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A new prognostic model based on serum apolipoprotein AI in patients with HBV-ACLF and acutely decompensated liver cirrhosis

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Abstract

Background/Aim To investigate the prognostic value of circulating apolipoprotein AI (apoAI) levels and develop a new prognostic model in individuals with acute-on-chronic liver failure (ACLF) and acute decompensation (AD) of liver cirrhosis caused by hepatitis B virus (HBV) infection.

Methods Baseline levels of serum lipids were measured, and data concerning the presence of complications were collected from 561 HBV-ACLF and AD patients. Survival analysis was conducted by log-rank test. Proportional hazards model was used to perform multivariate analysis. The dynamics of serum apoAI levels were also explored in 37 HBV-ACLF patients.

Results In the cohort, the negatively correlation was found between the Model for End-Stage Liver Disease (MELD) score and serum apoAI levels ($r = -0.7946$, $P < 0.001$). Circulating apoAI concentration was an independent risk factor for 90-day survival according to Cox multivariate analysis. A new prognostic score-integrated serum lipid profile for ACLF patients (Lip-ACLF score = 0.86×International Normalized Ratio (INR) + 0.0034×total bilirubin (TBIL) (μmol/L) + 0.99× hepatorenal syndrome (HRS) (HRS: no/1; with/2) + 0.50×hepatic encephalopathy (HE) (grade/ponint: no/1; 1–2/2; 3–4/3) − 2.97×apoAI (g/L) + 5.2) was subsequently designed for the derivation cohort. Compared to MELD score, Child-Turcotte-Pugh (CTP) score or apoAI, Lip-ACLFs was superior for the prediction of 90-day outcomes (receiver operating characteristic curve (ROC): 0.930 vs. 0.885, 0.833 or 0.856, all $P < 0.01$), as was the validation cohort (ROC 0.906 vs. 0.839, 0.857 or 0.837, all $P < 0.05$). In Kaplan–Meier survival analysis, low apoAI levels (< 0.42 g/L) at baseline indicated poor prognosis in ACLF and AD patients. Among the 37 patients, the deceased individuals were characterised with significantly decreased serum apoAI levels during the follow-up test compared with those at

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baseline ($P < 0.05$), whereas in patients with a good prognosis, the serum apoAI levels remained stable during the follow-up.

Conclusion In HBV-ACLF and AD patients, lower serum apoAI levels suggest greater disease severity and 90-day mortality risk. For predicting the short-term prognosis of these patients, the new Lip-ACLF score might serve as a potential model.

Keywords Hepatitis B, Serum lipids, Acute-on-chronic-live failure, apoAI, Liver cirrhosis

Introduction

Acute-on-chronic liver failure, facilitating by acute events, usually happens in the basis of chronic liver disease and has multiple organ dysfunction with poor short-term survival [1]. Acute decompensation (AD) in cirrhosis patients is triggered by infection, acute bleeding of esophageal and gastric varices, ascites, hepatitis B virus (HBV) flare-up, jaundice and hepatic encephalopathy [2]. Most of the biochemical processes of lipids take place in the liver, such as the synthesis, metabolism and secretion of lipoproteins [3, 4]. Serum lipid and lipoprotein levels are clearly decreased during liver cirrhosis or liver failure [5]. Plasma concentration of high-density lipoprotein cholesterol (HDL-C) could serve as a biological indicator for system damage and predict poor prognosis in suspected sepsis individuals [6].

In liver cirrhosis, the levels of lipids, including HDL-C, are significantly decreased [7]. Poor prognosis was more often found in severe sepsis cirrhotic individuals with low circulating apolipoprotein AI levels (apoAI) [8]. ApoAI have a hepato-protective effect in liver ischaemia–reperfusion injury through regulating pyroptosis of macrophage [9]. Patients with serum levels of apoAI < 50 mg/dl had poor 90-day prognosis in chronic liver failure [5]. In a recent study, apolipoprotein AI was stratified according to two optimized cut-offs: 0.380 g/L and 0.826 g/L [10]. The cut-off values were not consistent with those used in previous prognostic analyses. Moreover, there have been no studies on the prognostic value of apoAI or a prognostic model integrating apoAI in HBV-related ACLF and AD patients.

Although prognostic role of apoAI have been investigated, some issues warrant further investigation, as follows: (i) in HBV-ACLF and AD patients, there is no appropriate cut-off value for serum apoAI levels to predict short-term prognosis; and (ii) the relationship between dynamic changes in apoAI concentrations and the survival probability of patients has not been revealed. In this study, the hypothesis was that serum apoAI levels are significantly associated with disease severity grade, infection incidence and prognosis in HBV-related ACLF and AD patients. The prognostic value of the serum apoAI was investigated, and a new prognostic model integrating the apoAI was developed for individuals with HBV-ACLF and AD. Moreover, the dynamic changes in serum apo AI levels in patients with different prognoses were further investigated.

Methods

Study population

From March 2012 to November 2022, data from 561 HBV-ACLF and AD patients were retrospectively collected at Ruijin Hospital. During 90 days after admission, patients who died or received liver transplantation (LT) were considered to have a poor prognosis. Liver decompensation was diagnosed according the incidence of complications [2, 11, 12]. ACLF patients were diagnosed according to previous consensus recommendations for ACLF [1]. Furthermore, serum levels of apoAI were detected dynamically for 37 HBV-AD and ACLF patients in the cohort. Chronic liver disease induced by autoimmune hepatitis, viral infections other than HBV, drug-induced liver injury or had received steroids within 6 months were excluded. Within 3 days after admission, antiviral therapy (e.g., tenofovir, entecavir, or tenofovir alafenamide) was given to patients who had not received anti-HBV therapy. The presence of the following comorbidities was recorded: nonhepatic comorbidities (type 2 diabetes mellitus [T2DM], obesity and hypertension) and hepatic comorbidities (nonalcoholic fatty liver disease [NAFLD]). More detailed definitions of the comorbidities are provided in the Supplementary Information. Patients with T2DM or hypertension received dietary therapy or specialist treatment, and appropriate adjustments were made according to specialist recommendations after admission.

Lipid assays and laboratory parameters

Baseline serum lipid profile including apoAI were detected via a standardized process at Ruijin Hospital. Serum samples for measuring lipid profiles, including apoAI, were collected in the early morning on an empty stomach. Thus, the influence of diet and activity on the measurement of serum apoAI levels is largely reduced. The serum lipid analyses were performed on a Beckman Coulter AU5800 analyser (California). Serum ApoA-I levels were determined by immunoturbidimetry. Serum total cholesterol (TC) and triglyceride (TG) levels were detected with cholesterol oxidase method and glycerol-3-phosphate-peroxidase chromogenic (GPO-POD)

methods, respectively [13]. The serum low-density lipoprotein cholesterol (LDL) and HDL-C concentration was determined with the protective reagent and the immunoseparation method respectively [14]. According to previous studies, the assessment of ACLF patients at Days 3–7 can aid in making clinical decisions [15]. The dynamic changes in the MELD score at 14 days were notably different between groups divided by 3-month outcomes in liver failure [16]. Lipid profile levels were dynamically measured on Days 3–7 and Days 10–14 after baseline in the 37 patients. During 24 h after enrolment, clinical parameters and laboratory tests were performed.

