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Association of alkaline phosphatase to albumin ratio with all-cause mortality in critically ill patients with cirrhosis: a retrospective study

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Abstract

Background Cirrhosis is the end stage of many chronic liver diseases, which seriously affects the quality of life of patients. The alkaline phosphatase to albumin ratio (APAR) index is a new indicator related to the prognostic risk of many diseases. This study was aimed at exploring the association between the APAR index and the risk of all-cause mortality in patients with cirrhosis.

Methods Patients with cirrhosis who were 18 years of age or older and admitted to the intensive care unit were included from the Medical Information Mart for Intensive Care IV (MIMIC-IV) - Version 3.0 database in this study. The primary endpoint of this study was all-cause mortality at 365- days, with secondary endpoints at 90-days and 28-days after admission. The hazard ratio (HR) and 95% CI between the APAR index and endpoints were calculated using the Cox proportional hazards model. A restricted cubic spline (RCS) regression model was created to explore the relationship between the APAR index and cirrhosis. Furthermore, we explored the predictive value of the APAR index in different populations of cirrhosis through subgroup analysis.

Results A total of 2,109 patients with cirrhosis were included from the MIMIC-IV database. After adjusting for potential covariates, APAR as a continuous variable was significantly positively associated with all-cause mortality at 28-days (HR: 2.007, 95% CI: 1.369, 2.948; $P < 0.001$), 90-days (HR: 2.392, 95% CI: 1.642, 3.495; $P < 0.001$), and 365-days (HR: 2.418, 95% CI: 1.660, 3.534; $P < 0.001$) in cirrhotic patients. When APAR was a categorical variable, compared with patients in the lower APAR group, the risk of 365-days all-cause mortality in patients of the higher APAR group significantly increased (HR: 1.451, 95%CI: 1.197, 1.758). APAR was linearly related to all-cause mortality at 28-days, 90-days and 365-days after admission (P for non-linearity = 0.221, 0.390, and 0.344, respectively). Subgroup analysis indicated that among patients with cirrhosis complicated with hepatorenal syndrome, those without spontaneous

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peritonitis or portal hypertension/esophageal varices, and those receiving human albumin infusion, elevated APAR levels were significantly associated with an increased risk of long-term death.

Conclusions A higher APAR index is significantly associated with the risk of all-cause mortality in cirrhosis. APAR may be a potential biomarker for evaluating the long-term prognosis of critically ill patients with cirrhosis.

Keywords Albumin, Alkaline phosphatase, Alkaline phosphatase to albumin ratio, Cirrhosis, All-cause mortality

Introduction

Cirrhosis is a type of diffuse liver damage caused by the long-term progression of multiple chronic liver diseases, and its pathohistological manifestations include diffuse fibrosis of the liver parenchyma and pseudofollicular formation [1]. As the end stage of multiple chronic liver diseases, cirrhosis can not only cause a series of serious complications such as portal hypertension (PHT), hepatorenal syndrome (HRS), and ascites, but also significantly increase the risk of chronic kidney disease (CKD) and adverse cardiovascular events, which seriously affects patients' quality of life [2–4]. In addition, critically ill cirrhotic patients have a significantly increased risk of death [5], and meta-analysis has shown that the 90-days mortality rate of patients with decompensated cirrhosis can be as high as 58% globally [6]. Previous studies commonly use the Child-Pugh score and the Model for End-Stage Liver Disease (MELD) to predict the prognosis of cirrhosis patients [7]. However, these scoring systems involve multiple variables and are relatively cumbersome to apply. Therefore, exploring new and simpler clinical prognostic indicators is of significant importance.

Alkaline phosphatase to albumin ratio (APAR) is a novel indicator combining alkaline phosphatase (ALP) and albumin (ALB), which has been widely used in various conditions, including chronic kidney disease, coronary atherosclerosis and pancreatic ductal adenocarcinoma [8, 9]. ALP is a hydrolytic enzyme widely distributed in the liver, biliary tract, bone, and other tissues, and is commonly used clinically to assess hepatobiliary disease, bone disease, and other systemic disorders. Elevated levels are usually indicative of damage to the biliary system or cholestasis and are strongly associated with cirrhosis. Lammers et al. [10] found that, after one year and up to five years of follow-up, a log-linear relationship between ALP levels and the risk of liver transplantation and death was found; higher ALP levels were linked to a worse transplant-free survival. ALB is a major plasma protein synthesized by the liver and plays an important role in maintaining plasma colloid osmotic pressure, transporting substances, and regulating fluid balance. Serum ALB level can reflect the synthetic function of the liver and systemic nutritional status and is an important indicator for assessing the progression and prognosis of cirrhotic patients [11].

Therefore, APAR, as a composite indicator combining ALP and ALB, may have superior efficacy in predicting the prognosis of cirrhosis patients. However, evidence regarding the association between APAR and the risk of all-cause mortality in patients with cirrhosis is limited. In this study, we aimed to analyze data from cirrhotic patients in the Medical Information Mart for Intensive Care IV (MIMIC-IV) database to explore the value of APAR in predicting the risk of death in cirrhotic patients.

Methods

Study design and population

The Medical Information Mart for Intensive Care IV (MIMIC-IV) version 3.0 database, a sizable database created and maintained by the MIT Computational Physiology Laboratory, contains comprehensive medical records of patients admitted to the intensive care unit (ICU) of Beth Israel Deaconess Medical Center. This retrospective study examined health-related data from this database. One of the authors, Tao Zheng, who complied with the database access criteria, carried out the data extraction (ID: 63484863). Patients with cirrhosis who were 18 years of age or older and admitted to the ICU for the first time were included in this study based on the International Classification of Diseases, Ninth and Tenth Revision. Of all the 3,726 participants, the following were the criteria for exclusion: (1) patients who spent less than 24 h in the ICU; (2) patients without ALP or ALB data; (3) patients without demographic information; (4) patients with heart rate or breathing being zero. Ultimately, 2,109 individuals were recruited for this study and assigned to three groups according to the APAR level (Fig. 1).

