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Original Article

Relationship between anion gap and in-hospital mortality in intensive care patients with liver failure: a retrospective propensity score matching analysis

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Abstract: Objectives: To elucidate the association between anion gap (AG) and in-hospital mortality in intensive care patients with liver failure. Methods: Demographic and clinical characteristics of intensive care patients with liver failure in the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database were collected, and binomial logistic and Cox regression was conducted to investigate the association between AG and in-hospital mortality. The area under the receiver operating characteristic (ROC) curve (AUC) was conducted to characterize the performance of AG in predicting in-hospital mortality, and was compared with the albumin corrected anion gap (ACAG) and the End-Stage Liver Disease (MELD) score. The Kaplan-Meier curve was plotted for in-hospital survival analysis of AG and patients with liver failure. The propensity score matching (PSM) analysis was performed to mitigate selection bias. Results: AG was an independent risk factor for in-hospital mortality in intensive care patients with liver failure. Before PSM, the AUCs of AG, ACAG, and MELD were 0.666, 0.682, and 0.653, respectively. After PSM, the AUCs of AG, ACAG, and MELD scores were 0.645, 0.657, and 0.645, respectively, and there is no difference in the predictive performance of the three indicators upon comparison. Compared with the low-AG (≤20 mmol/L) group, the hazard ratio (HR) for in-hospital death of the high-AG (>20 mmol/L) group was determined to be 2.1472 (before PSM)/1.8890 (after PSM). Conclusions: AG is associated with in-hospital mortality in intensive care patients with liver failure and demonstrates a moderate predictive value, which is comparable to the predictive power of the MELD score. AG may serve as an indirect marker of in-hospital mortality of patients with liver failure by reflecting the degree of metabolic acidosis.

Keywords: Anion gap, liver failure, MIMIC-IV, in-hospital mortality, propensity score matching

Introduction

Liver failure, also known as hepatic failure, is attributed to a variety of etiological factors (such as viruses, alcohol, drugs, etc.) and manifests as severe liver damage, which in turn leads to severe impairment or decompensation of metabolism, detoxification, synthesis, and biotransformation [1]. Liver failure is classified into four categories according to the history, onset characteristics and speed of disease progression: acute liver failure (ALF, ALF is classified as fulminant hepatic failure or subfulminant hepatic failure [2]), subacute liver failure, acute/subacute-on-chronic liver failure, and chronic liver failure. Liver failure is not an independent clinical diagnosis; rather, it represents a functional assessment. Given the exceedingly high mortality rate associated with liver failure, prognosis assessment ought to be conducted throughout the entire diagnostic and treatment process, with a particular emphasis on the critical importance of early prognosis assessment [1], which will assist medical personnel in formulating appropriate and timely diagnostic and therapeutic strategies, thereby potentially reducing mortality rates.

The End-Stage Liver Disease (MELD) score is extensively utilized as an indicator of disease

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severity to predict mortality from end-stage liver disease [3], and it also has certain value in the prognosis assessment of liver failure [1]. The King's College Criteria (KCC) is commonly used in the prognostic assessment of ALF [4], however, Peláez-Luna *et al*. found that an ALF in-hospital mortality score (ALFIHMS) has higher prognostic predictive value than KCC and MELD [5]. One study [6] found that for the prediction of death in ALF, the AUC of the MELD score was about 0.7, while the KCC was around 0.65, which is of low predictive value as a scoring system. Another study found that lactate combined with creatinine was a better predictor of mortality for non-acetaminophen-induced ALF than the MELD score, but this has not been validated [7]. In conclusion, the selection of the key indicator is particularly important if an efficient predictive scoring system is to be constructed.

Anion gap (AG) represents a parameter derived from the calculated difference between serum anion and cation concentrations. Several studies have demonstrated that high levels of AG are positively associated with the severity of many diseases, and AG can also predict mortality in these diseases, such as coronary artery disease, aortic aneurysm, and acute kidney injury (AKI) [8-10]. AG is closely related to acid-base disorders, and has important clinical value in the clinical judgment of metabolic acidosis. In addition to the kidneys and lungs, the liver is also an important organ that regulates acid-base balance, and liver dysfunction may be accompanied by complex acid-base disorders [11-13]. Respiratory alkalosis is the most common acid-base disorder, but metabolic acidosis alone or in combination with respiratory alkalosis often occurs [13]. Another study suggests that the urinary AG may help differentiate chronic respiratory alkalosis from hyperchloremic metabolic acidosis in liver disease patients when blood gases are unavailable. A negative urinary AG suggests a low likelihood of chronic respiratory alkalosis [13]. Currently, there are few studies on AG and liver failure, and the link between serum AG and the prognosis of liver failure is inconclusive, considering the above association between AG and liver failure, we hypothesized that serum AG might be closely associated with prognosis in patients with liver failure in intensive care, and focused on the prognostic value of AG in these patients.

The MELD score is a well-established scoring index to evaluate the severity of patients with end-stage liver disease and is often used to measure the risk of death in patients. Thus, we introduced MELD as a reference for comparison. In addition, albumin is inextricably linked to liver disease. Hypoalbuminemia, which is associated with mild metabolic alkalosis, can result from reduced synthetic function due to liver disease [14]. Meanwhile, the reduction of serum albumin can reduce the AG to mask the degree of acidosis, which needs to be properly corrected in clinical interpretation, otherwise it will lead to underestimation [15]. Hatherill *et al*. [16] proposed that albumin corrected anion gap (ACAG) may be more suitable for screening patients admitted to the intensive care unit (ICU) for metabolic acidosis. We therefore simultaneously explored the association of ACAG with prognosis in liver failure.