Development and validation of Lip-ACLFs for HBV-ACLF and AD

Two cohorts were separated by admission time. The derivation cohort ($n = 289$) was enrolled between 2012/03 and 2017/12. Univariate analysis was conducted to select risk prognostic factor(s) in the derivation cohort. Then multivariate Cox regression analysis was performed to calculate estimated coefficients and develop a new prognostic model. The new model, called Lip-ACLFs, was compared with other prognostic models for evaluating 90-day mortality risk. In the validation cohort ($n = 272$) admitted between 2018/01 and 2022/11, Lip-ACLFs were tested using the parameters of the derivation cohort.

Statistical analysis

The data were analysed using GraphPad Prism (version 8.0), SPSS v26 (Chicago, Illinois, USA), R 4.2.3 (Vienna, Austria) for Windows. Continuous variables were shown by the median (Q1-Q3), categorical variables are described by frequency (percentage). Student's t test was conducted when data satisfying normal distribution, otherwise Mann–Whitney test was performed. A log-rank test was performed to compare the survival rate. Cox regression was used to examine the impact of one or several different independent variables on survival (a given endpoint) analysis [17]. In previous studies, prognostic models were also derived from Cox regression analysis [18, 19]. The areas under of ROC cures (AUROCs) of different prognostic models were assessed using DeLong's test (MedCalc software version 20.104).

Results

Analysis of 561 ACLF and AD patients stratified by 90-day outcomes

There were 262 ACLF patients and 299 AD patients included in the study. The clinical parameters (survivors, $n = 443$; nonsurvivors, $n = 118$) are shown in Table 1. Compared with survivors, nonsurvivors had the higher levels of international normalized ratio (INR), total bilirubin (TBIL), leukocyte count and higher disease grade (MELD score) (all $P < 0.001$). The percentage of nucleoside analogue (NUC) cessation induced liver failure was higher in nonsurvival group compared to survival group ($P = 0.01$). Compared with survivors, nonsurvivors had lower serum sodium concentrations ($P < 0.0001$).

Compared with those of survivors, the incidences of complications such as hepatorenal syndrome (HRS) (39.0% vs. 3.6%), hepatic encephalopathy (HE) (III-IV) (20.3% vs. 1.6%) and infection (72% vs. 37.9%) were significantly greater in nonsurvivors (all $P < 0.0001$) (Table 1). The nonsurviving group had obviously lower concentrations of apoAI and HDL-C, but not TG, than did the surviving group (all $P < 0.05$). The proportions of comorbidities (obesity, type 2 DM, hypertension or NAFLD) were comparable between the two groups (Table 1).

Lower ApoAI levels were associated with a greater severity of ACLF and AD

As shown in Fig. 1A and B, when patients were stratified by grades of Child-Turcotte-Pugh (CTP) (A/B/C grade) or MELD, patients with C grade or MELD score > 26 had the lowest serum apoAI levels among the three subgroups (both $P < 0.0001$).

Negative correlations of ApoAI levels with the number of complications and the infection incidence rate

When these patients were divided by the number of complications, serum apoAI levels of individuals with 2 or more complications were obviously lower compared to those with 1 or no complications (Fig. 1C). Patients with infection had obviously lower serum apoAI levels than those without infection did (Fig. 1D). Moreover, the optimized apoAI cut-off value of < 0.42 g/L for prognosis predicting was determined via Youden's index. The MELD score, incidence rate of infection and mortality rate at 90 days in individuals with serum apoAI levels ≥ 0.42 g/L were lower than those in patients with apoAI levels < 0.42 g/L ($P < 0.0001$) (Fig. 2A, B and C).

Prognostic value of apoAI and multivariate analysis

The MELD scores of ACLF and AD patients were negatively correlated with circulating apoAI concentration; in contrast, positively correlation was found between circulating albumin levels with apoAI concentrations (Fig. 3A, B).

The clinical parameters of the derivation cohort were compared to validation cohort (Table S1). Significant differences were demonstrated in the clinical parameters (ALT, AST, Na), 90-day mortality rate and severity of disease (incidence rate of HRS, MELD score) between the two cohorts ($P < 0.05$). Univariate analysis was first performed in the derivation cohort to identify significant baseline factors for prognosis (sex, the INR, TBIL, Cr, Na, HDL, LDL, TC, apoAI, albumin, leukocytes, HRS, infection, ascites and HE, $P < 0.05$) (Table 2). Multivariate

Table 1 Clinical characteristics of ACLF and DLC patients according to the clinical outcome (90-d survival)

