
NMR[a]	8.38 (5.63–11.12)	10.24 (7.41–12.73)	8.83 (6.76–11.54)	6.26 (8.25–11.69)	0.264
sTREM-1 (pg/mL)[a]	474.62 (365.21–638.16)	186.75 (128.28–318.82)	198.89 (124.00–282.18)	146.78 (111.14–175.73)	<0.001
AFP (ng/mL)[b]	28.61 (6.04–220.13)	3.52 (2.17–5.26)	2.99 (2.24–5.13)	–	<0.001

ACLF, acute-on-chronic liver failure; CH, chronic hepatitis without cirrhosis and failure; LC, liver cirrhosis; HS, health subjects; sTREM-1, soluble triggering receptor expressed-on myeloid cells-1; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; Cr, creatinine; WBC, white blood cell count; PLT, platelet count; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NMR, blood neutrophil-to-monocyte ratio; PWR, platelet-to-white blood cell ratio. [a]Compared among the four groups. [b]Compared among the CH, LC and ACLF groups.

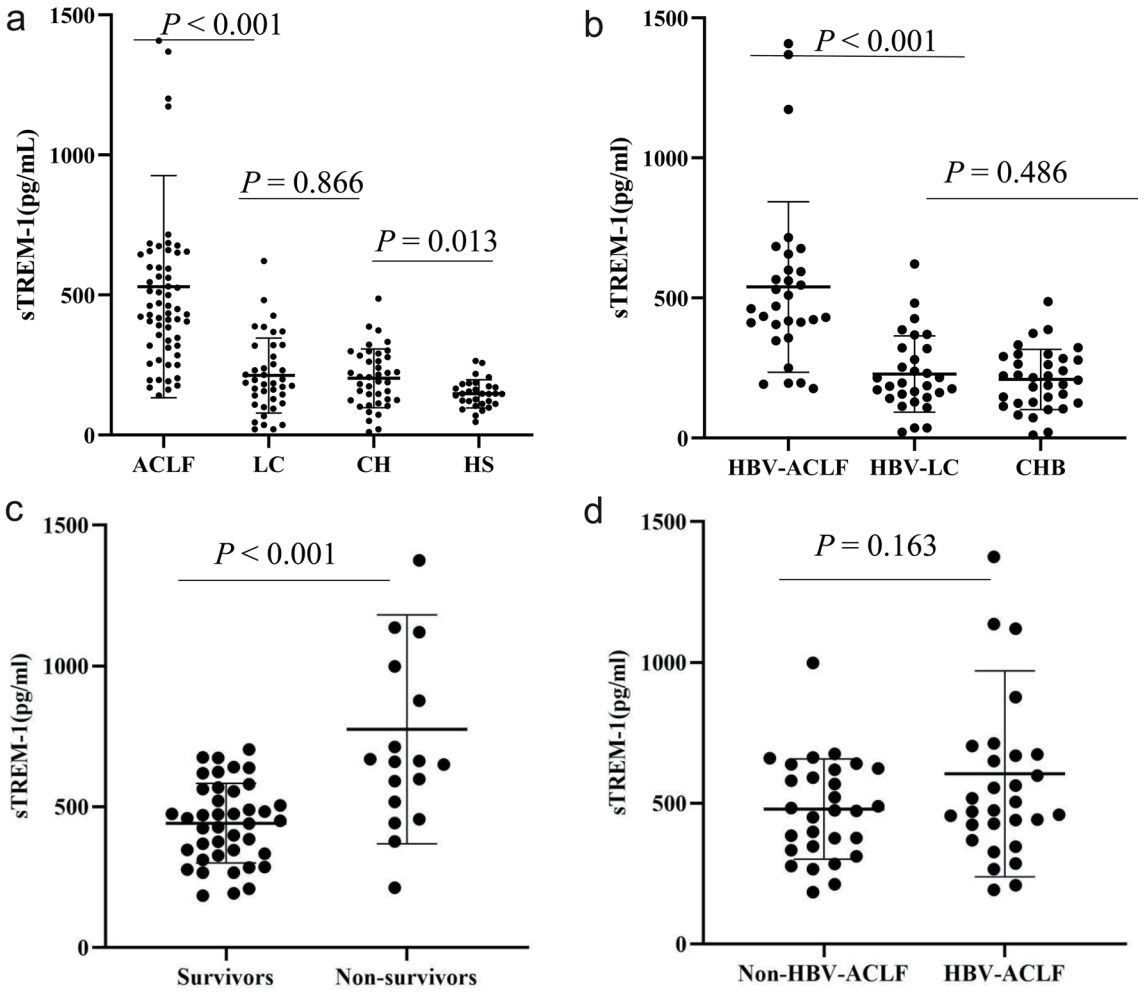

Fig. 1. (a) Comparison of serum sTREM-1 levels among the four groups: ACLF, LC (liver cirrhosis), CH (chronic hepatitis without cirrhosis and failure), and HS group; (b) Comparison of serum sTREM-1 levels among CHB, HBV-LC, and HBV-ACLF; (c) Comparisons between the survivors and non-survivors groups; (d) Comparisons between HBV-ACLF and non-HBV-ACLF.

[128.28–318.82] pg/mL), and HS (146.78 [111.14–175.73] pg/mL) (p < 0.001, Table 1). There was no significant difference in serum sTREM-1 between CH and LC patients (p = 0.866, Fig. 1a).

In China, chronic HBV infection is the most common etiology of liver failure, and ACLF accounts for more than 80% of these cases. Therefore, the serum sTREM-1 of patients with HBV infection was further analyzed. The results revealed that the serum sTREM-1 level was also the highest in HBV-ACLF patients, followed by the level in liver cirrhosis with HBV (HBV-LC) and chronic viral hepatitis B (CHB) patients (Fig. 1b). There was no significant difference in serum sTREM-1 levels between HBV-ACLF and non-HBV-ACLF patients (p > 0.05, Fig. 1d).