Methods

Database

The Medical Information Mart for Intensive Care-IV (MIMIC-IV) is a public database containing real hospital stay information for patients admitted to a tertiary academic medical center from 2008-2019 in Boston, MA, USA. Author Hu completed the "Protecting Human Research Participants" exam (record ID: 37474354) and executed a data use agreement, thus was granted access to MIMIC-IV data, and was allowed to conduct this study.

This study was ethically approved by an affiliate of the Massachusetts Institute of Technology (No. 27653720). MIMIC-IV database information was deidentified, and patient identifiers (such as patient name, address, telephone number, and dates) were removed [17]. Given these considerations, obtaining informed consent from the patients was deemed unnecessary.

Study population

This study focused on patients admitted to the ICU with liver failure, and we did not intend to distinguish between different types of liver failure. Intensive care patients with liver failure in

the MIMIC-IV database included in this study were diagnosed as: acute and subacute hepatic failure with coma (ICD = K7201, ICD stands for International Classification of Diseases, version 10), acute and subacute hepatic failure without coma (ICD = K7200), alcoholic hepatic failure with coma (ICD = K7041), alcoholic hepatic failure without coma (ICD = K7040), chronic hepatic failure with coma (ICD = K7211), chronic hepatic failure without coma (ICD = K7210), hepatic failure, unspecified with coma (ICD = K7291), and hepatic failure, unspecified without coma (ICD = K7290). Postprocedural hepatic failure (ICD = K9182) was excluded from this study population. Notably, the MIMIC database records had the diagnosis of liver failure as "hepatic failure" rather than "liver failure". Additional exclusion criteria included patients with a length of stay in hospital <24 hours, repeated ICU admissions, and missing data on albumin or AG.

The following information on the enrolled patients was collected: age, gender, Charlson Comorbidity Index (an index to quantify comorbidities [18], including congestive heart failure, chronic pulmonary disease, malignant cancer, etc.), coexistence of coma (hepatic encephalopathy), length of stay in hospital, length of stay in ICU, and laboratory tests (including hemoglobin, white blood cells, platelets, blood urea nitrogen/BUN, creatinine, international normalized ratio/INR, prothrombin time/PT, alanine aminotransferase/ALT, aspartate aminotransferase/AST, total bilirubin/TBil, albumin, and AG). For laboratory tests, we took the average values of the patient on the first day of admission.

Calculations for the MELD score and ACAG followed these formulas: MELD = 3.78 *ln [TBil (mg/dL)] + 11.2 *ln [INR] + 9.57 *ln [creatinine (mg/dL)] + 6.43; ACAG (mmol/L) = [4.4-{albumin (g/dL)}] *2.5 + AG (mmol/L).

Statistical analysis

Following normality assessment with the Kolmogorov-Smirnov test, continuous variables conforming to a normal distribution were presented as mean ± standard deviation (M ± SD), and an independent sample t-test was applied for intergroup comparisons; continuous variables not adhering to a normal distribution were reported as the median with interquartile range (IQR), and the Wilcoxon rank-sum test was utilized for their comparison. Categorical variables were denoted as the sample size (percentage), and the chi-square test was employed for comparisons.

To balance the baseline between the death survival group, we performed the propensity score matching (PSM) analysis that included the following potential confounders: age, comorbidity status (Charlson Comorbidity Index), and hepatic encephalopathy status (coma). The PSM analysis was conducted using a logistic regression model, employing a 1:1 nearest neighbor matching algorithm with a caliper of 0.01, without replacement. We performed binomial logistic regression and Cox regression (with a *p*-value of less than 0.1 in univariable analysis included in multivariable analysis) to identify independent risk factors for in-hospital mortality in patients with liver failure. We plotted the receiver operating characteristic (ROC) curves of AG/ACAG/MELD separately and compared the areas under the curves (AUCs) (by the Z test, following the method of Delong *et al*. [19]).

In-hospital mortality constitutes a time-to-event variable. Patient follow-up occurs during hospitalization, with the event being patient death. If the patient is discharged alive, the data is censored. Therefore, the in-hospital mortality can be used for survival analysis [20]. We performed an in-hospital survival analysis by the log-rank test based on the theory, and according to the optimal cut-off value corresponding to the ROC curve of AG, the AG values were divided into two groups, and the Kaplan-Meier survival curve was plotted.

Statistical analyses were conducted using R software (version 4.1.2) and MedCalc statistical software (version 19.6.1), and a *p*-value of less than 0.05 was deemed to indicate statistical significance.

Results

The study ultimately included 871 patients (the flowchart is shown in **Figure 1**). Before PSM, the age of the patients and the proportion of patients with coma in the death group were higher than those in the survival group, while the length of hospital stay was significantly shorter. The white blood cell count, blood urea nitrogen level, creatinine level, INR, prothrom-

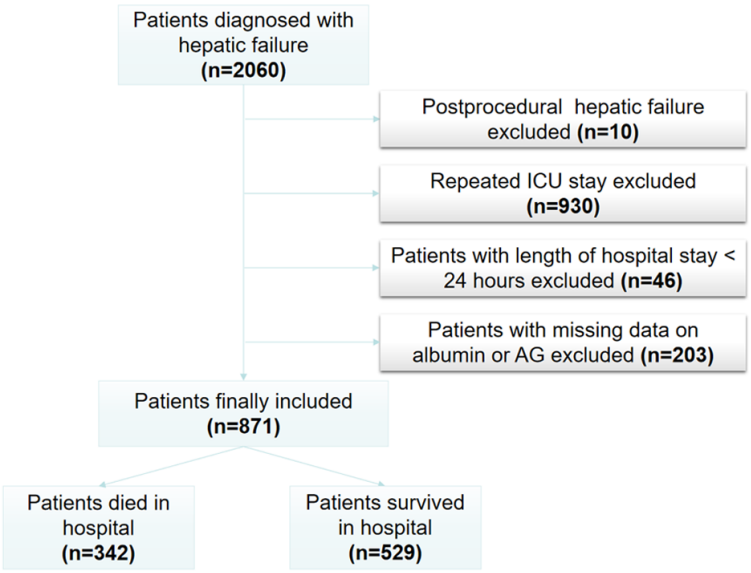

Figure 1. Flowchart. ICU = Intensive Care Unit, AG = Anion Gap.

bin time, total bilirubin, AG level, ACAG level, and MELD score in the death group were significantly higher than those in the survival group, while albumin was significantly lower.