Characteristics	Total (*n* = 561)	Survivors (*n* = 443)	Nonsurvivors (*n* = 118)	*P* Value
Age, (y)	51 (42–61)	51 (43–61)	51 (41–60)	0.86
Sex (male), n (%)	449 (80.0%)	348 (78.6%)	101 (85.6%)	0.089
HBV markers				
HBeAg (+), n (%)	221 (39.4%)	184 (41.5%)	37 (31.4%)	**0.044**
HBV reactivation				
Spontaneous reactivation, n (%)	382 (68.1%)	299 (67.5%)	83 (70.3%)	0.01
NUC cessation, n (%)	69 (12.3%)	47 (10.6%)	22 (18.7%)	
NUC resistance, n (%)	15 (2.7%)	12 (2.7%)	3 (2.5%)	
Without reactivation, admission for complication, n (%)	95 (16.9%)	85 (19.2%)	10 (8.5%)	
Haematology				
Hb (g/L)	120 (104–132)	120.0 (103.0-132.3)	119.0 (105.8–132.0)	0.99
Leukocytes ($\times 10^9$/L)	4.7 (3.0-6.6)	4.2 (2.9–6.1)	6.3 (4.5–9.2)	**0.0001**
Thrombocytes ($\times 10^9$/L)	75 (52–112)	73.0 (49.0-112.0)	80.0 (60.8–110.0)	0.14
INR	1.5 (1.3–1.8)	1.4 (1.2–1.7)	2.0 (1.7–2.5)	**0.0001**
Biochemistry				
ALT (U/L)	77 (33–271)	63.0 (30.0-223.0)	117.0 (65.8-464.3)	**0.0002**
AST (U/L)	105 (48–230)	81.0 (43.0-185.0)	181.5 (110.5-445.8)	**0.0001**
TBIL (μmol/L)	136.6 (37.8-341.3)	86.5 (31.2-254.4)	424.0 (305.5-496.7)	**0.0001**
Albumin (g/L)	29 (25–33)	29 (26–33)	27 (24–31)	0.0001
Na (mmol/L)	138 (135–140)	139 (136–141)	135.0 (131.0-138.0)	**0.0001**
Cr (μmol/L)	69 (59–82)	69.0 (59.0–81.0)	72.0 (62.0-91.3)	0.068
Serum lipid profiles				
HDL-C	0.50 (0.28–1.01)	0.66 (0.33–1.09)	0.27 (0.22–0.39)	**0.018**
LDL-C	1.50 (0.81–2.17)	1.63 (1.04–2.24)	0.74 (0.32–1.60)	**0.0001**
TG	1.00 (0.76–1.47)	1.00 (0.75–1.47)	1.02 (0.80–1.58)	0.99
TC	2.74 (1.91–3.57)	2.97 (2.19–3.80)	1.83 (1.18–2.45)	**0.0001**
ApoAI	0.54 (0.28–0.96)	0.67 (0.36–1.03)	0.21 (0.15–0.34)	**0.0001**
Comorbidities				
Obesity	215 (38.3%)	162 (36.6%)	53 (44.9%)	0.098
NAFLD	32 (5.7%)	23 (5.2%)	9 (7.6%)	0.37
T2DM and IGT	113 (20.1%)	90 (20.3%)	23 (19.5%)	0.898
Hypertension	80 (14.3%)	65 (14.7%)	15 (12.7%)	0.766
Liver-related complications				
Ascites, n (%)	432 (77.0%)	332 (74.9%)	100 (84.7%)	**0.025**
HRS, n (%)	62 (11.1%)	16 (3.6%)	46 (39.0%)	**0.0001**
Bacterial infection	253 (45.1%)	168 (37.9%)	85 (72.0%)	**0.0001**
HE(III-IV), n (%)	31 (5.5%)	7 (1.6%)	24 (20.3%)	**0.0001**
GEVB, n (%)	44 (7.8%)	32 (7.2%)	12 (10.2%)	0.29
Prognosis				
MELD score	18.3 (12.6–23.8)	16.3 (11.9–21.1)	26.6 (23.4–29.6)	**0.0001**

Notes. The values are presented as numbers (%) or medians (quartile range). Boldface P values indicate statistical significance

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; HBV, hepatitis B virus; NUC, nucleoside analogues; Hb, haemoglobin; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; Cr, creatinine; TG, triglyceride; TC, total cholesterol, LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; apo AI, apolipoprotein AI; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; IGT, impaired glucose tolerance; HRS, hepatorenal syndrome; HE, hepatic encephalopathy; GEVB, gastroesophageal variceal bleeding; MELD, model for end-stage liver disease

Cox analysis including the aforementioned clinical factors was performed, and apoAI, TBIL, INR, HE and HRS were identified as independent factors for 90-day outcome (Table 2).

Development and validation of Lip-ACLFs

According to the abovementioned multivariate Cox analysis, a new prognostic model was developed and shown below: Lip-ACLFs = 0.86×INR + 0.0034×TBIL (μmol/L) + 0.99×HRS (no/1; with/2) + 0.50×HE (grade/point, no/1; 1–2/2; 3–4/3) − 2.97×apoAI (g/L) + 5.2. The new Lip-ACLF score was developed using the regression

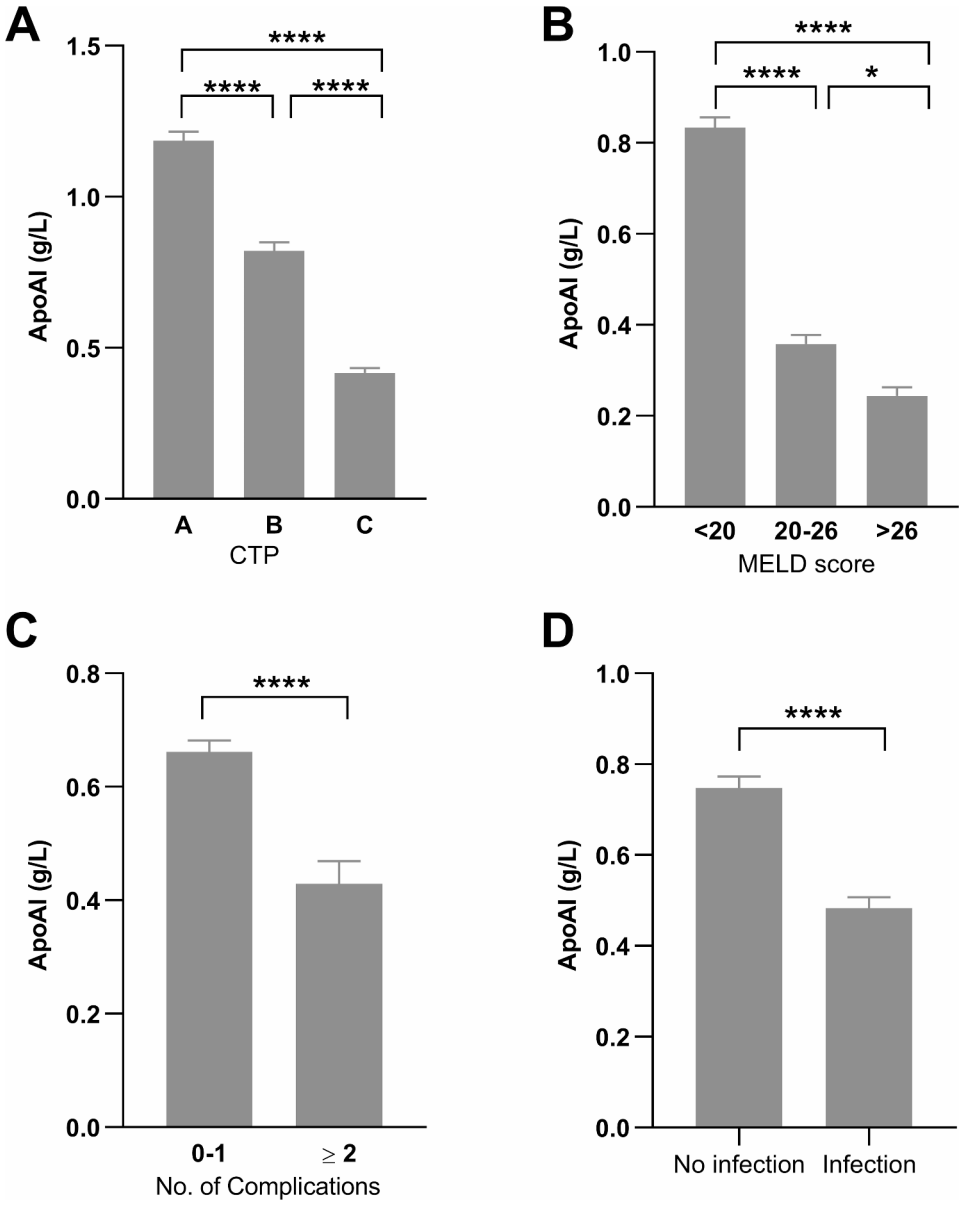

Fig. 1 Comparison of serum apoAI levels according to CTP scores (**A**), MELD scores (**B**), number of complications (**C**) and infection status (**D**) in the whole cohort. No., number, **** $P < 0.0001$, * $P < 0.05$.