Elevated serum sTREM-1 as predictor for the prognosis of ACLF patients

The serum sTREM-1 level was significantly higher in the non-survivors group (661.51 [494.36–1,028.82] pg/mL), when compared to the survivors group (440.92 [308.00–523.21] pg/mL) (p = 0.001, Fig. 1c). Furthermore, the age, INR, MELD score, and MELD-Na score were significantly higher, while the platelet-to-white blood cell ratio (PWR) and serum sodium were lower in the non-survivors group, when compared to the survivors group (p < 0.05, Table 2). Next, the predictive factors for 90-day mortality in ACLF patients was further analyzed by multivariate logistic regression analysis (Table 3). The results revealed that sTREM-1 (OR: 1.007, 95% CI: 1.002–1.013, p = 0.007), INR (OR: 2.725, 95% CI: 1.004–7.963, p = 0.049), and serum sodium (OR: 0.819, 95% CI: 0.683–0.983, p = 0.032) were the independent factors for predicting the 90-day mortality. Regression analysis equation logit (p) = 19.836 + 0.007 × sTREM-1 (pg/mL) − 0.836 × Na^+ (mmol/L) + 1.003 × INR. The model in the likelihood ratio test (Omnibus Tests of model Coefficients) had statistical significance (X^2 = 31.44, p < 0.001), and had good goodness of fit in the Hosmer-Lemeshow test (X^2 = 4.228, p = 0.836).

The AUC for serum sTREM-1 was 0.82 (95% CI: 0.68–0.85, p < 0.001), and the cut-off value was 506.19 pg/mL. This was used to indicate the prognosis of ACLF, with a sensitivity of 77.78%, a specificity of 75.61%, a PPV of 88.57%, and a NPV of 58.33%. The AUC for logit (p) was 0.89 (95% CI: 0.78–1.00, p < 0.001). This was used to predict the prognosis of ACLF, with a sensitivity of 70%, a specificity of 89.74%, a PPV of 77.78%, and a NPV of 85.37% (Table 4

Table 2. Comparison of characteristics between survivors and non-survivors in patients with ACLF