After 1:1 matching with age, CCI, and coma (despite no pre-matching difference in CCI between the groups, it was included to preempt potential post-matching imbalance), the age, the proportion of patients with coma of the two groups reached a balance. The AG, ACAG and MELD scores of the death group were still significantly higher, while the albumin was significantly lower than that of the survival group. The remaining baseline data or laboratory tests are shown in **Table 1**.

Logistic regression analysis

Owing to collinearity between AG and ACAG, solely AG was incorporated into the regression analysis. Before PSM, the results showed that both AG (OR = 1.115, 95% CI: 1.086-1.145, *P*<0.001) and MELD (OR = 1.064, 95% CI: 1.047-1.082, *P*<0.001) were independent risk factors for in-hospital mortality in patients with liver failure in intensive care (**Table 2**).

After PSM (**Table 3**), AG remained a risk factor for in-hospital mortality (OR = 1.110, 95% CI: 1.074-1.147, *P*<0.001), while MELD was not associated with the mortality (OR = 1.028, 95% CI: 0.996-1.062, *P* = 0.089). It should be noted that no collinearity was detected between the MELD score and other indicators.

Cox regression analysis

In Cox regression analysis, we defined follow-up time as the longest number of days of survival for patients who experienced a death event. The Cox regression analysis we performed showed that both AG (before PSM, OR = 1.083, 95% CI: 1.062-1.104, *P*<0.001; after PSM, OR = 1.087, 95% CI: 1.065-1.109, *P*<0.001) and MELD (before PSM, OR = 1.034, 95% CI: 1.010-1.058, *P* = 0.005; after PSM, OR = 1.026, 95% CI: 1.002-1.050, *P* = 0.030) were independent risk factors for in-hospital mortality in patients with liver failure in intensive care (**Tables 4** and **5**).

Comparison of ROC curves

Before performing PSM, the AUCs of AG, ACAG, and MELD were 0.666, 0.682, and 0.653, respectively, among which ACAG had the highest Youden's index (0.2738) and sensitivity (67.84%), and AG had the highest specificity (75.24%) (**Table 6**; **Figure 2**). The Z test results are as follows: AG vs ACAG, Z = 0.0121, *P* = 0.012; AG vs MELD, Z = 0.597, *P* = 0.551; ACAG vs MELD, Z = 1.369, *P* = 0.171, which means that there was no significant difference in predictive power between MELD and AG/ACAG, while ACAG has a slight advantage in predictive value over AG.

After PSM, the AUCs of AG, ACAG, and MELD scores were 0.645, 0.657, and 0.645, respectively, among which ACAG had the highest Youden's index (0.2384) and sensitivity (54.49%), and MELD had the highest specificity (82.04%) (**Table 7**; **Figure 3**). The Z test results are as follows: AG vs ACAG, Z = 1.677, *P* = 0.094; AG vs MELD, Z = 0.0228, *P* = 0.982; ACAG vs MELD, Z = 0.482, *P* = 0.630, indicating that there is no difference in the predictive performance of the three indicators when compared with each other.

Table 1. Demographic and clinical characteristics

Characteristics	Before PSM			After PSM		
	Death (n = 342)	Survival (n = 529)	*p*	Death (n = 323)	Survival (n = 323)	*p*
Age*, year	60.5±14.1	57.6±15.5	0.012	60.9±13.9	61.0±14.3	0.932
Gender (male)	198 (57.9)	321 (60.7)	0.413	186 (57.6)	192 (59.4)	0.632
CCI*	6 (5-9)	4 (6-8)	0.121	6 (5-9)	7 (5-9)	0.579
Coma*	27 (7.9)	13 (2.5)	<0.001	8 (2.5)	8 (2.5)	1.000
LOS Hos, day	7.8 (2.9-15.8)	15.7 (8.7-26.6)	<0.001	7.9 (3.1-15.8)	15.9 (8.8-26.9)	<0.001
LOS ICU, day	3.9 (1.9-8.9)	3.7 (1.8-7.4)	0.406	3.9 (1.8-8.9)	4.0 (1.9-7.7)	0.819
Hb, g/dL	9.3 (8.0-11.5)	9.5 (8.1-11.2)	0.787	9.3 (8.0-11.5)	9.5 (8.0-11.1)	0.644
WBC, 10^9/L	13.7 (9.0-20.0)	11.6 (7.6-16.5)	<0.001	13.6 (9.0-20.0)	12.1 (7.7-17.0)	0.004
PLT, 10^9/L	116 (67-184)	121 (75-184)	0.689	116 (70-182)	124 (71-186)	0.598
BUN, mmol/L	34.0 (19.5-56.0)	29.0 (16.8-47.0)	0.004	35.0 (20.0-56.0)	32.0 (19.5-51.0)	0.253
Cr, mg/dL	1.85 (1.25-2.80)	1.45 (0.90-2.25)	<0.001	1.85 (1.25-2.80)	1.60 (1.00-2.65)	0.004
INR	2.1 (1.6-2.7)	1.8 (1.4-2.3)	<0.001	2.1 (1.6-2.8)	1.8 (1.4-2.3)	<0.001
PT, s	22.6 (17.4-30.0)	19.2 (15.4-25.0)	<0.001	23.0 (17.5-30.3)	19.1 (15.5-24.7)	<0.001
ALT, U/L	110 (36-516)	77 (29-473)	0.114	108 (35-483)	67 (27-427)	0.052
AST, U/L	265 (82-897)	172 (62-690)	0.004	236 (81-893)	144 (53-653)	0.001
TBil, mg/dL	3.0 (1.1-10.9)	2.1 (1.0-6.0)	0.002	3.0 (1.1-10.8)	2.0 (1.0-5.5)	0.001
ALB, g/dL	2.85 (2.35-3.40)	3.00 (2.60-3.50)	0.001	2.85 (2.35-3.40)	2.90 (2.50-3.50)	0.038
AG, mmol/L	20.0 (16.0-24.5)	16.5 (14.0-20.0)	<0.001	20.0 (16.0-24.5)	17.0 (14.5-20.5)	<0.001
ACAG, mmol/L	23.3 (19.9-28.8)	20.0 (17.0-23.5)	<0.001	23.3 (20.0-28.6)	20.6 (17.8-23.9)	<0.001
MELD score	30.5 (23.0-39.0)	25.4 (19.0-31.7)	<0.001	30.4 (23.0-39.0)	26.0 (19.5-32.0)	<0.001