coefficient of each risk factor (Table 2), and a constant was added to avoid negative values. In the ROC analysis (Fig. 3C), in the derivation cohort, the AUROCs of MELD scores, CTP scores or apoAI levels were lower than those of Lip-ACLFs in predicting 90-day mortality (0.885, 0.833 or 0.856 vs. 0.930, $P < 0.01$). The Lip-ACLFs was subsequently tested in the validation cohort, which revealed that the Lip-ACLFs had higher AUROCs than did the MELD scores, CTP scores or apoAI (0.906 vs. 0.839, 0.857 or 0.837, all $P < 0.05$) (Fig. 3D).

Serum apoAI levels and 90-day survival of ACLF and AD patients

The whole cohort was stratified into groups according to the abovementioned apoAI cut-off value (≥ 0.42 g/L or not) or apoAI quartiles (q1: < 0.28, q2: 0.28–0.54, q3: 0.54–0.96, q4: >0.96). The group with lower serum apoAI levels (< 0.42 g/L) had a significantly greater mortality probability than the other group (≥ 0.42 g/L) did ($P < 0.0001$) (Fig. 4A). The q1 and q2 patients had a greater 90-day mortality probability (q1: 48.7%, q2 20.0%) than the patients with higher serum apoAI levels did (q3: 7.7%, q4: 0.8%) ($P < 0.0001$) (Fig. 4B).

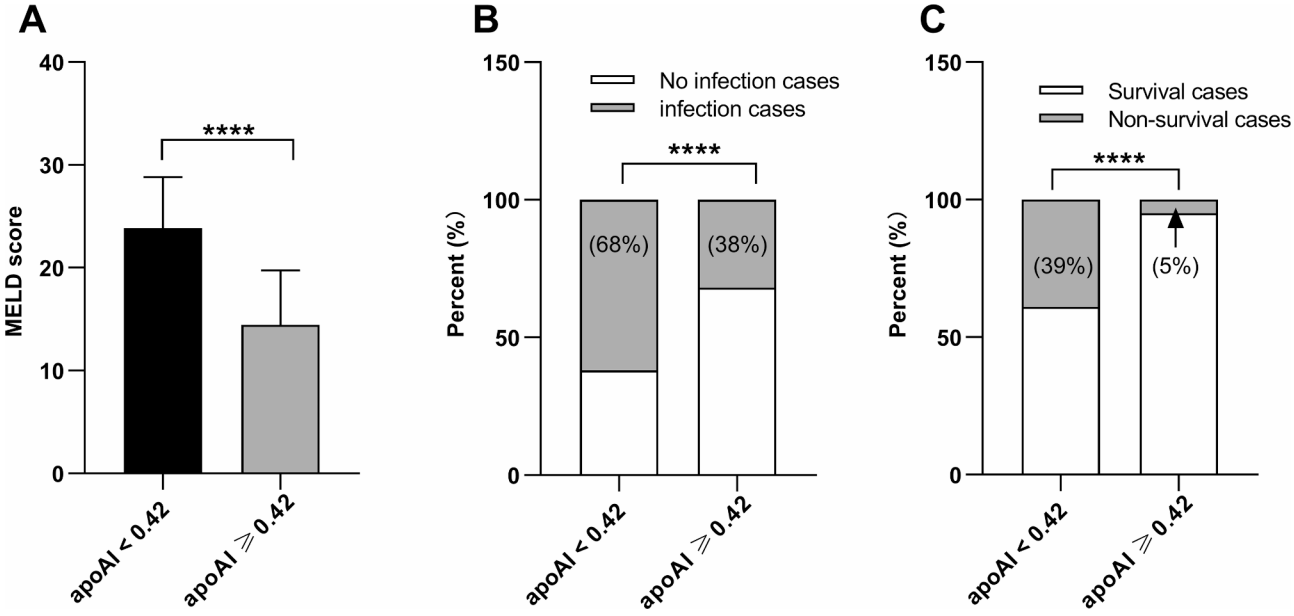

Fig. 2 Comparison of the MELD score, incidence rate of infection and survival rates according to the serum apoAI strata in the whole cohort (**A**, **B** and **C**). **** $P < 0.0001$

Continuous measurement in serum apoAI

Further study was performed to investigate whether there were significant differences in apoAI dynamic changes during the disease course between patients with different disease prognoses. The detailed characteristics of the 37 patients whose apoAI levels were dynamically monitored are shown in Table S2. The circulating apoAI levels of 37 patients were dynamically measured (baseline, 2nd time point: 3–7 days; 3rd time point: 10–14 days). Among the 37 patients, in the survival individuals, the serum levels of apoAI were not reduced significantly ($P > 0.05$) (Fig. 5A). In the deceased group, apoAI levels decreased progressively at the 2nd and 3rd time points ($P < 0.05$) (Fig. 5B).

Discussion

Serum lipid profile has prognostic value in hepatitis E virus-triggered ACLF [18] or reflect liver damage in hepatitis B infected patients [20]. ApoAI, which is the main structural component of HDL, has protective effects on endothelial cells and limits oxidative damage [21]. In this study, among HBV-ACLF and AD patients, serum apoAI levels were independently associated with 90-day survival. Compared with MELD scores or CTP scores, Lip-ACLFs have greater prognostic value. Dynamic changes in serum apoAI levels could also predict the prognosis of ACLF and AD. It was speculated that lower levels of serum apoAI may reflect serious liver injury. The prognostic value of base and dynamic changes of apoAI levels in HBV-ACLF patients further support the findings of previous studies.