Variables	Survivors (*n* = 41)	Non-survivors (*n* = 18)	*p*-value
Age (years)	52.37 ± 12.15	61.39 ± 7.72	0.005
Male (*n*,%)	32/78.05	12/66.67	0.363
HBV (*n*, %)	18/43.90	12/66.67	0.111
ALT (U/L)	115.00 (41.00–493.50)	244.50 (109.70–392.50)	0.249
AST (U/L)	145.00 (103.00–472.00)	198.00 (135.50–469.00)	0.223
TBIL (μmol/L)	277.10 (207.00–369.30)	322.65 (210.95–396.70)	0.564
ALB (g/L)	30.88 ± 4.38	29.54 ± 3.72	0.265
INR	2.09 ± 0.60	2.74 ± 0.91	0.002
Na^+ (mmol/L)	137.04 ± 3.31	133.72 ± 5.12	0.019
Cr (μmol/L)	72.00 (54.50–95.50)	67.00 (42.50–144.50)	0.980
WBC ($\times 10^9$/L)	6.82 ± 4.00	6.58 ± 1.83	0.745
PLT ($\times 10^9$/L)	101.34 ± 58.30	87.67 ± 58.30	0.413
PLR	92.53 (66.27–145.67)	86.31 (58.62–199.12)	0.612
NLR	4.83 (2.54–6.74)	5.08 (3.81–12.4)	0.229
PWR	15.38 (11.27–23.87)	11.3 (9.03–14.34)	0.039
NMR	8.61 (5.38–10.82)	8.16 (6.91–11.46)	0.640
MELD	22.81 ± 5.48	27.09 ± 6.34	0.012
MELD-Na	19.57 ± 8.02	29.13 ± 12.10	0.005
sTREM-1 (pg/mL)	440.92 (308.00–523.21)	661.51 (494.36–1,028.82)	0.001

and Fig. 2).

In order to further assess the relationship between the INR (Fig. 3a), MELD score (Fig. 3b), sTREM-1 (Fig. 3c), logit (*p*) (Fig. 3d), and 90-day mortality in ACLF patients, these patients were divided into two groups, according to the cut-off values in Table 4. The Kaplan-Meier survival curves revealed that the high INR, MELD, sTREM-1, or logit (*p*) group was correlated with the low 90-day survival rate (Fig. 3).

Discussion

In the guidelines, ACLF is defined as acute irritation in the state of chronic basic liver disease, which leads to acute liver

Table 3. Logistics regression analysis for variables associated with 90-day mortality in patients with ACLF

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (years)	1.083	1.020–1.151	0.010			
TBIL (μmol/L)	1.000	0.996–1.005	0.822			
ALB (g/L)	0.925	0.808–1.060	0.262			
INR	3.455	1.359–8.780	0.009	2.725	1.004–7.963	0.049
Cr (μmol/L)	1.008	0.998–1.018	0.107			
Na^+ (mmol/L)	0.820	0.705–0.953	0.009	0.819	0.683–0.983	0.032
PLR	0.932	0.880–0.986	0.015			
NLR	1.047	0.960–1.142	0.302			
PWR	0.978	0.928–1.030	0.397			
NMR	1.034	0.901–1.186	0.634			
MELD	1.133	1.020–1.258	0.020			
MELD-Na	1.106	1.033–1.183	0.004			
sTREM-1 (pg/mL)	1.007	1.003–1.011	0.002	1.007	1.002–1.013	0.007

sTREM-1, soluble triggering receptor expressed-on myeloid cells 1; TBIL, total bilirubin; ALB, albumin; Cr, creatinine; WBC, white blood cell count; PLT, platelet count; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio.

Table 4. Receiver operating characteristics curve for prognostic variables in patients with ACLF

Variable	*p*-value	Cut-off value	AUC (95%CI)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Logit (*p*)	<0.001	0.36	0.89 (0.78–1.00)	70.00	89.74	85.37	77.78
sTREM-1 (pg/mL)	<0.001	506.19	0.82 (0.68–0.85)	77.78	75.61	88.57	58.33
MELD-Na	0.002	23.90	0.76 (0.61–0.90)	72.22	80.49	86.84	61.91
INR	0.002	2.01	0.75 (0.62–0.88)	83.33	63.41	89.66	50.00
MELD	0.022	25.12	0.69 (0.53–0.84)	66.67	68.29	82.35	48.00

NPV, negative predictive value; PPV, positive predictive value.

failure, with a remaining system organ failure of ≥1. Without liver transplantation, the risk of death in 28 days is very high.[2,3] Therefore, assessing the patient's risk of deterioration is essential for adjustments in its monitoring, and in classifying and judiciously using scarce resources for treatment to reduce mortality. However, commonly used biomarkers in clinical practice are not convenient or accurate enough to determine the development and mortality of ACLF. Thus, the sensitivity and reliable biomarkers or models are necessary to identify patients with high risk of deterioration in clinical practice for ACLF treatment.