Data collection

A Structured Query Language (SQL) was executed in order to extract information using PostgreSQL (version 13.7.2) and Navicat Premium (version 16). Five key domains could be used to categorize the extraction of prospective variables: (1) Demographic aspects: age and sex; (2) Physical signs: heart rate (HR), temperature (TT, ℉), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2); (3) laboratory index: white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, ALB, total bilirubin (TBIL), glucose, serum creatinine

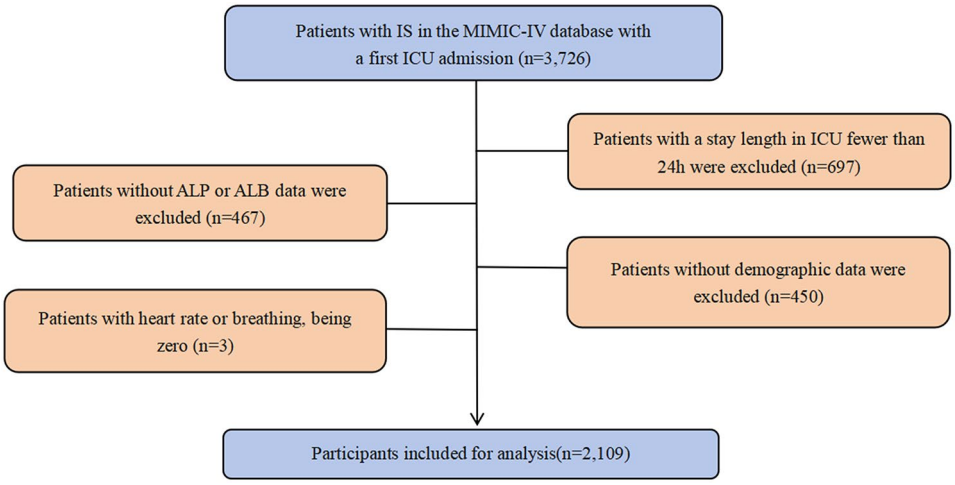

Fig. 1 Flow chart for the selection of participants in the cohort study

(Scr), serum sodium (Na^+), serum potassium (K^+), and international normalized ratio (INR); (4) Clinical score index: Model for End-Stage Liver Disease (MELD), Systemic Inflammatory Response Syndrome (SIRS), Charlson Comorbidity Index (CCI), Acute Physiology Score III (APSIII), and Sequential Organ Failure Assessment score (SOFA); (5) Comorbidities: Hypertension, DM, hyperlipidemia, cardiovascular disease (CVD), myocardial infarction (MI), heart failure (HF), stroke, chronic kidney disease (CKD), cancer (CA), and acute kidney injury (AKI); (6) Complications of cirrhosis: spontaneous peritonitis (SBP), hepatorenal syndrome (HRS), hepatic encephalopathy (HE), ascites, esophageal varices (EV), portal hypertension (PHT).

Refer to previous studies, the APAR index was calculated by using the following formulas:

APAR = log10 [ALP (IU/L)/ALB(g/L)].

It is worth noting that the first ALP and albumin values measured upon admission to the ICU were used for calculating the APAR.

Furthermore, covariates with more than 20% missing values were removed from the analysis in order to remove the impact of missing data. And multiple interpolations were used to interpolate covariates with less than 20% missing values [12].

Clinical outcomes

The primary endpoint of this study was all-cause mortality at 365-days after admission. Secondary endpoints included all-cause mortality at 90-days and 28-days after admission. Survival time was determined by the date of death in the MIMIC-IV database.

Statistical analysis

The APAR values were used to stratify the features of baseline patients. Classification variables were expressed as frequency, and continuous variables as mean ± standard deviation (SD). Analysis of variance (ANOVA) or independent sample t-test was used to examine the normally distributed continuous variables. The Kruskal-Wallis test was used to assess continuous variables that were not regularly distributed. Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test.

Additionally, the endpoint incidence within groups determined by the APAR values was determined using the Kaplan-Meier survival. Variables with a variance inflation factor above 10 were eliminated. The hazard ratio (HR) and 95% CI between the APAR index and endpoints were calculated using the Cox proportional hazards model. Three models were used to account for confounding factors: Model 1 (unadjusted), Model 2 (adjusted for age and sex), and Model 3 (adjusted for age, sex, WBC, RBC, HGB, PLT, ALT, AST, ALP, ALB, glucose, Na+, K+, CCI, SOFA, hypertension, DM, hyperlipidemia, CVD, MI, HF, stroke, CKD, CA AKI, SBP, HRS, HE, ascites, EV, PHT, Human ALB infusion and MELD).

The tertile level was used to compute the *P* values for trends. The first tertile of the APAR index was used as the reference group, and the index was either incorporated into the models as a continuous variable or as a categorical variable. A restricted cubic spline regression model with four knots was also applied to examine potential nonlinear associations between APAR index levels and all-cause mortality in critically cirrhosis patients. The R statistical software (R version 4.3) was used for all statistical studies. Statistical significance was defined as $P < 0.05$, and all reported P values were two-sided.