Abbreviations: PSM = Propensity Score Matching, CCI = Charlson Comorbidity Index, LOS = Length of Stay, Hos = Hospital, ICU = Intensive Care Unit, Hb = Hemoglobin, WBC = White Blood Cell, PLT = Platelets, BUN = Blood Urea Nitrogen, Cr = Creatinine, INR = International Normalized Ratio, PT = Prothrombin Time, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, TBil = Total Bilirubin, ALB = Albumin, AG = Anion Gap, ACAG = Albumin Corrected Anion Gap, MELD = Model for End-stage Liver Disease. *Variables included in the PSM.

Table 2. Binomial Logistic regression analysis (before the propensity score matching)

Variable	Univariable		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.013 (1.004-1.022)	0.006	1.017 (1.003-1.031)	0.014
Gender (male)	0.891 (0.676-1.175)	0.413		
CCI	1.042 (0.997-1.090)	0.067	1.004 (0.941-1.071)	0.914
Hemoglobin	0.990 (0.931-1.052)	0.736		
WBC	1.030 (1.013-1.048)	<0.001	1.020 (1.002-1.038)	0.028
Platelets	1.000 (0.999-1.002)	0.649		
BUN	1.007 (1.002-1.012)	0.007	1.000 (0.993-1.007)	0.989
Creatinine	1.118 (1.033-1.209)	0.006	0.878 (0.778-0.991)	0.035
INR	1.477 (1.277-1.708)	<0.001	1.252 (0.025-62.63)	0.910
PT	1.036 (1.023-1.050)	<0.001	0.988 (0.691-1.412)	0.946
ALT	1.000 (1.000-1.000)	0.251		
AST	1.000 (1.000-1.000)	0.217		
TBil	1.030 (1.015-1.045)	<0.001	1.023 (1.004-1.043)	0.020
Albumin	0.700 (0.568-0.863)	0.001	0.672 (0.531-0.851)	0.001
Anion gap	1.115 (1.086-1.145)	<0.001	1.110 (1.074-1.147)	<0.001
MELD score	1.064 (1.047-1.082)	<0.001	1.028 (0.996-1.062)	0.089

Abbreviations: CCI = Charlson Comorbidity Index, WBC = White Blood Cell, BUN = Blood Urea Nitrogen, INR = International Normalized Ratio, PT = Prothrombin Time, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, TBil = Total Bilirubin, MELD = Model for End-stage Liver Disease.

Table 3. Binomial Logistic regression analysis (after the propensity score matching)

Variable	Univariable		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	0.999 (0.989-1.010)	0.920		
Gender (male)	0.926 (0.677-1.267)	0.632		
CCI	0.996 (0.945-1.049)	0.874		
Hemoglobin	1.009 (0.941-1.081)	0.807		
WBC	1.022 (1.003-1.040)	0.020	1.014 (0.996-1.033)	0.120
Platelets	1.000 (0.998-1.002)	0.965		
BUN	1.004 (0.998-1.009)	0.208		
Creatinine	1.077 (0.981-1.183)	0.121		
INR	1.414 (1.204-1.660)	<0.001	4.649 (0.053-406.84)	0.501
PT	1.032 (1.017-1.047)	<0.001	0.882 (0.588-1.325)	0.545
ALT	1.000 (1.000-1.000)	0.611		
AST	1.000 (1.000-1.000)	0.303		
TBil	1.041 (1.021-1.061)	<0.001	1.035 (1.010-1.061)	0.006
Albumin	0.780 (0.622-0.978)	0.031	0.694 (0.540-0.893)	0.005
Anion gap	1.106 (1.073-1.140)	<0.001	1.101 (1.062-1.141)	<0.001
MELD score	1.059 (1.040-1.079)	<0.001	1.003 (0.971-1.037)	0.837

Abbreviations: CCI = Charlson Comorbidity Index, WBC = White Blood Cell, BUN = Blood Urea Nitrogen, INR = International Normalized Ratio, PT = Prothrombin Time, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, TBil = Total Bilirubin, MELD = Model for End-stage Liver Disease.