The expression of serum lipids not only results from liver injury [22] but also mediates anti-inflammatory effects via the transcriptional regulator ATF3 [23]. rHDL may alleviate the inflammatory reaction by lipopolysaccharide [24]. COVID-19 patients' respiratory symptoms and inflammatory parameters improved when they received an apoAI-containing HDL mimetic [25]. Lipid metabolism may affect the disease progression of HBV-ACLF and AD patients. The concentrations of circulating lipids were decreased in individuals with liver cirrhosis and liver failure [26, 27]. In this study, a lower circulating level of apoAI indicated a greater degree of disease severity. For patients with end-stage liver diseases, MELD scores have been widely used for evaluating prognosis [28]. When ACLF patients and AD patients have comparable MELD scores, there is an urgent need to search for new biomarkers that could further improve MELD score's predictive accuracy.

In the present study, individuals with MELD scores > 18 were stratified by an optimized apoAI cut-off (< 0.42 g/L), and the subgroup with lower serum apoAI levels had a poorer prognosis than the other subgroup did (Figure S1). Moreover, patients with more than one complication had significantly lower serum apoAI levels. Similarly, lower circulating apoAI concentration was detected in HEV-ACLF patients who presented with more than two organ failures than those in other groups [18]. These results demonstrated that a lower level of apoAI has significant prognostic value in identifying patients with a greater 90-day mortality risk. Early interventions, such as liver transplantation, need to be considered for patients with early-stage disease. There was great heterogeneity in the cohort with high MELD scores. Although the prognostic value of apoAI was comparable to that of MELD

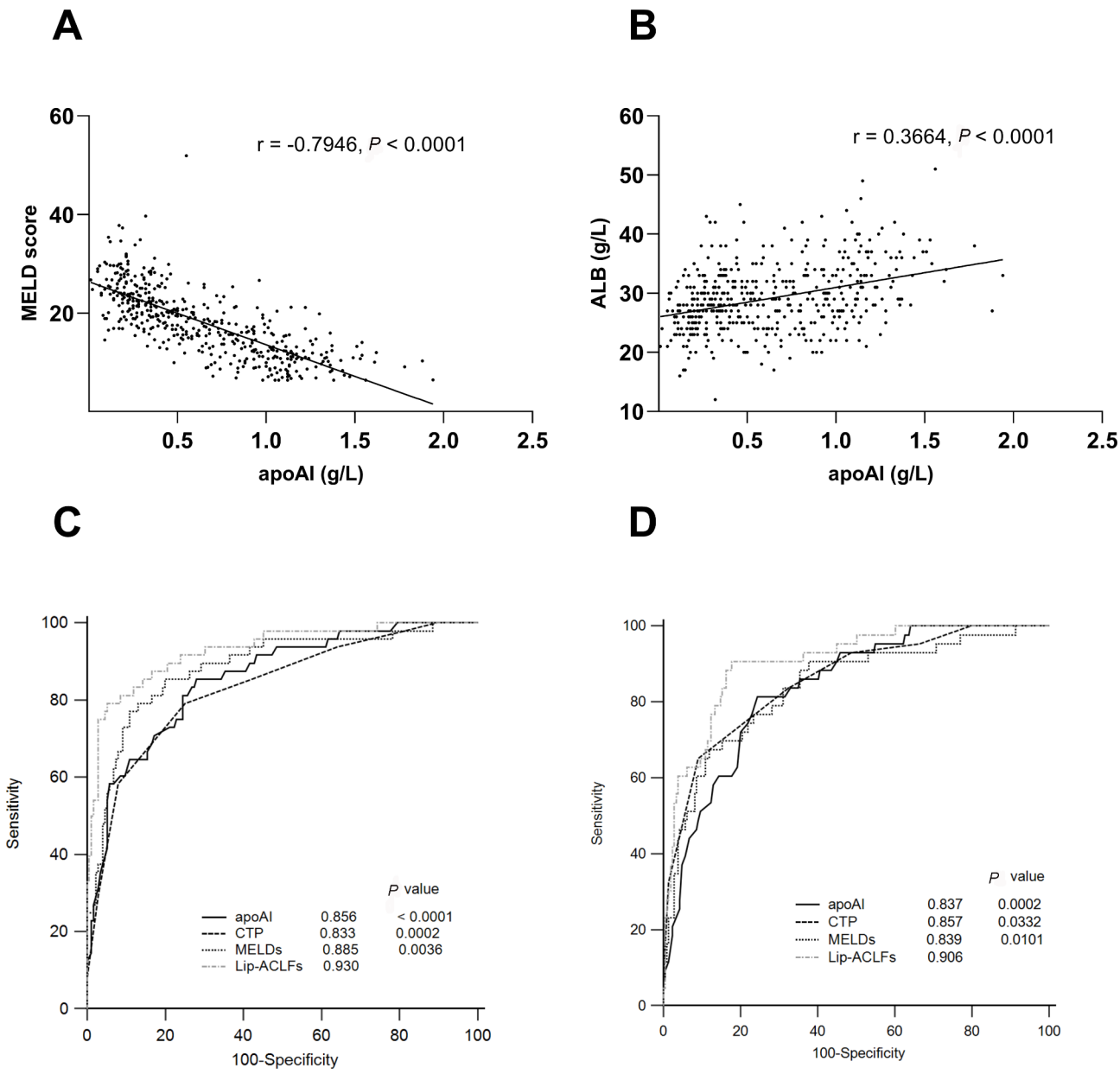

Fig. 3 (**A**) The MELD scores were negatively correlated with circulating apoAI concentration. (**B**) Serum apoAI levels were positively correlated with serum albumin levels in the whole cohort. (**C**) In the derivation cohort, the AUROCs of MELD scores, CTP scores, apoAI levels and Lip-ACLFs. (**D**) In the validation cohort, the AUROCs of MELD scores, CTP scores, apoAI levels and Lip-ACLFs

scores or CTP scores, the prognostic model integrating apoAI (Lip-ACLFs) performed better than MELD scores and CTP scores in predicting prognosis. In addition, serum apoAI levels can be easily detected and monitored dynamically in the clinic. The new prognostic model, the Lip-ACLF score, is based on three clinical testing parameters (INR, TB and apoAI) and the presence of two complications (HRS and/or HE). The Lip-ACLF score has a simpler calculation process and is easy to implement in clinical practice compared to MELD score. This would improve the accuracy of current prognostic prediction models for early clinical decision-making. The validation cohort (late enrolment) had a lower disease severity and 90-day mortality rate than did the derivation cohort (early enrolment), which may be attributed to the current update of antiviral therapy awareness according to the guidelines and the progress of health education for patients.