Results

Baseline characteristics

A total of 2,109 critically ill patients with cirrhosis were selected for final data analysis. The average age of the included patients was 59.00 ± 12.69 years, and 1,378 (65.34%) were male. According to the values of the APAR index, enrolled patients were divided into three groups (Tertile 1: 0.615–1.426; Tertile 2: 1.426–1.652; Tertile 3: 1.652–2.772). According to Table 1, with the T1 group as the reference, as the APAR index increases, the levels of WBC, PLT, ALT, AST, ALP, ALB, TBIL, glucose, and MELD tend to be higher. The severity of illness score also increases, while the prevalence of AKI and CA rises, and the prevalence of SBP decreases ($P < 0.05$).

Clinical outcomes

The incidence of primary and secondary outcomes among groups based on APAR tertiles was examined using the Kaplan-Meier survival analysis curves. At 28-days, 90-days, and 365-days after admission, the risk of all-cause mortality in cirrhotic patients in the higher APAR level group was significantly higher than in the lower APAR group. (A: log-rank $P < 0.0001$; B: log-rank $P < 0.0001$; C: log-rank $P < 0.0001$) (Fig. 2).

Cox proportional risk analysis was used to analyze the association between the APAR and all-cause mortality. When the APAR was a continuous variable, the findings indicated that the APAR was a significant predictor of 28-days mortality in the three models (Model 1, HR: 2.537, 95% CI: 1.828, 3.527; $P < 0.001$). Model 2, HR: 2.510, 95% CI: 1.809, 3.491; $P < 0.001$. Model 3, HR: 2.007, 95% CI: 1.369, 2.948; $P < 0.001$), 90-days in the three models (Model 1, HR: 2.703, 95% CI: 1.964, 3.730; $P < 0.001$). Model 2, HR: 2.675, 95% CI: 1.944, 3.694; $P < 0.0001$. Model 3, HR: 2.392, 95% CI: 1.642, 3.495; $P < 0.001$), and 365-days in the three models (Model 1, HR: 2.726, 95% CI: 1.981, 3.762; $P < 0.001$). Model 2, HR: 2.696, 95% CI: 1.959, 3.722; $P < 0.0001$. Model 3, HR: 2.418, 95% CI: 1.660, 3.534; $P < 0.001$). When APAR was a classification variable, patients in Tertile 3 had a significantly lower risk of 28-days (HR: 1.366, 95% CI: 1.11, 1.681; $P = 0.003$), 90-days (HR: 1.438, 95% CI: 1.186, 1.743; $P < 0.001$), and 365-days (HR: 1.451, 95% CI: 1.197, 1.758; $P < 0.001$) all-cause mortality in the fully adjusted model 3 (Table 2).

Furthermore, we observed that the relationship between the APAR and all-cause mortality was linear in 28-days, 90-days, and 365-days after admission after adjusting for all confounding factors. (P for non-linearity = 0.221, P for non-linearity = 0.390, P for non-linearity = 0.344, respectively) (Fig. 3).

Subgroup analysis

The predictive value of the APAR index for all-cause mortality was further analyzed in different subgroups, including age, sex, hypertension, stroke, CA, DM, hyperlipidemia, HF, MI, CVD, HRS, HE, SBP, EV, PHT, MELD and Human ALB infusion. By threshold effect analysis, the turning point was found to be 1.1834 at 28-days after admission, 1.1841 at 90-days after admission, and 1.1841 at 365-days after admission.

Subgroup analyses revealed a statistically significant association between APAR and 28-days all-cause mortality in cirrhotic patients exclusively within the following subgroups: age > 65, male, non-stroke, non-DM, non-hyperlipidemic, non-HF, non-MI, non-HRS, non-HE, non-SBP, non-ascites, non-EV, non-PHT, low-risk MELD, as well as the CVD and albumin infusion subgroups ($P < 0.05$, Fig. 3A). A statistically significant association between APAR and 90-days all-cause mortality in cirrhotic patients was observed exclusively in the following subgroups: non-stroke, non-HF, non-SBP, non-EV, non-PHT, as well as the DM, HRS, and albumin infusion subgroups ($P < 0.05$, Fig. 3B). A statistically significant association between APAR and 365-days all-cause mortality in cirrhotic patients was observed exclusively in male and in the following subgroups: non-stroke, non-hyperlipidemic, non-HF, non-SBP, non-EV, non-PHT, as well as the DM, HRS, and albumin infusion subgroups ($P < 0.05$, Fig. 3C).

Interactions indicated that overall, no significant interaction was found for most categories except for history of diabetes (P for interaction > 0.05). It was significantly associated with a higher risk of death in the DM group (HR: 2.43, 95% CI: 1.19–4.97; $P = 0.015$) at 365-days after admission (Fig. 4).

Discussion

In this retrospective cohort study, which included 2,109 patients, we observed a higher risk of all-cause mortality in patients with cirrhosis who had higher APAR levels, and RCS analyses showed a linear association between APAR and the risk of all-cause mortality at days 28, 90, and 365 in patients with cirrhosis. Subgroup analyses and interactions indicated that the association between APAR and the risk of death in patients with cirrhosis was more prominent in patients with diabetes mellitus and stoke. Our findings suggest that higher APAR levels are an independent risk factor for all-cause mortality risk in cirrhotic patients. This finding suggests the potential of APAR as a marker for assessing long-term outcomes in patient with cirrhosis.