Table 4. Cox regression analysis (before the propensity score matching)

Variable	Univariable		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.010 (1.003-1.018)	0.005	1.012 (1.004-1.021)	0.004
Gender (male)	0.920 (0.742-1.140)	0.446		
CCI	1.028 (0.993-1.063)	0.119		
Hemoglobin	1.003 (0.957-1.052)	0.892		
WBC	1.017 (1.008-1.026)	<0.001	1.011 (1.000-1.021)	0.045
Platelets	1.000 (0.999-1.002)	0.538		
BUN	1.005 (1.001-1.008)	0.008	0.999 (0.994-1.004)	0.794
Creatinine	1.079 (1.025-1.137)	0.004	0.910 (0.837-0.990)	0.029
INR	1.268 (1.174-1.370)	<0.001	1.878 (0.186-18.94)	0.593
PT	1.022 (1.015-1.029)	<0.001	0.946 (0.767-1.167)	0.603
ALT	1.000 (1.000-1.000)	0.440		
AST	1.000 (1.000-1.000)	0.040	1.000 (1.000-1.000)	0.457
TBil	1.017 (1.007-1.026)	<0.001	1.010 (0.997-1.023)	0.148
Albumin	0.731 (0.619-0.863)	0.001	0.707 (0.598-0.836)	0.001
Anion gap	1.085 (1.069-1.102)	<0.001	1.083 (1.062-1.104)	<0.001
MELD score	1.052 (1.038-1.066)	<0.001	1.034 (1.010-1.058)	0.005

Abbreviations: CCI = Charlson Comorbidity Index, WBC = White Blood Cell, BUN = Blood Urea Nitrogen, INR = International Normalized Ratio, PT = Prothrombin Time, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, TBil = Total Bilirubin, MELD = Model for End-stage Liver Disease.

Comparison of Kaplan-Meier curves

The determined optimal cut-off value for AG was 20 mmol/L, consistent both before and after PSM. Before PSM, the median survival time of the low-AG group (≤20 mmol/L) was 42.410 days (95% CI: 32.587-85.482), compared to 16.991 days (95% CI: 12.987-23.700)

Table 5. Cox regression analysis (after the propensity score matching)

Variable	Univariable		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.001 (0.993-1.008)	0.876		
Gender (male)	0.959 (0.769-1.196)	0.711		
CCI	0.991 (0.955-1.029)	0.645		
Hemoglobin	1.020 (0.972-1.071)	0.422		
WBC	1.012 (1.002-1.021)	0.015	1.008 (0.997-1.018)	0.165
Platelets	1.000 (0.999-1.001)	0.863		
BUN	1.002 (0.999-1.006)	0.222		
Creatinine	1.054 (0.995-1.117)	0.075	0.893 (0.826-0.966)	0.005
INR	1.208 (1.118-1.305)	<0.001	7.087 (0.432-116.1)	0.170
PT	1.017 (1.010-1.024)	<0.001	0.839 (0.650-1.081)	0.175
ALT	1.000 (1.000-1.000)	0.947		
AST	1.000 (1.000-1.000)	0.046	1.000 (1.000-1.000)	0.469
TBil	1.018 (1.008-1.028)	<0.001	1.011 (0.998-1.025)	0.104
Albumin	0.806 (0.684-0.950)	0.010	0.732 (0.622-0.862)	<0.001
Anion gap	1.079 (1.061-1.097)	<0.001	1.087 (1.065-1.109)	<0.001
MELD score	1.045 (1.031-1.059)	<0.001	1.026 (1.002-1.050)	0.030

Abbreviations: CCI = Charlson Comorbidity Index, WBC = White Blood Cell, BUN = Blood Urea Nitrogen, INR = International Normalized Ratio, PT = Prothrombin Time, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, TBil = Total Bilirubin, MELD = Model for End-stage Liver Disease.

Table 6. Comparison of the receiver operating characteristic curves (before the propensity score matching)

Factor	AUC	95% CI	Optimal cut-off	Sensitivity	Specificity	Youden's index
AG	0.666	0.633-0.697	20	48.54	75.24	0.2377
ACAG	0.682	0.650-0.713	21.125	67.84	59.55	0.2738
MELD	0.653	0.620-0.685	28.524	59.65	64.08	0.2373

Abbreviations: AUC = Area Under the ROC Curve, AG = Anion Gap, ACAG = Albumin Corrected Anion Gap, MELD = Model for End-stage Liver Disease.

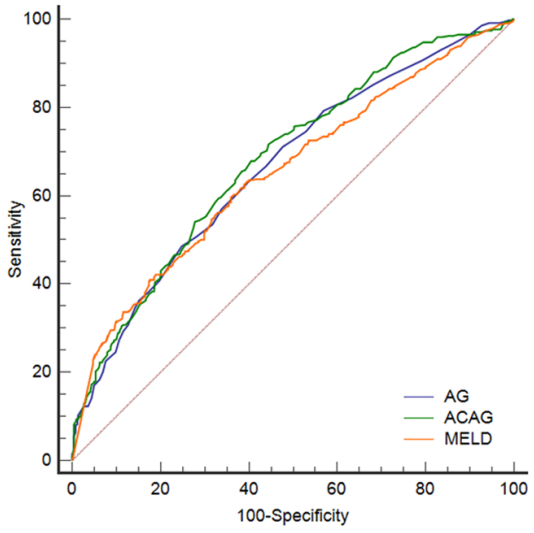

Figure 2. ROC curves of AG, ACAG, and MELD (before the propensity score matching). ROC = Receiver the Operating Characteristic, AG = Anion Gap, ACAG = Albumin Corrected Anion Gap, MELD = Model for End-stage Liver Disease.

for the high-AG group (>20 mmol/L) (**Figure 4**). Compared with the low-AG group, the hazard ratio (HR) for in-hospital death of the high-AG group was 2.1472 (95% CI: 1.7058-2.7029).