Although previous studies have performed prognostic analysis in patients with liver failure stratified by the apoAI level [5, 10], detailed information on the dynamic changes in apoAI levels has not been

Table 2 Multivariate analysis of 90-day mortality in the derivation cohort via the Cox regression model

	Univariate Analysis		Multivariate Analysis		*P* value
	HR (95% CI)	*P* value	HR (95% CI)	Regression coefficient	
age	0.985 (0.967–1.004)	0.114			
Sex	0.429 (0.197–0.934)	0.0033			
apoAI	0.012 (0.003–0.049)	< 0.001	0.051 (0.004–0.650)	-2.97	0.022
TC	0.437 (0.324–0.589)	< 0.001			
TG	1.068 (0.745–1.531)	0.719			
HDL	0.049 (0.015–0.165)	< 0.001			
LDL	0.438 (0.295–0.651)	< 0.001			
WBC	1.129 (1.084–1.177)	< 0.001			
TBIL	1.005 (1.004–1.006)	< 0.001	1.003 (1.001–1.006)	0.0034	0.004
Albumin	0.911 (0.867–0.956)	< 0.001			
Cr	1.009 (1.005–1.014)	< 0.001			
Na	0.878 (0.842–0.915)	< 0.001			
INR	2.592 (2.125–3.162)	< 0.001	2.371 (1.533–3.665)	0.86	< 0.001
Obesity	1.35 (0.855–2.133)	0.198			
Ascites	1.507 (1.095–2.075)	0.012			
Infection	2.870 (1.753–4.698)	< 0.001			
HE	2.614 (1.981–3.448)	< 0.001	1.644 (1.080–2.502)	0.50	0.020
HRS	8.973 (5.619–14.329)	< 0.001	2.682 (1.226–5.870)	0.99	0.014

Abbreviations: HR, hazard ratio; apoAI, apolipoprotein AI; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; WBC, white blood cell count; TBIL, total bilirubin; Cr, creatinine; INR, international normalized ratio; HE: hepatic encephalopathy; HRS, hepatorenal syndrome

specifically investigated. In this study, dynamic changes in apoAI were investigated in patients with different disease prognoses. Small intestine and liver are the main places for synthesis of apoAI, which served as the main protein component of HDL [29]. In Wolf et al.'s study, HDL and apoAI were decreased at 1–7 d post-LT and clearly recovered at 14 or 30 days post-LT [30]. Dynamic changes in certain serum lipid concentrations during LT are correlated with the extent of liver regeneration and function [30]. In this study, serum apoAI levels of individuals with a poor prognosis decreased from baseline at the 2nd time point and became more obvious later at the 3rd time point. Among patients with a good prognosis, serum apoAI levels were comparable over the course of disease. It was inferred that the decrease in serum apoAI levels reflected impaired liver functional reserve or hepatocyte regeneration in patients with a poor prognosis. Li et al. reported that in a mouse model, apoAI enhanced hepatocyte regeneration 48 h after LT through the AMPK-PGC-1α pathway to regulate mitochondrial biogenesis [31].

It has been reported that apoAI alleviates lung injury and protects against sepsis by binding to lipoteichoic acid [32]. HDL can protect against endotoxin [33] and downregulate proinflammatory response [34]. Furthermore, rHDL inhibited LPS-induced cytokine overproduction in cirrhosis patients ex vivo [24]. ApoAI has been found to have an anti-inflammatory effect on systemic inflammation [35] in sepsis and HIV [36]. In ACLF, robust systemic inflammation could lead to tissue injury and subsequent organ(s) failure [37]. In this study, lower apoAI levels indicated a greater number of complications (such as ascites and HRS). ApoAI may play an anti-inflammatory role by neutralizing LPS, downregulating inflammatory factor expression and stabilizing the function of endothelial cells. It was reported that apoAI enhances the antibiotic efficacy of lysocin E [38]. In the cohort of this study, higher circulating concentration of apoAI indicated the lower incidence of infection. These results suggest that the lipid profile might have protective value against infection in HBV-ACLF and AD patients.

Strengths and limitations

The levels of serum apoAI decreased across the clinical grades as did the presence of complications or infection. Serum apoAI could act as a robust prognostic parameter in decompensated liver cirrhosis and ACLF induced by HBV. The ApoAI level-integrated prognostic model (Lip-ACLFs) has good potential for use in the clinical prediction of 90-day outcomes. Some limitations exist in the study. Above all, patients' enrolment was retrospectively collected, and some patients were transferred to the hospital of this study after receiving treatment in local hospitals, so selection bias might exist. Second, the levels of serum hormones, such as thyroid hormones, which may be involved in the regulation of serum lipids, were not investigated. Third, in this study, most cases of ACLF occurred after a flare of HBV or self-withdrawal of NUC, and serum apoAI levels were not accessible early in the onset of disease (pre-ACLF). In future prospective

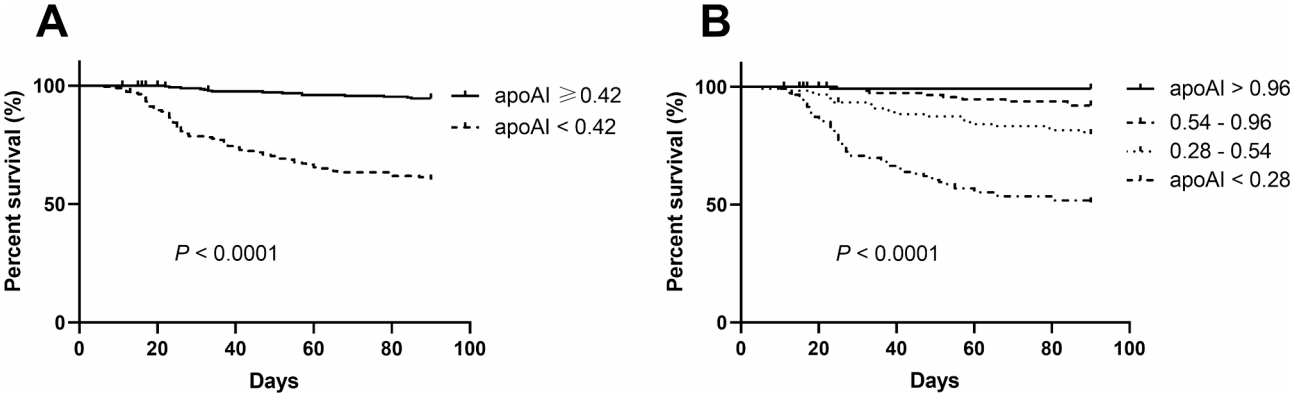

Fig. 4 The survival probability curve of the whole cohort stratified according to optimized apoAI cut-off value (≥ 0.42 g/L) (**A**) or apoAI quartiles (**B**)