In the present study, the serum sTREM-1 level was statistically significantly higher in ACLF patients, when compared to the LC, CH and HS groups ($p < 0.001$). The pathophysiological mechanisms of ACLF manifest as persistent inflammatory responses and immune dysfunction, which lead to systemic inflammatory response syndrome and immune paralysis, further increasing the susceptibility to sepsis.[17] Furthermore, the exacerbation of HBV, bacterial infection and alcohol use, as the main precipitating factors, can trigger inflammation through pathogen-associated molecular patterns (PAMPs). This leads to the release of inflammatory mediators, tissue damage, and cell apoptosis/necrosis, which in turn, contributes to the release of damage-associated molecular patterns (DAMPs), further accentuating the inflammatory process.[1,18,19] TLRs/NLRs are PRRs that have an important function in inflammation, and recognizes distinct PAMPs and DAMPs. At present, it is generally considered that TREM-1 is a kind of innate immune receptor, which can amplify inflammation in inflammatory diseases by regulating the secretion of proinflammatory cytokines.[4–6] At the same time, TREM-1 and TLR-4 are stimulated to activate common signaling pathways, including PI3K, ERK1/2, IRAK1 and NF-κB activation, resulting in the synergistic production of pro-inflammatory mediators.[20] Furthermore, the inhibition of TREM-1 by inhibitory peptides is associated with the decrease in lipopolysaccharide (LPS)-induced cytokine production, such as MCP-1, TNFα, IL1β and IL10.[7] Recently, studies have indicated that in carbon tetrachloride-induced chronic liver injury and fibrosis mice, TREM-1 can only be detected in liver macrophages and monocytes, and that this was highly upregulated in Kupffer cells, circulating monocytes, and monocyte-derived macrophages. Furthermore, TREM-1 signaling promotes proinflammatory cytokine production and the mobilization of inflammatory cells to the injury location, subsequently aggravating the liver injury, inflammatory cell infiltration and fibrogenesis.[21] In gallstone patients without excessive alcohol consumption, elevated TREM-1 and decreased TREM-2 mRNA levels are closely correlated to the severity of fatty liver disease.[22] In addition, the inhibition of TREM-1 improves the inflammation and activation of inflammatory response cells in mice with alcoholic liver disease.[23]

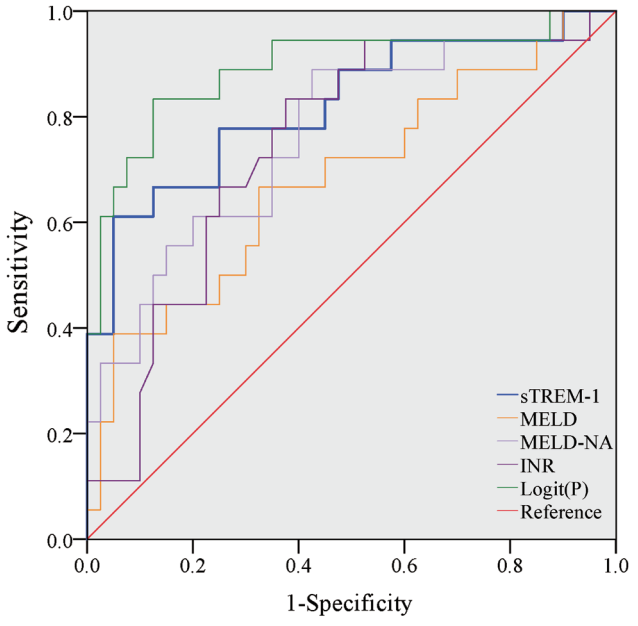

Fig. 2. Receiver operating characteristics (ROC) curve analysis for the prediction of 90-day mortality by sTREM-1, MELD, MELD-Na, INR and logit (*p*).