After PSM, the median survival time of the low-AG group was 26.669 days (95% CI: 20.642-37.842), compared to 12.987 days (95% CI: 8.917-16.854) for the high-AG group (**Figure 5**). In comparison to the low-AG group, the HR for in-hospital death of the high-AG group was 1.8890 (95% CI: 1.4990-2.3806).

Discussion

This study is the inaugural demonstration that AG constitutes an independent risk factor for in-hospital mortality among intensive care patients with liver failure. In comparison to the low-AG group, the HR for in-hospital death of the high-AG group was 2.1472 (before PSM)/1.8890 (after PSM), indicating that patients

Table 7. Comparison of the receiver operating characteristic curves (after the propensity score matching)

Factor	AUC	95% CI	Optimal cut-off	Sensitivity	Specificity	Youden's index
AG	0.645	0.607-0.682	20	48.61	72.76	0.2136
ACAG	0.657	0.619-0.694	22.875	54.49	69.35	0.2384
MELD	0.645	0.607-0.682	33.673	40.87	82.04	0.2291

Abbreviations: AUC = Area Under the ROC Curve, AG = Anion Gap, ACAG = Albumin Corrected Anion Gap, MELD = Model for End-stage Liver Disease.

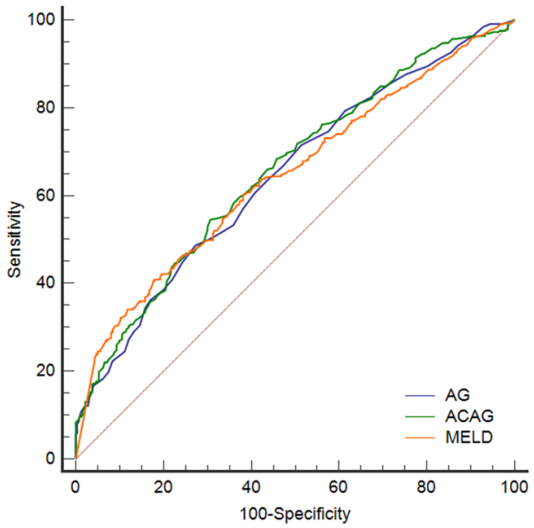

Figure 3. ROC curves of AG, ACAG, and MELD (after the propensity score matching). ROC = Receiver the Operating Characteristic, AG = Anion Gap, ACAG = Albumin Corrected Anion Gap, MELD = Model for End-stage Liver Disease.

with an AG greater than 20 mmol/L had approximately twice the risk of in-hospital mortality compared to those with an AG of 20 mmol/L or less. The AUC of AG for predicting in-hospital mortality in patients with liver failure was 0.666 (before PSM)/0.645 (after PSM), which denoted a moderate predictive value, with its predictive power showing no statistical difference from the MELD score. However, ACAG did not significantly enhance predictive power beyond AG, implying that ACAG offers no additional value over AG in the clinical management of liver failure.

The AG can be calculated from the difference between the routinely measurable cations and anions in plasma, i.e., AG = {[sodium]+[potassium]} - {[chloride]+[bicarbonate]}. Given the low concentration of potassium, the calculation of AG predominantly relies on sodium, chloride, and bicarbonate levels. When liver disease is advanced, the most common imbalance of sodium is hypervolemic hyponatremia [21]. In patients with end-stage liver disease, hypokalemia is more common, and systemic potassium levels may be reduced by as much as 30% to 40% in patients with liver disease [22, 23]. Meanwhile, electrolyte disturbances in the liver failure can vary widely, depending largely on the severity of liver disease and the presence or absence of AKI. In the absence of AKI, the kidneys compensate by excreting bicarbonate while retaining chloride, ultimately resulting in hyperchloremia. The administration of diuretics in the context of renal insufficiency may exacerbate hypokalemia. Overall, changes in these ions are not synchronized, and relying on the complexity of electrolyte changes in patients with liver disease to explain the link between AG and liver failure does not seem feasible.

The typical range for AG is 8-16 mmol/L, with a mean value of 12 mmol/L. At present, an AG exceeding 16 mmol/L serves as the threshold for diagnosing metabolic acidosis with an elevated AG. We tried to explore the relationship between AG and liver failure from the perspective of acid-base disorders. As liver disease advances to decompensation, metabolic acidosis becomes the prevalent acid-base disturbance, typically stemming from the liver's impaired capacity to metabolize and eliminate systemic lactate [21]. Patients with decompensated liver disease often develop type A lactic acidosis due to altered systemic hemodynamics, followed by impaired tissue perfusion and excessive lactate production. However, almost all patients with chronic liver disease develop type B lactic acidosis due to the decreased utilization of lactate by gluconeogenesis [21]. It is common for individuals with liver disease to concurrently manifest both types of lactic acidosis [24]. In alcoholic liver disease, the oxidation of ethanol shifts the pyruvate-lactate equi-