APAR, a newly discovered biomarker for assessing the prognosis of critically ill patients, has been investigated in several systemic diseases such as sepsis, chronic kidney disease, cardiovascular disease, etc [8, 13, 14]., and it has a good predictive efficacy and clinical guidance significance. However, fewer studies have been conducted in the field of liver disease. In the present study,

Table 1 Characteristics and outcomes of participants categorized by APAR index

Categories	Overall	Tertile 1	Tertile 2	Tertile 3	*P*
	(*n* = 2,109)	(*n* = 703)	(*n* = 703)	(*n* = 703)	
Age, years	59.00 ± 12.69	59.71 ± 12.05	58.04 ± 12.77	59.25 ± 13.18	0.033
Gender (%)					0.117
Female	731 (34.66)	233 (33.14)	233 (33.14)	265 (37.70)	
Male	1,378 (65.34)	470 (66.86)	470 (66.86)	438 (62.30)	
HR, beats/min	92.97 ± 19.68	89.95 ± 18.97	93.22 ± 19.31	95.73 ± 20.32	< 0.001
SpO2 (%)	97.26 ± 19.19	97.17 ± 3.47	97.95 ± 32.85	96.66 ± 3.64	0.001
TT, F°	97.89 ± 4.52	97.99 ± 4.56	97.86 ± 4.73	97.82 ± 4.26	0.032
MAP, mmHg	82.85 ± 132.61	87.68 ± 228.39	80.93 ± 17.66	79.95 ± 17.13	0.092
RBC, K/uL	3.04 ± 0.75	3.04 ± 0.75	3.01 ± 0.75	3.07 ± 0.74	0.405
WBC, K/uL	11.97 ± 8.15	10.02 ± 5.78	11.60 ± 7.47	14.28 ± 10.05	< 0.001
HGB, g/L	9.56 ± 2.14	9.52 ± 2.21	9.48 ± 2.15	9.68 ± 2.07	0.173
PLT, K/uL	124.74 ± 91.62	110.07 ± 69.62	120.50 ± 96.73	143.65 ± 102.04	< 0.001
ALT, IU/L	136.15 ± 365.31	140.26 ± 361.91	127.67 ± 320.38	140.52 ± 408.65	< 0.001
AST, IU/L	323.30 ± 1185.82	269.04 ± 753.60	291.27 ± 901.64	409.59 ± 1682.33	< 0.001
ALP, IU/L	127.30 ± 99.30	62.88 ± 16.90	103.08 ± 23.70	215.94 ± 127.08	< 0.001
ALB, g/L	2.97 ± 0.66	3.30 ± 0.62	2.97 ± 0.59	2.65 ± 0.59	< 0.001
TBIL, mg/dL	6.96 ± 9.27	5.88 ± 8.86	7.18 ± 9.41	7.84 ± 9.45	< 0.001
Glucose, mg/dL	146.11 ± 85.82	150.22 ± 69.86	144.84 ± 74.46	143.26 ± 108.01	< 0.001
Na^+, mmol/L	136.25 ± 6.95	137.41 ± 6.21	136.48 ± 6.61	134.86 ± 7.71	< 0.001
K^+, mmol/L	4.27 ± 0.88	4.26 ± 0.85	4.29 ± 0.89	4.25 ± 0.90	0.757
Scr, mg/dl	1.85 ± 1.72	1.85 ± 1.74	1.70 ± 1.49	2.00 ± 1.91	0.053
MELD	20.69 ± 11.45	19.79 ± 11.75	20.46 ± 10.84	21.82 ± 9.45	0.004
INR	1.94 ± 0.82	1.90 ± 0.80	1.95 ± 0.80	1.97 ± 0.86	0.053
SOFA	8.68 ± 4.25	8.54 ± 4.19	8.67 ± 4.21	8.84 ± 4.34	0.796
APS III	61.00 ± 24.90	58.42 ± 25.13	59.66 ± 24.09	64.94 ± 25.02	< 0.001
CCI	5.96 ± 2.76	5.92 ± 2.67	5.76 ± 2.69	6.20 ± 2.89	0.014
SIRS (%)					0.005
0	18 (0.85)	3 (0.43)	7 (1.00)	8 (1.14)	
1	182 (8.63)	78 (11.10)	59 (8.39)	45 (6.40)	
2	656 (31.10)	240 (34.14)	218 (31.01)	198 (28.17)	
3	887 (42.06)	273 (38.83)	300 (42.67)	314 (44.67)	
4	366 (17.35)	109 (15.50)	119 (16.93)	138 (19.63)	
Hypertension (%)					0.735
No	1456 (69.04)	483 (68.71)	480 (68.28)	493 (70.13)	
Yes	653 (30.96)	220 (31.29)	223 (31.72)	210 (29.87)	
Diabetes (%)					0.169
No	1518 (71.98)	494 (70.27)	524 (74.54)	500 (71.12)	
Yes	591 (28.02)	209 (29.73)	179 (25.46)	203 (28.88)	
Hyperlipidemia (%)					0.518
No	1721 (81.60)	583 (82.93)	571 (81.22)	567 (80.65)	
Yes	388 (18.40)	120 (17.07)	132 (18.78)	136 (19.35)	
CVD (%)					0.083
No	1710 (81.08)	574 (81.65)	584 (83.07)	552 (78.52)	
Yes	399 (18.92)	129 (18.35)	119 (16.93)	151 (21.48)	
MI (%)					0.989
No	2011 (95.35)	670 (95.31)	671 (95.45)	670 (95.31)	
Yes	98 (4.65)	33 (4.69)	32 (4.55)	33 (4.69)	
Heart failure (%)					0.228
No	1733 (82.17)	581 (82.65)	588 (83.64)	564 (80.23)	
Yes	376 (17.83)	122 (17.35)	115 (16.36)	139 (19.77)	
Stroke (%)					0.207
No	2021 (95.83)	668 (95.02)	681 (96.87)	672 (95.59)	

Table 1 (continued)