The present study also revealed that for ACLF, the serum sTREM-1 level was higher in the non-survivors group, when compared to the survivors group. Recently, studies have revealed that for hospitalized patients with infection in tropical, middle-income countries, such as Thailand, sTREM-1 increases with the clinical severity of the illness, as determined by the modified Sequential Organ Failure Assessment (SOFA) score.[24] Solely sTREM-1 can provide a comparable mortality discrimination, and the accuracy of mortality discrimination can be increased by combining this with other clinical biomarkers.[24] For patients with sepsis, severe sepsis and septic shock, the sTREM-1 level is positively associated with the Acute Physiologic and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, and SOFA score, and this has an earlier predictive value for 28-day mortality.[11] The similarity between sepsis and ACLF is that tremendous pro-inflammatory mediators are released, leading to excessive inflammatory response, multiple organ failure, and eventually, death. Recent studies have revealed that sTREM-1 levels are significantly elevated in ACLF patients with sepsis, when compared to patients without sepsis, and its diagnostic value for sepsis is higher, when compared to that of leukocytes, procalcitonin, and C-reactive protein.[25] The use of sTREM-1 may improve the awareness of bacterial infections in patients with cirrhosis, and contribute to the

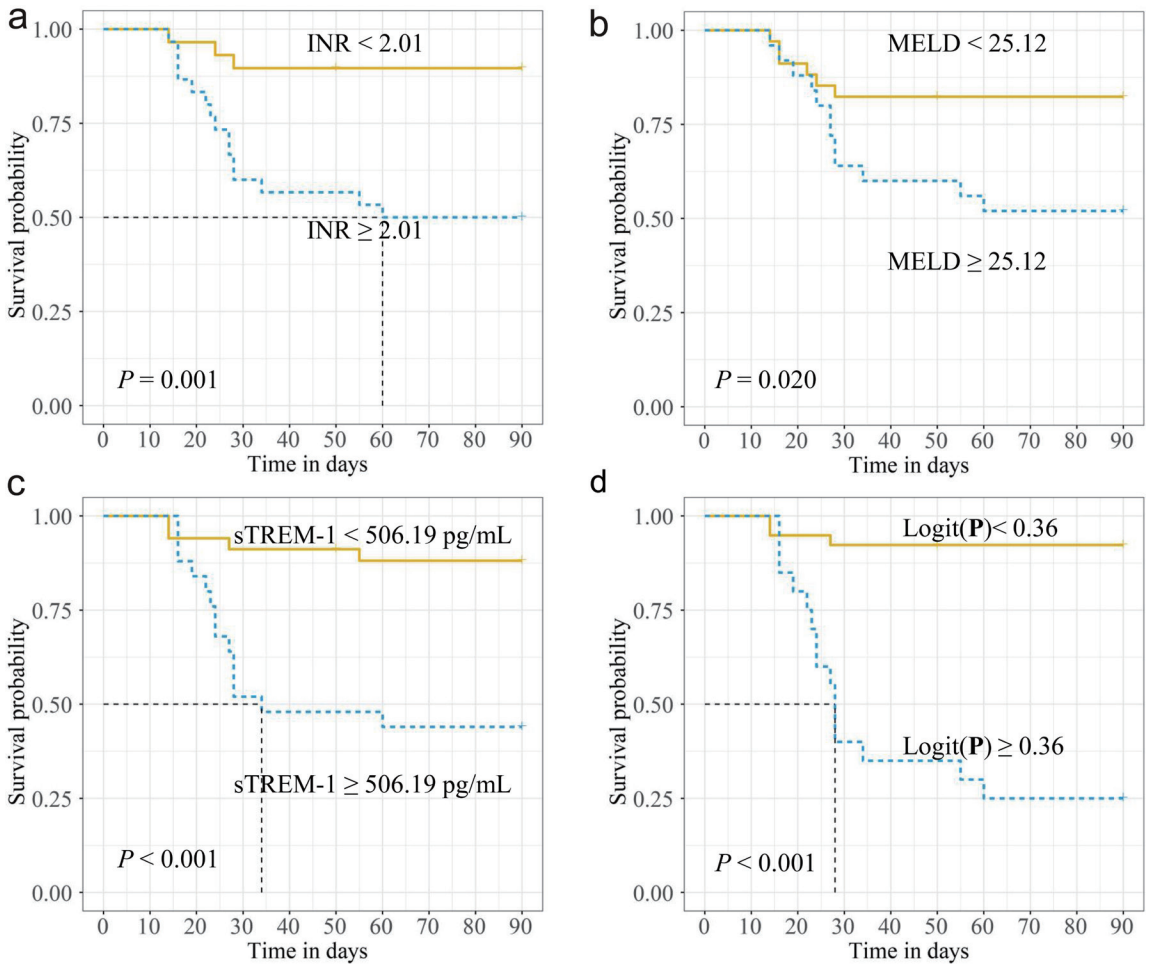

Fig. 3. (a) Kaplan-Meier survival curves for patients with INR ≥2.01 and INR <2.01; (b) Kaplan-Meier survival curves for patients with MELD score ≥25.12 and MELD score <25.12; (c) Kaplan-Meier survival curves for patients with sTREM-1 ≥506.19 pg/mL and sTREM-1 <506.19 pg/mL; (d) Kaplan-Meier survival curves for patients with logistic regression analysis equation logit (*p*) of *p* < 0.36 and *p* ≥ 0.36.

prognostic risk assessment for such patients.[26] It is noteworthy that the present study revealed that there was no particularly obvious difference in sTREM-1 levels between patients infected and uninfected with ACLF. Since the elevated TREM-1 was correlated to the degree of inflammation in the present patients, the inflammation was not merely caused by the infection, and the sample size was not large enough, the data related to sepsis in the present study were not separately displayed.

It was further revealed that the serum sodium, INR, and sTREM-1 levels were independent risk factors for the 90-day mortality of ACLF patients. Sodium is an essential factor for the osmotic pressure balance of human body fluids. Patients with liver disease are often combined with hyponatremia due to the excessive dose of diuretics, or the disorder of solute-free water excretion by the kidney.[27] A number of studies have suggested that hyponatremia is closely correlated with hepatic encephalopathy and hepatorenal syndrome.[28] The serum sodium level is notably correlated to short-term survival among candidates for liver transplant.