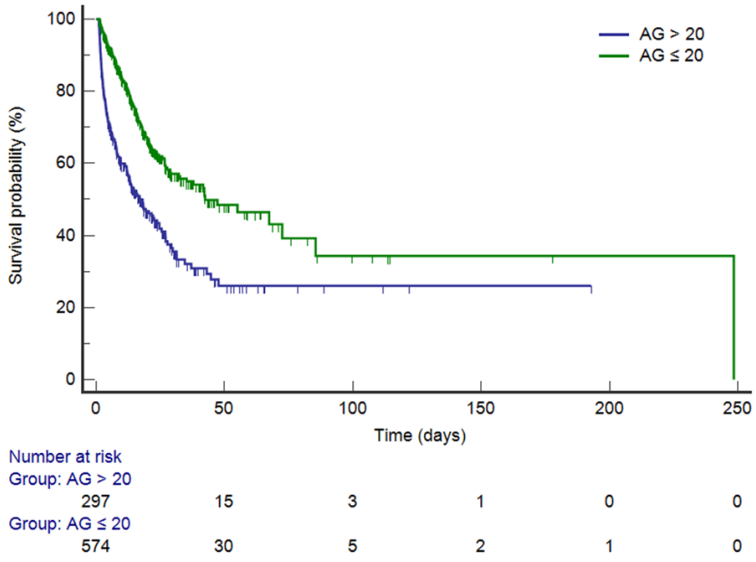

Figure 4. Kaplan-Meier survival curves by AG category (before the propensity score matching, log-rank *P*<0.0001). AG = Anion Gap.

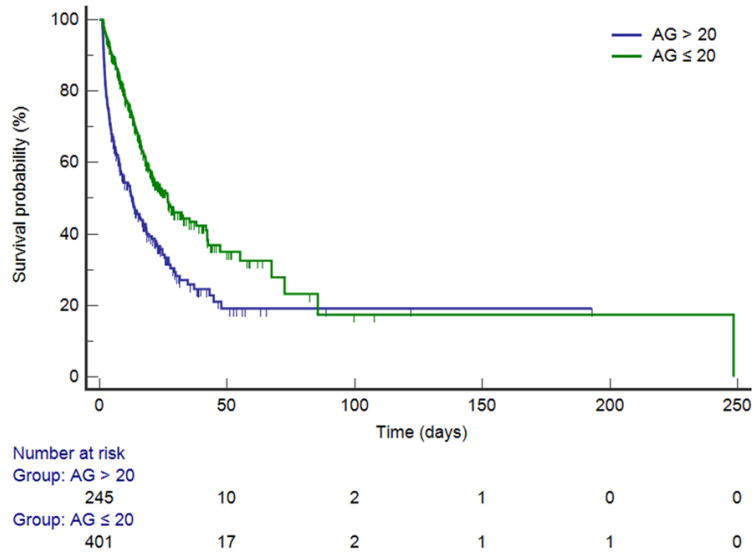

Figure 5. Kaplan-Meier survival curves by AG category (after the propensity score matching, log-rank *P*<0.0001). AG = Anion Gap.

librium toward lactate, further aggravating lactic acidosis [21]. Ultimately, lactic acidosis manifests as metabolic acidosis characterized by an elevated AG.

Liver disease is also intricately linked to another form of metabolic acidosis, ketoacidosis. Ketoacids (including acetoacetate, β-hydroxybutyrate) are usually results from incomplete carbohydrate or fat metabolism by liver mitochondria [14], and patients with a history of alcohol abuse are prone to blood ketoacid formation [21]. Chronic liver disease could also predispose patients to glucose intolerance and the associated diabetic ketoacidosis [21, 25]. Similarly, ketoacidosis also manifests as metabolic acidosis with an elevated AG. A study suggests that initial risk stratification based on AG and metabolic acidosis may facilitate appropriate management and improve clinical outcomes, especially in patients without other well-defined ICU admission criteria. Meanwhile, higher AG at ICU admission was significantly associated with higher mortality [26]. In conclusion, AG may serve as a reflection of the severity of lactic acidosis/ketoacidosis, and then cooperate with metabolic acidosis to predict the mortality of liver failure. It is noteworthy that, given the challenge of quantifying metabolic acidosis, AG might be a more practical marker in clinical settings.

Regarding ACAG, at physiological pH levels, albumin functions as a weak acid, so hypoalbuminemia due to dysfunction of hepatic synthesis induces only mild metabolic alkalosis [14]. This may be the underlying reason for the minimal effect of ACAG on metabolic alkalosis and ultimately its role in liver failure not better than the AG. Our study also found that while the MELD score may be apt for prognosticating survival in end-stage liver disease, it falls short in forecasting outcomes in liver failure. Serum creatinine, bilirubin, and INR, parameters in MELD scoring, are readily influenced by extraneous non-hepatic factors, thereby impeding accurate assessment of liver disease severity. For instance, serum creatinine can be directly affected by the presence or absence of renal disease. Statistically, the MELD formula normalizes the natural logarithms of these variables, then

employs Cox proportional hazards regression or univariate analysis to identify the most influential variables for inclusion in multiple linear regression analysis. Subsequently, a linear regression model is formulated. However, given the complexity of diseases and the frequent correlations among observed disease indicators, collinearity among variables emerges, diminishing the efficacy of linear regression models in addressing complex multivariate issues. This issue likely underpins the limited predictive utility of the MELD scoring system. Our study highlights the importance of AG in predicting in-hospital mortality in patients with liver failure, and we advocate for its heightened consideration in the development of future prognostic scoring systems.

We must acknowledge some limitations of this study. Firstly, the precise etiology of liver failure progression in all patients was not traceable, nor could we exclude those whose liver failure stemmed from other organ failure due to the limitations of the MIMIC database; however, this broadens the applicability of our conclusions to various forms of liver failure. Also, our study lacks external validation to confirm the findings presented herein. Secondly, we did not collect information on advanced treatment performed in the hospital, such as artificial liver supportive care or liver transplantation. Additionally, the significant number of missing initial lactate values, the absence of data on concurrent ketoacidosis in patients, and the unavailability of Child-Pugh scores are factors that could potentially affect the outcomes of this study. Lastly, the majority of patients in this study were diagnosed with acute and subacute liver failure (approximately 54%), but in the USA and Western Europe, the most common cause of acute liver failure is drug-induced liver injury, and in developing countries it remains viral hepatitis [27]. Therefore, it is still unknown whether these conclusions are applicable to other countries and races, and rigorous prospective randomized controlled trials are still needed to be confirmed in the future.