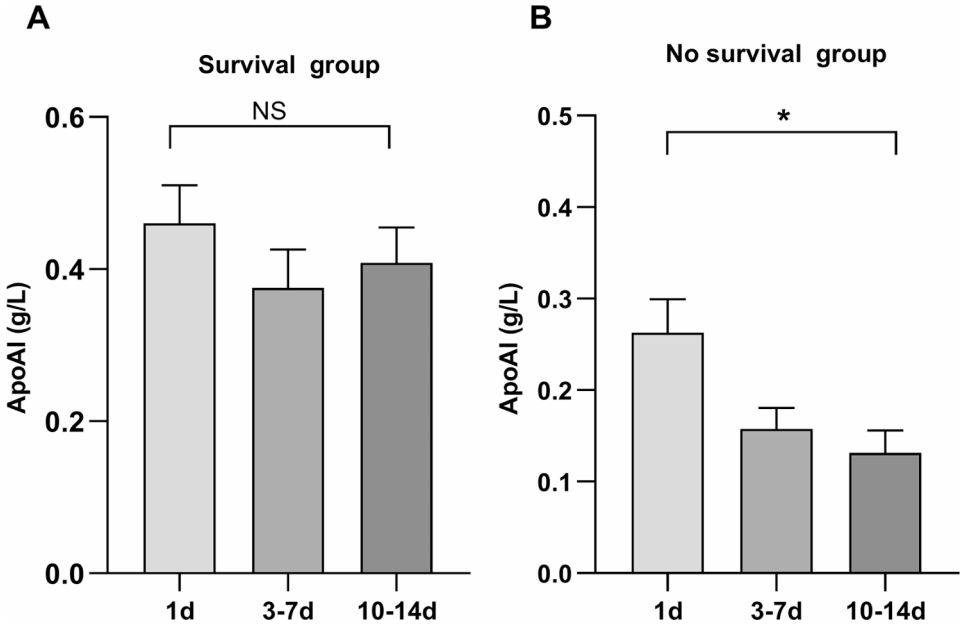

Fig. 5 Longitudinal serum apoAI level analysis of 37 patients from the validation cohort according to 90-day outcome. In the survival group (**A**) and nonsurvival group (**B**), serum levels of apoAI were measured at baseline, at the 2nd time point (3–7 days) and at the 3rd time point (10–14 days). * $P < 0.05$

studies, determining serum apoAI levels at disease onset would be helpful for understanding the hepatoprotective mechanisms of apoAI in ACLF. In addition, serum cytokines, which may reflect the inflammatory state of HBV-AD and ACLF patients, were not measured in the cohort. The correlations between the lipid profile and serum cytokines in the cohort warrant further investigation. Finally, in alcoholic or drug-induced liver failure, whether circulating ApoAI has the same predictive value warrants further study.

Conclusion

In conclusion, lower serum apoAI levels were correlated with more severe illness and a greater risk of infections. The Lip-ACLF score, which includes serum apoAI levels, may serve as a promising model to predict the prognosis of AD and ACLF patients.

Abbreviations

LDL-C	Low-density lipoprotein cholesterol
ACLF	Acute-on-chronic liver failure
ALT	Alanine aminotransferase
TC	Total cholesterol
AD	Acute decompensation
apoAI	Apolipoprotein AI
NUC	Nucleoside analogue
AST	Aspartate aminotransferase
Cr	Creatinine
GEVB	Gastroesophageal variceal bleeding
Hb	Haemoglobin
HBV	Hepatitis B virus
TBIL	Total bilirubin
HRS	Hepatorenal syndrome
HDL-C	High-density lipoprotein cholesterol
HE	Hepatic encephalopathy
INR	International normalized ratio
TG	Triglyceride
LT	Liver transplantation
NAFLD	Nonalcoholic fatty liver disease
MELD	Model for End-Stage Liver Disease

Supplementary Information

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Supplementary Material 1

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Author contributions
Study conception and design: Q. Xie, R. Yin, X. Xiang. Clinical data collection was performed by R. Mo, Z. Zhang, Y. Zhou, Y. Wang, C. Qian, P. Yin, C. Zhang, H. Fu. Statistical work and draft writing were done by R. Mo and Z. Zhang.

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Data availability
The data used or analyzed in the present study are available from the corresponding authors on reasonable request.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The research was approved through the human Ethical Committee of Ruijin Hospital.

Informed consent
Informed consent was waived because this was a retrospective study.