Categories	Overall	Tertile 1	Tertile 2	Tertile 3	*P*
	(*n* = 2,109)	(*n* = 703)	(*n* = 703)	(*n* = 703)	
Yes	88 (4.17)	35 (4.98)	22 (3.13)	31 (4.41)	
CKD (%)					0.161
No	1760 (83.45)	580 (82.50)	602 (85.63)	578 (82.22)	
Yes	349 (16.55)	123 (17.50)	101 (14.37)	125 (17.78)	
AKI (%)					0.012
No	809 (38.36)	293 (41.68)	276 (39.26)	240 (34.14)	
Yes	1300 (61.64)	410 (58.32)	427 (60.74)	463 (65.86)	
CA (%)					< 0.001
No	1931 (91.56)	655 (93.17)	656 (93.31)	620 (88.19)	
Yes	178 (8.44)	48 (6.83)	47 (6.69)	83 (11.81)	
Human ALB infusion(%)					0.110
No	740 (35.09)	257 (36.56)	258 (36.7)	225 (32.01)	
Yes	1369 (64.91)	446 (63.44)	445 (63.3)	478 (67.99)	
Complications of cirrhosis					
HRS (%)					0.231
No	1751 (83.03)	571 (81.22)	595 (84.64)	585 (83.21)	
Yes	358 (16.97)	132 (18.78)	108 (15.36)	118 (16.79)	
HE (%)					0.901
No	1884 (89.33)	627 (89.19)	631 (89.76)	626 (89.05)	
Yes	225 (10.67)	76 (10.81)	72 (10.24)	77 (10.95)	
SBP (%)					0.022
No	1877 (89.00)	611 (86.91)	623 (88.62)	643 (91.47)	
Yes	232 (11.00)	92 (13.09)	80 (11.38)	60 (8.53)	
Ascites (%)					0.156
No	733 (34.76)	264 (37.55)	237 (33.71)	232 (33.00)	
Yes	1376 (65.24)	439 (62.45)	466 (66.29)	471 (67.00)	
EV (%)					0.325
No	1698 (80.51)	576 (81.93)	554 (78.81)	568 (80.80)	
Yes	411 (19.49)	127 (18.07)	149 (21.19)	135 (19.20)	
PHT (%)					0.168
No	1107 (52.49)	372 (52.92)	350 (49.79)	385 (54.77)	
Yes	1002 (47.51)	331 (47.08)	353 (50.21)	318 (45.23)	

Abbreviations: HR, heart rate; SpO2, peripheral oxygen saturation; TT, temperature; MAP, mean arterial pressure; RBC, red blood cell count; WBC, white blood cell count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALB, albumin; TBIL, total bilirubin; FPG, fasting plasma glucose; Na+, serum sodium; K+, serum potassium; Scr, serum creatinine; INR, International Normalized Ratio; SOFA, Sequential Organ Failure Assessment score; APSIII, Acute Physiology Score III; CCI, Charlson Comorbidity Index; SIRS, Systemic Inflammatory Response Syndrome; CVD, cardiovascular disease; MI, myocardial infarction; CKD, chronic kidney disease; AKI, acute kidney injury; CA, cancer; HRS, hepatorenal syndrome; HE, hepatic encephalopathy; SBP, spontaneous peritonitis; EV, esophageal varices; PHT, portal hypertension; MELD, Model for End-Stage Liver Disease