[29] The MELD-Na score, which was modified from the MELD score, and includes total bilirubin, INR, creatinine and sodium, has a better prognostic ability for the prognosis of patients with ACLF, when compared to the MELD score.[16] The INR is derived from the prothrombin time (PT), as a common clinical practice to correct the deficiency of coagulation factors. Patients with cirrhosis have a complex balanced hemostasis between the pro-coagulant and anticoagulant. Recently, studies have revealed that the changes in coagulation in ACLF overlaps with the changes in acute decompensation (AD).[30,31] Compared to patients with AD, ACLF patients usually present with hypocoagulable features, and these are initially characterized by prolonged fibrin formation time, clot formation time, and decreased clot hardness. The difference is in the persistence of the coagulation abnormalities in patients with ACLF during the follow-up period, and normalization occurs in patients with AD. Any further deterioration of coagulation dysfunction after admission indicates systemic inflammation, which would lead to a higher short-term mortality rate.[30,31] In the present study, the regression equation derived using serum sodium, sTREM-1 and INR revealed an AUC of 0.89. This was used to indicate the prognosis for the 90-day mortality of ACLF patients, with a sensitivity of 70% and a specificity of 89.7%. Furthermore, the predictive ability of logit (*p*) was more accurate, when compared to the MELD and MELD-Na scores.

Conclusions

In summary, serum sTREM-1 is a valuable factor for predict-

ing the 90-day survival rate of patients with ACLF, and combining this with the INR and sodium in the logistic regression model may improve the accuracy in predicting the prognosis. Considering the single-center data obtained for the present study, there may be some bias. Furthermore, there was a lack of dynamic laboratory monitoring and external validity verification. Therefore, the universality needs to be further verified. Further researches based on various etiologies, with a larger number of subjects, are necessary to evaluate the association between sTREM-1 and ACLF, and explore the mechanism of higher sTREM-1 levels.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript (JJC and YH); critical revision of the manuscript for important intellectual content (TH, JJC and YH); administrative, technical, or material support, and study supervision (TH). All authors read and approved the final version of the manuscript.

Ethics statement

The protocol was approved by the Ethics Committee of the Third Central Hospital of Tianjin (No. SZX-IRB-SOP-016[F]-002-01). All participants provided a written informed consent, and the study was conducted in accordance with the Declaration of Helsinki. This study is registered in the Chinese clinical trials registry, with registration identification number: ChiCTR1900021539.

Data sharing statement

The data cannot be shared publicly due to patient confidentiality. However, the data can be obtained from the corresponding author upon reasonable request.

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