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References

1. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, Saigal S, Saraf N, Soin AS, Devarbhavi H, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int. 2019;13(4):353–90.
2. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, Valsecchi MG. Clinical states of cirrhosis and competing risks. J Hepatol. 2018;68(3):563–76.
3. Cicognani C, Malavolti M, Morselli-Labate AM, Zamboni L, Sama C, Barbara L. Serum lipid and lipoprotein patterns in patients with liver cirrhosis and chronic active hepatitis. Arch Intern Med. 1997;157(7):792–6.
4. Chrostek L, Supronowicz L, Panasiuk A, Cylwik B, Gruszewska E, Flisiak R. The effect of the severity of liver cirrhosis on the level of lipids and lipoproteins. Clin Exp Med. 2014;14(4):417–21.
5. Trieb M, Rainer F, Stadlbauer V, Douschan P, Horvath A, Binder L, Trakaki A, Knuplez E, Scharnagl H, Stojakovic T, et al. HDL-related biomarkers are robust predictors of survival in patients with chronic liver failure. J Hepatol. 2020;73(1):113–20.
6. Cirstea M, Walley KR, Russell JA, Brunham LR, Genga KR, Boyd JH. Decreased high-density lipoprotein cholesterol level is an early prognostic marker for organ dysfunction and death in patients with suspected sepsis. J Crit Care. 2017;38:289–94.
7. Arain SQ, Talpur FN, Channa NA, Ali MS, Afridi HI. Serum lipid profile as a marker of liver impairment in hepatitis B cirrhosis patients. Lipids Health Dis. 2017;16(1):51.
8. Tsai M-H, Peng Y-S, Chen Y-C, Lien J-M, Tian Y-C, Fang J-T, Weng H-H, Chen P-C, Yang C-W, Wu C-S. Low serum concentration of apolipoprotein A-I is an indicator of poor prognosis in cirrhotic patients with severe sepsis. J Hepatol. 2009;50(5):906–15.
9. Chen RX, Jiang WJ, Liu SC, Wang ZY, Wang ZB, Zhou T, Chen YA, Wang JF, Chang J, Wang YR, et al. Apolipoprotein A-1 protected hepatic ischaemia-reperfusion injury through suppressing macrophage pyroptosis via TLR4-NF-kappaB pathway. Liver Int. 2023;43(1):234–48.
10. Gurbuz B, Guldiken N, Reuken P, Fu L, Remih K, Preisinger C, Bruha R, Lenicek M, Petrtyl J, Reissing J, et al. Biomarkers of hepatocellular synthesis in patients with decompensated cirrhosis. Hepatol Int. 2023;17(3):698–708.
11. Shi Y, Yang Y, Hu Y, Wu W, Yang Q, Zheng M, Zhang S, Xu Z, Wu Y, Yan H, et al. Acute-on-chronic liver failure precipitated by hepatic injury is distinct from that precipitated by extrahepatic insults. Hepatology. 2015;62(1):232–42.
12. Chinese Society of, Hepatology CMA, Xu X, Duan Z, Ding H, Li W, Jia J, Wei L, Linghu E, Zhuang H. Chinese guidelines on the management of ascites and its related complications in cirrhosis. Hepatol Int. 2019;13(1):1–21.
13. Jaruratanasirikul S, Thammaratchuchai S, Puwanant M, Mo-Suwan L, Sriplung H. Progression from impaired glucose tolerance to type 2 diabetes in obese children and adolescents: a 3-6-year cohort study in southern Thailand. J Pediatr Endocrinol Metab. 2016;29(11):1267–75.
14. Islam SMT, Osa-Andrews B, Jones PM, Muthukumar AR, Hashim I, Cao J. Methods of low-density lipoprotein-cholesterol measurement: Analytical and clinical applications. EJIFCC. 2022;33(4):282–94.
15. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, Laleman W, Trebicka J, Elkrief L, Hopf C, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62(1):243–52.
16. Zheng YB, Huang ZL, Wu ZB, Zhang M, Gu YR, Su YJ, Lin CS, Zhu RH, Lin BL, Gao ZL. Dynamic changes of clinical features that predict the prognosis of acute-on-chronic hepatitis B liver failure: a retrospective cohort study. Int J Med Sci. 2013;10(12):1658–64.
17. Andrade C, Survival Analysis K-M, Curves, Regression C. Basic concepts. Indian J Psychol Med. 2023;45(4):434–5.
18. Chen C, Zhu A, Ye S, Li W, Fei L, Huang Q, Chen L. A new dyslipidemia-based scoring model to predict transplant-free survival in patients with hepatitis E-triggered acute-on-chronic liver failure. Lipids Health Dis. 2023;22(1):80.
19. Wu T, Li J, Shao L, Xin J, Jiang L, Zhou Q, Shi D, Jiang J, Sun S, Jin L, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut. 2018;67(12):2181–91.
20. Arain SQ, Talpur FN, Channa NA, Ali MS, Afridi HI. Serum lipids as an indicator for the alteration of liver function in patients with hepatitis B. Lipids Health Dis. 2018;17(1):36.
21. Assmann G, Nofer JR. Atheroprotective effects of high-density lipoproteins. Annu Rev Med. 2003;54:321–41.
22. Trieb M, Horvath A, Birner-Gruenberger R, Spindelboeck W, Stadlbauer V, Taschler U, Curcic S, Stauber RE, Holzer M, Pasterk L, et al. Liver disease alters high-density lipoprotein composition, metabolism and function. Biochim Biophys Acta. 2016;1861(7):630–8.
23. De Nardo D, Labzin LI, Kono H, Seki R, Schmidt SV, Beyer M, Xu D, Zimmer S, Lahrmann C, Schildberg FA, et al. High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nat Immunol. 2014;15(2):152–60.
24. Galbois A, Thabut D, Tazi KA, Rudler M, Mohammadi MS, Bonnefont-Rousselot D, Bennani H, Bezeaud A, Tellier Z, Guichard C, et al. Ex vivo effects of high-density lipoprotein exposure on the lipopolysaccharide-induced inflammatory response in patients with severe cirrhosis. Hepatology. 2009;49(1):175–84.

25. Faguer S, Del Bello A, Danet C, Renaudineau Y, Izopet J, Kamar N. Apolipoprotein-A-I for severe COVID-19-induced hyperinflammatory states: a prospective case study. Front Pharmacol. 2022;13:936659.
26. Manka P, Olliges V, Bechmann LP, Schlattjan M, Jochum C, Treckmann JW, Saner FH, Gerken G, Syn WK, Canbay A. Low levels of blood lipids are associated with etiology and lethal outcome in acute liver failure. PLoS ONE. 2014;9(7):e102351.
27. Cui B, Guo G, Hui Y, Wang X, Liu W, Sun C. The prognostic value of high-density lipoprotein cholesterol in patients with decompensated cirrhosis: a propensity score matching analysis. J Clin Lipidol. 2022;16(3):325–34.
28. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim W. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.
29. Zamanian-Daryoush M, DiDonato JA. Apolipoprotein A-I and Cancer. Front Pharmacol. 2015;6:265.
30. Wolf JH, Holmes MV, Fouraschen S, Keating BJ, Baker T, Emond J, Rader DJ, Shaked A, Olthoff KM. Serum lipid expression correlates with function and regeneration following living donor liver transplantation. Liver Transpl. 2016;22(1):103–10.
31. Li CX, Chen LL, Li XC, Ng KT-P, Yang XX, Lo CM, Guan XY, Man K. ApoA-1 accelerates regeneration of small-for-size fatty liver graft after transplantation. Life Sci. 2018;215:128–35.
32. Jiao YL, Wu MP. Apolipoprotein A-I diminishes acute lung injury and sepsis in mice induced by lipoteichoic acid. Cytokine. 2008;43(1):83–7.
33. Levine DM, Parker TS, Donnelly TM, Walsh A, Rubin AL. In vivo protection against endotoxin by plasma high density lipoprotein. Proc Natl Acad Sci U S A. 1993;90(24):12040–4.
34. Wurfel MM, Kunitake ST, Lichenstein H, Kane JP, Wright SD. Lipopolysaccharide (LPS)-binding protein is carried on lipoproteins and acts as a cofactor in the neutralization of LPS. J Exp Med. 1994;180(3):1025–35.
35. Guo L, Morin EE, Yu M, Mei L, Fawaz MV, Wang Q, Yuan Y, Zhan CG, Standiford TJ, Schwendeman A, et al. Replenishing HDL with synthetic HDL has multiple protective effects against sepsis in mice. Sci Signal. 2022;15(725):eabl9322.
36. Daskou M, Mu W, Sharma M, Vasilopoulos H, Heymans R, Ritou E, Rezek V, Hamid P, Kossyvakis A, Sen Roy S, et al. ApoA-I mimetics reduce systemic and gut inflammation in chronic treated HIV. PLoS Pathog. 2022;18(1):e1010160.
37. Arroyo V, Moreau R, Jalan R. Acute-on-chronic liver failure. N Engl J Med. 2020;382(22):2137–45.
38. Hamamoto H, Panthee S, Paudel A, Ishii K, Yasukawa J, Su J, Miyashita A, Itoh H, Tokumoto K, Inoue M, et al. Serum apolipoprotein A-I potentiates the therapeutic efficacy of lysocin E against Staphylococcus aureus. Nat Commun. 2021;12(1):6364.

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