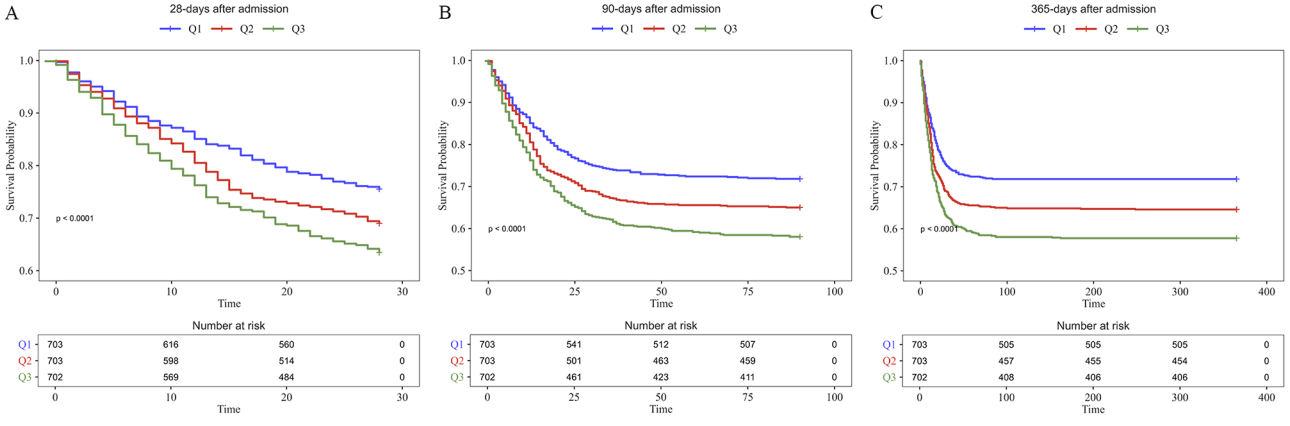

Fig. 2 Kaplan–Meier survival analysis curves for all-cause mortality

Table 2 The relationships between APAR and all-cause mortality

Categories	Model 1			Model 2			Model 3		
	HR (95% CI)	P-value	P for trend	HR (95% CI)	P-value	P for trend	HR (95% CI)	P-value	P for trend
28-days after admission									
Continuous variable per unit	2.537(1.828, 3.527)	< 0.001		2.510(1.809, 3.491)	< 0.001		2.007(1.369, 2.948)	< 0.001	
Tertile			< 0.001			< 0.001			0.004
Tertile 1($n = 703$)	Ref			Ref			Ref		
Tertile 2($n = 703$)	1.321(1.082, 1.614)	0.006		1.345(1.01, 1.644)	0.004		1.348(1.099, 1.653)	0.004	
Tertile 3($n = 703$)	1.627(1.342, 1.974)	< 0.001		1.632(1.345, 1.980)	< 0.001		1.366(1.111, 1.681)	0.003	
90-days after admission									
Continuous variable per unit	2.703(1.964, 3.730)	< 0.001		2.675(1.944, 3.694)	< 0.001		2.392(1.642, 3.495)	< 0.001	
Tertile			< 0.001			< 0.001			< 0.001
Tertile 1($n = 703$)	Ref			Ref			Ref		
Tertile 2($n = 703$)	1.304(1.082, 1.573)	0.005		1.322(1.096, 1.595)	0.004		1.356(1.12, 1.642)	0.002	
Tertile 3($n = 703$)	1.644(1.373, 1.968)	< 0.001		1.644(1.373, 1.969)	< 0.001		1.438(1.186, 1.743)	< 0.001	
365-days after admission									
Continuous variable per unit	2.726(1.981, 3.762)	< 0.001		2.696(1.959, 3.722)	< 0.001		2.418(1.660, 3.534)	< 0.001	
Tertile			< 0.001			< 0.001			< 0.001
Tertile 1($n = 703$)	Ref			Ref			Ref		
Tertile 2($n = 703$)	1.321(1.096, 1.592)	0.003		1.340(1.111, 1.615)	0.002		1.377(1.138, 1.667)	0.001	
Tertile 3($n = 703$)	1.656(1.384, 1.983)	< 0.001		1.656(1.383, 1.983)	< 0.001		1.451(1.197, 1.758)	< 0.001	

Model 1 (unadjusted)

Model 2 (adjusted for age and sex)

Model 3 (adjusted for age, sex, WBC, RBC, HGB, PLT, ALT, AST, ALP, ALB, glucose, Na+, K+, CCI, SOFA, hypertension, DM, hyperlipidemia, CVD, MI, HF, stroke, CKD, CA AKI, SBP, HRS, HE, ascites, EV, PHT, Human ALB infusion and MELD)

Abbreviations: HR, hazard ratio; CI, confidence interval

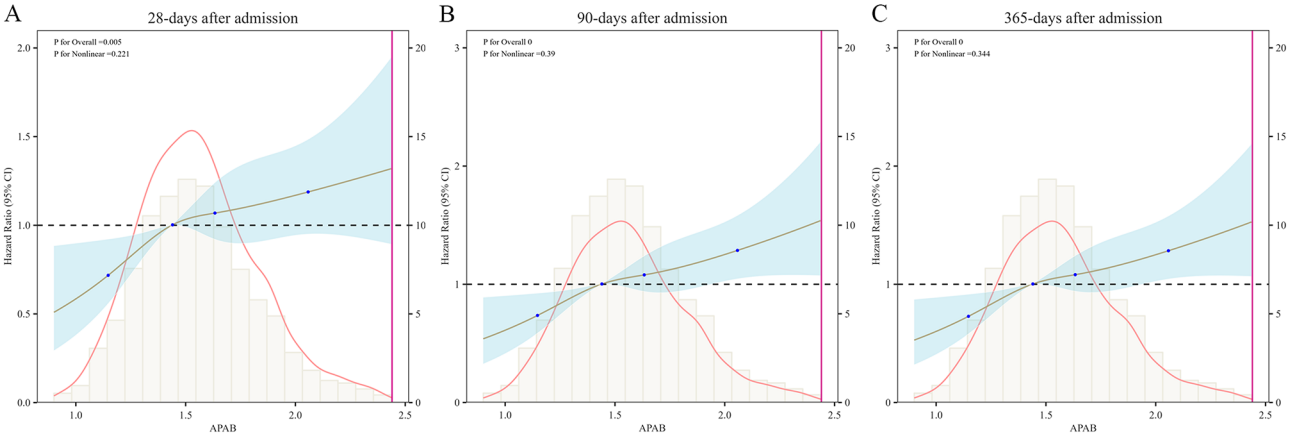

Fig. 3 Restricted cubic spline regression analysis for all-cause mortality. The heavy central lines represent the estimated adjusted hazard ratios, with blue bands denoting 95% confidence intervals. Abbreviations: APAR, alkaline phosphatase to albumin ratio; HR, hazard ratio. Adjusted for age, sex, WBC, RBC, HGB, PLT, ALT, AST, ALP, ALB, glucose, Na+, K+, CCI, SOFA, hypertension, DM, hyperlipidemia, CVD, MI, HF, stroke, CKD, CA AKI, SBP, HRS, HE, ascites, EV, PHT, Human ALB infusion and MELD