Conclusions

AG is associated with in-hospital mortality in intensive care patients with liver failure, demonstrating a moderate predictive value that is on par with the prognostic capabilities of the MELD score. Compared with AG, ACAG does not enhance predictive performance. AG may serve as an indirect marker of in-hospital mortality in liver failure patients by mirroring the extent of metabolic acidosis; however, this requires validation through rigorous prospective randomized controlled trials.

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Disclosure of conflict of interest

None.

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References

[1] Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association; Severe Liver Disease and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. Guideline for diagnosis and treatment of liver failure. Zhonghua Gan Zang Bing Za Zhi 2019; 27: 18-26.

[2] Bernuau J, Rueff B and Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis 1986; 6: 97-106.

[3] Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER and Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001; 33: 464-470.

[4] Batra Y and Acharya SK. Acute liver failure: prognostic markers. Indian J Gastroenterol 2003; 22 Suppl 2: S66-68.

[5] Peláez-Luna M, Martinez-Salgado J and Olivera-Martinez MA. Utility of the MAYO End-Stage Liver Disease score, King's College Criteria, and a new in-hospital mortality score in the prognosis of in-hospital mortality in acute liver failure. Transplant Proc 2006; 38: 927-929.

[6] Tujios S, Stravitz RT and Lee WM. Management of acute liver failure: update 2022. Semin Liver Dis 2022; 42: 362-378.

[7] Figueira ERR, Rocha-Filho JA, Lanchotte C, Nacif LS, de Paiva Haddad LB, Assalin AR,

Shinkado YR, Vintimilla AM, Galvao FHF and D'Albuquerque LAC. Creatinine-lactate score predicts mortality in non-acetaminophen-induced acute liver failure in patients listed for liver transplantation. BMC Gastroenterol 2021; 21: 252.
[8] Yang SW, Zhou YJ, Zhao YX, Liu YY, Tian XF, Wang ZJ, Jia DA, Han HY, Hu B, Shen H, Gao F, Wang LY, Lin J, Pan GZ, Zhang J, Guo ZF, Du J and Hu DY. The serum anion gap is associated with disease severity and all-cause mortality in coronary artery disease. J Geriatr Cardiol 2017; 14: 392-400.
[9] Chen Q, Chen Q, Li L, Lin X, Chang SI, Li Y, Tian Z, Liu W and Huang K. Serum anion gap on admission predicts intensive care unit mortality in patients with aortic aneurysm. Exp Ther Med 2018; 16: 1766-1777.
[10] Cheng B, Li D, Gong Y, Ying B and Wang B. Serum anion gap predicts all-cause mortality in critically ill patients with acute kidney injury: analysis of the MIMIC-III database. Dis Markers 2020; 2020: 6501272.
[11] Cohen RD. Roles of the liver and kidney in acid-base regulation and its disorders. Br J Anaesth 1991; 67: 154-164.
[12] Häussinger D. Liver regulation of acid-base balance. Miner Electrolyte Metab 1997; 23: 249-252.
[13] Ahya SN, José Soler M, Levitsky J and Batlle D. Acid-base and potassium disorders in liver disease. Semin Nephrol 2006; 26: 466-470.
[14] Scheiner B, Lindner G, Reiberger T, Schneeweiss B, Trauner M, Zauner C and Funk GC. Acid-base disorders in liver disease. J Hepatol 2017; 67: 1062-1073.
[15] Figge J, Jabor A, Kazda A and Fencl V. Anion gap and hypoalbuminemia. Crit Care Med 1998; 26: 1807-1810.
[16] Hatherill M, Waggie Z, Purves L, Reynolds L and Argent A. Correction of the anion gap for albumin in order to detect occult tissue anions in shock. Arch Dis Child 2002; 87: 526-529.
[17] Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA and Mark RG. MIMIC-III, a freely accessible critical care database. Sci Data 2016; 3: 160035.
[18] Charlson ME, Pompei P, Ales KL and MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-383.
[19] DeLong ER, DeLong DM and Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44: 837-845.
[20] Zhang Z, Xu X, Ni H and Deng H. Urine output on ICU entry is associated with hospital mortality in unselected critically ill patients. J Nephrol 2014; 27: 65-71.
[21] Bonavia A and Singbartl K. Kidney injury and electrolyte abnormalities in liver failure. Semin Respir Crit Care Med 2018; 39: 556-565.
[22] Casey TH, Summerskill WH and Orvis AL. Body and serum potassium in liver disease. I. Relationship to hepatic function and associated factors. Gastroenterology 1965; 48: 198-207.
[23] Casey TH, Summerskill WH, Bickford RG and Rosevear JW. Body and serum potassium in liver disease. II. Relationships to arterial ammonia, blood PH, and hepatic coma. Gastroenterology 1965; 48: 208-215.
[24] Madias NE. Lactic acidosis. Kidney Int 1986; 29: 752-774.
[25] García-Compeán D, González-González JA, Lavalle-González FJ, González-Moreno EI, Maldonado-Garza HJ and Villarreal-Pérez JZ. The treatment of diabetes mellitus of patients with chronic liver disease. Ann Hepatol 2015; 14: 780-788.
[26] Dafal A, Kumar S, Agrawal S, Acharya S and Nirmal A. Admission anion gap metabolic acidosis and its impact on patients in medical intensive care unit. J Lab Physicians 2021; 13: 107-111.
[27] Lopes D and Samant H. Hepatic failure. In: StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.