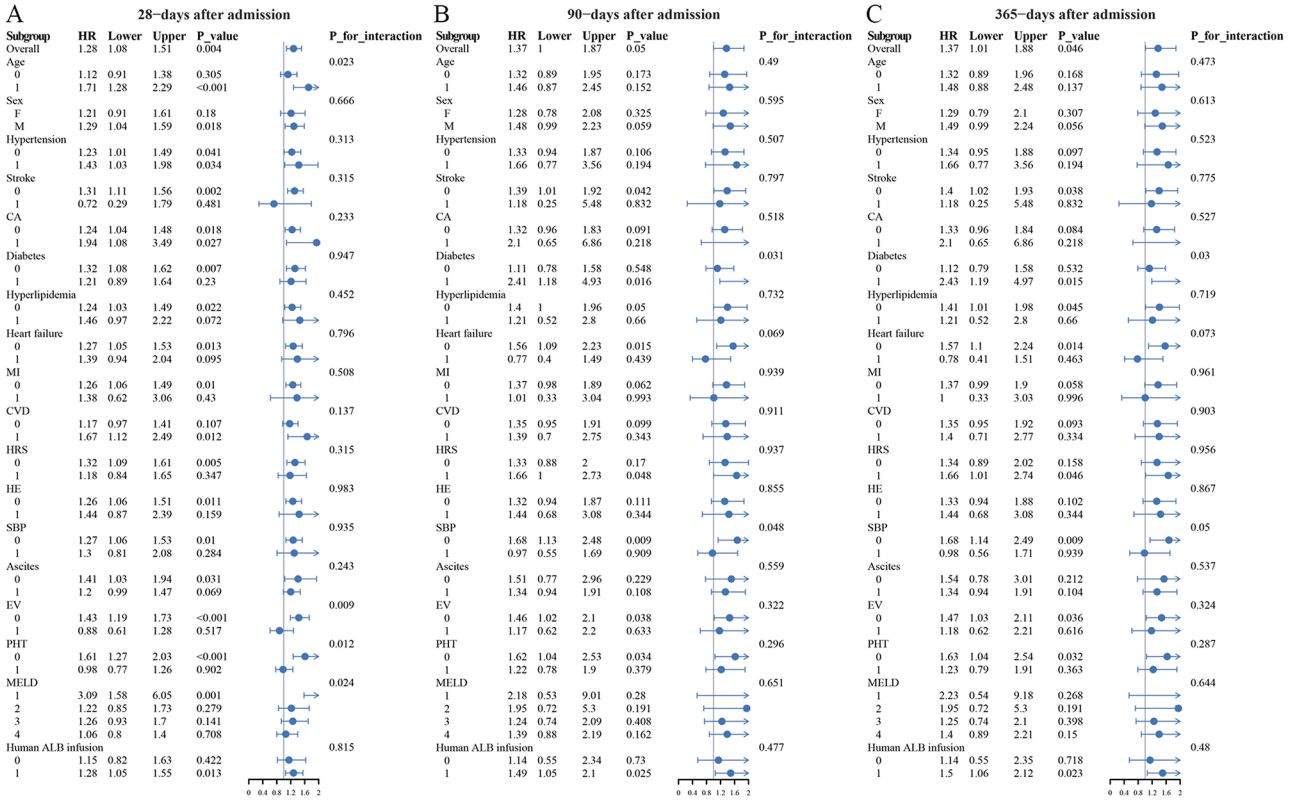

Fig. 4 Subgroup analysis for all-cause mortality in cirrhotic patients. In the age group, 0 represents < 65 years, and 1 represents ≥ 65 years. In the gender subgroup, F denotes female and M denotes male. In the MELD subgroup, 1, 2, 3, and 4 represent low, moderate, high, and very high risk, respectively. For all other subgroups, 0 represents absence and 1 represents presence. CVD, cardiovascular disease; MI, myocardial infarction; CKD, chronic kidney disease; AKI, acute kidney injury; CA, cancer; HRS, hepatorenal syndrome; HE, hepatic encephalopathy; SBP, spontaneous peritonitis; EV, esophageal varices; PHT, portal hypertension; MELD, Model for End-Stage Liver Disease

we retrieved a large number of critically ill cirrhotic patients and found that APAR was linearly and positively correlated with the risk of all-cause mortality at days 28, 90, and 365, with threshold inflection points of 1.1834, 1.1841, and 1.1841, respectively. This indicates that when the APAR level of patients with liver cirrhosis reaches approximately 1.18, the risk of poor prognosis increases significantly. Previous studies have suggested that APAR may also have significant prognostic value in other liver-related diseases. A retrospective cohort study involving 330 patients who underwent curative hepatectomy for hepatocellular carcinoma found that patients with a higher preoperative APAR had shorter disease-free survival and overall survival compared to those with a lower preoperative APAR. A preoperative APAR (≥ 1.74) serves as an independent risk factor affecting the poor prognosis of patients with hepatocellular carcinoma following curative hepatectomy [15]. In addition, Chen et al. [16] found that APAR was effective in predicting the risk of advanced fibrosis in patients with choledochal cysts, with an area under the curve of up to 0.761 (0.673 ~ 0.850).

An elevated APAR typically reflects an increase in ALP levels or a decrease in ALB levels. Oxidative stress may promote the secretion of ALP by modulating its gene expression and enzymatic activity [17]. Therefore, ALP can be used as an indirect indicator of the level of oxidative stress, especially in liver and biliary tract diseases, where elevated ALP may indicate increased oxidative stress and inflammatory state. Oxidative stress and chronic inflammation play a key role in the development, progression, and complication formation of cirrhosis [18]. On the one hand, oxidative stress leads to the overproduction of free radicals (ROS/RNS), which can directly damage cell membrane lipids (lipid peroxidation), DNA (mutations and breaks), and proteins (enzyme activity and structural disruption), thus affecting hepatocellular function and exacerbating liver injury [19, 20]. On the other hand, oxidative stress and inflammation are causative and mutually reinforcing. Inflammatory factors induce vasodilatation and hepatic failure, leading to insufficient renal perfusion, which in turn triggers hepatorenal syndrome (HRS) and renal failure [21, 22]. In addition, oxidative stress can disrupt the blood-brain barrier, allowing ammonia and other neurotoxic substances to enter the central nervous system and induce hepatic encephalopathy [23]. Albumin is an important indicator

for assessing hepatic synthetic function, and a decrease in its level suggests impaired hepatic synthetic function, which is a key marker of decompensated cirrhosis and liver failure [24]. Low albumin leads to a decrease in plasma colloid osmolality, which can exacerbate ascites, lower limb edema, and pleural effusion, which can lead to the formation of refractory ascites and increase the risk of spontaneous peritonitis (SBP), which can significantly increase the mortality rate of patients [25, 26]. In addition, albumin has anti-inflammatory and immunomodulatory effects, which can remove endotoxin (LPS) and reduce inflammatory responses [27]. When albumin levels decrease, the body's immune function is weakened, and patients with cirrhosis are more prone to bacterial infections (e.g., SBP, pneumonia, and sepsis) [28], and infections are one of the major causes of death in patients with decompensated cirrhosis. Meanwhile, albumin plays an important role in blood ammonia metabolism, and a decrease in its level can lead to a decrease in ammonia clearance and an increase in blood ammonia levels, thus increasing the risk of hepatic encephalopathy (HE) and further aggravating the condition [29]. In summary, APAR is a novel indicator of combined alkaline phosphatase and albumin formation and is a reliable biomarker of prognosis in a variety of diseases. Our study further found its significant clinical value in responding to the functional status of the liver as well as determining the prognosis of patients with cirrhosis and can be used as an independent prognostic factor.

Subgroup analysis indicated that among patients with cirrhosis complicated with HRS, those without SBP or PHT/EV, and those receiving human ALB infusion, elevated APAR levels were significantly associated with an increased risk of long-term death. In patients with cirrhosis, elevated APAR may reflect disease progression through the following mechanisms: elevated ALP suggests abnormal biliary excretion, whereas decreased ALB levels usually indicate reduced hepatic synthetic function. In patients with combined HRS, cholestasis promotes endoplasmic reticulum stress response, inducing apoptosis and renal injury [30, 31]. In contrast, hypoalbuminemia leads to an imbalance in glomerular filtration pressure, which triggers sodium retention and acute kidney injury [32]. Elevated APAR levels may reflect worsening of hepatic-renal failure, which increases the risk of all-cause mortality. In the subgroup receiving human albumin infusion, higher APAP was strongly associated with an increased risk of all-cause mortality in cirrhosis, which may be related to therapeutic resistance mechanisms [33]. Although exogenous albumin improves blood volume and relieves symptoms, it cannot replace hepatic synthetic functions and correct cholestasis. However, its underlying mechanism still needs to be further explored.

This study has certain strengths. Firstly, according to our limited knowledge, we constructed a large-scale cohort study to investigate the relationship between the APAR index and the risk of all-cause mortality in patients with cirrhosis, which provides some reference for the prognosis assessment of patients with cirrhosis. Second, we corrected for many indicators, including demographic data, laboratory data, and comorbidities, to minimize the influence of potential confounders on the results. Furthermore, APAR, as an easily accessible biochemical indicator (a routine test), can complement Child-Pugh or MELD scores, especially in resource-limited healthcare settings. However, this study also has some limitations. Firstly, due to the exclusion of patients with missing key clinical indicators (such as ALP and ALB) or a short length of hospital stay, we were unable to perform a systematic comparison between included and excluded patients. This may have introduced an unquantifiable selection bias. Secondly, the study is based on a single-center, predominantly Western ICU database and lacks external validation in other populations, so the findings may not fully generalize to different ethnic groups, etiologies of cirrhosis, or non-ICU settings. In the future, large-scale, multicenter, prospective studies across diverse regions and clinical settings are necessary to further validate the robustness and generalizability of our findings. Thirdly, even though we adjusted for multiple covariates, due to the availability and complexity of the data, we were unable to adjust for all potential covariates, such as liver-specific therapies, dietary factors, medications, and lifestyle habits. Moreover, although our subgroup analysis based on MELD scores preliminarily suggested that APAR did not show significant differences in predicting 90-days and 365-days all-cause mortality among patients with varying severity of cirrhosis, this study was limited by the lack of detailed etiological data (e.g., viral vs. alcoholic cirrhosis) and the absence of standard liver prognostic scores such as Child-Pugh and ALBI. As a result, the performance of APAR in evaluating different severities of liver disease and prognostic comparison remains somewhat limited. As a retrospective study, our research has inherent limitations in establishing causal relationships. Finally, due to the lack of serial APAR measurements, we relied solely on APAR values at admission, which prevented us from evaluating the dynamic association between changes in APAR over time and patient outcomes. Therefore, the findings of this study should be interpreted with caution.

Conclusion

We found that APAR was linearly and positively associated with the risk of all-cause mortality on days 28, 90, and 365 in patients with severe cirrhosis and revealed the interaction between metabolic disorders (diabetes

mellitus) and the progression of liver disease through the construction of a large-sample, multidimensional retrospective cohort study. This finding suggests the potential of APAR as a marker for assessing long-term outcomes in this patient population.

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Author contributions
Hongye Peng and Tao Zheng: manuscript writing, analysis, interpretation of results, editing, and revising. interpretation of results, and editing. Na Zeng, Yating Han and Zuohu Niu: drawing, data sorting, interpretation of results, and editing. Shaojie Duan and Yu Wang: research design, interpretation of results, and manuscript writing and editing. All authors contributed to the manuscript and approved the submitted version.

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Data availability
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics statement
According to local legislation and institutional requirements, this research involving humans does not require ethical approval. According to national legislation and system requirements, this study does not require the written informed consent of the subjects or their legal guardians/close relatives.

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