Metabolic acidosis in critically ill patients with cirrhosis: Epidemiology and short-term mortality risk factors

Feng Gao[1], Miao-Tong Lin[2], Xing-Yi Yang[1], Meng-Xing Cai[3], Hao-Nan[4], Wei Xie[1], Zhi-Ming Huang[1]

[1]Department of Gastroenterology and Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[2]Department of Emergency Medicine, Intensive Care, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[3]Department of Cardiovascular Medicine, the Heart Center, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[4]Department of Respiratory Medicine, the Third People's Hospital of Yueqing, Wenzhou, China

Cite this article as: Gao F, Lin MT, Yang XY, et al. Metabolic acidosis in critically ill patients with cirrhosis: Epidemiology and short-term mortality risk factors. Turk J Gastroenterol 2019; 30(10): 883-91.

ABSTRACT

Background/Aims: Metabolic acidosis is a common complication in patients with cirrhosis at the intensive care units (ICUs) and associated with increased mortality. The aim of our research was to explore the epidemiology and risk factors of metabolic acidosis in critically ill patients with cirrhosis.

Materials and Methods: A total of 975 patients with cirrhosis were selected into our study, and all participants were followed up for at least 28 days. Cox regression model and machine-learning algorithm were used to identify the importance of different risk factors, respectively. Finally, an improved prognostic model as Model for End-stage Liver Disease and metabolic acidosis (MELD-MA) was developed.

Results: Among the 975 patients with liver cirrhosis, 506 had metabolic acidosis, including 257 patients who had decompensated metabolic acidosis at ICU admission. The 28-day mortality was 41% (206/506) in patients with metabolic acidosis. Bilirubin (hazard ratio (HR): 1.023, 95% confidence interval (CI): 1.011-1.036), international normalized ratio (HR: 1.527, 95% CI: 1.332-1.750), pH (HR: 0.173, 95% CI: 0.047-0.640), BE-Lac (HR: 0.907, 95% CI: 0.868-0.948), and BE-Na (HR: 0.923, 95% CI: 0.859-0.991) were considered as independent prognostic parameters for 28-day mortality. MELD-NA had significantly higher discrimination (area under the receiver operating characteristic curve 0.79) than MELD and Child-Pugh score.

Conclusion: Critically ill patients with cirrhosis have a high mortality rate and poor prognosis because of the high prevalence of metabolic acidosis. Lactic acidosis is the worst prognosis of all types of metabolic acidosis. MELD-MA performs well on the short-term mortality assessment in critically ill patients with cirrhosis and metabolic acidosis.

Keywords: Cirrhosis, acid-base disturbance, metabolic acidosis, epidemiology, mortality risk

INTRODUCTION

Liver cirrhosis is considered as an irreversible end result of chronic liver inflammation and fibrosis (1). Long-term liver fibrosis can lead to severe liver dysfunction (2). In addition to the kidney and lungs, the liver is a crucial acid-base regulation organ (3), playing an important role in lactate metabolism, ketogenesis, albumin synthesis, and urea production (4-7). Therefore, severe liver damage may lead to metabolic disorders, causing metabolic acidosis (8). Moreover, as complications in liver cirrhosis, extrahepatic organ dysfunction, such as hepatic encephalopathy, ascites, and acute renal failure, may cause and aggravate acidosis (9).

Metabolic acidosis is a common reason for intensive care unit (ICU) admission and associated with increased ICU mortality (8,10). A recent study, including 178 patients with cirrhosis, demonstrated that metabolic acidosis was connected with poor prognosis in patients with cirrhosis (11). To properly evaluate the underlying acid-base disorders in patients with liver disease, Scheiner et al. (7) advocated that the physical-chemical model should be applied to clinical practice.

Gilfix et al. (12) simplified the physical-chemical acid-base model, which explains metabolic acid-base disorders based on base excess (BE) subsets. The physical-chemical acid-base model includes the following five variables: lactate, water (plasma dilution), chloride, albumin, and unmeasured anions (UMA). Lactic acidosis is usually considered as independently related with increased ICU mortality (13). Tissue hypoperfusion will result in increased lactate production, and the deterioration of hepatocyte function in cirrhosis will result in decreased hepatic lactate disposal (14). Patients with cirrhosis with ascites are always accompanied by hyponatremia, which is caused by the activation of the renin-angiotensin-aldosterone system and antidiuretic hormone release because of

Corresponding Author: **Zhi-Ming Huang; wyyhzm@126.com**
Received: **October 18, 2018** Accepted: **January 14, 2019**

DOI: **10.5152/tjg.2019.18813**

portal hypertension induced by insufficient effective circulating blood volume (15,16). Dilution with free water (pH=7.00) will induce hyponatremia and acidify plasma (pH=7.40) (17). The occurrence of hyperchloremic acidosis is considered as the following reasons: compensation for chronic respiratory alkalosis (18), diarrhea, and input of a large amount of saline. Albumin is regarded as a weak acid. Patients with cirrhosis often have hypoalbuminemia (19), which can compensate for metabolic acidosis, resulting in normal pH values.

The aim of our research was to explore the epidemiology and short-term mortality risk factors in a single-center large cohort of critically ill patients with cirrhosis and metabolic acidosis, which may help to improve patients' management and prognosis.

MATERIAL AND METHODS

Database

The study population's dataset was extracted from the Medical Information Mart for Intensive Care III (20), which is a large, freely accessible database established by the Beth Israel Deaconess Medical Center. Access to the database was obtained after completing the National Institute of Health's training course named "Protecting Human Research Participants."

Medical Information Mart for Intensive Care III (MIMIC-III) is a freely accessible database. The institutional review boards of the Massachusetts Institute of Technology had approved the establishment of the MIMIC-III. Ethics committee approval was not necessary for this manuscript.

Our study is a retrospective observational study, and all the information about patients in the database was anonymous, informed consent was not necessary for this manuscript.

Definition

Diagnosis of liver cirrhosis was based on clinical evidence of liver dysfunction or portal hypertension, abnormal liver function tests, ultrasound or computed tomography findings, and histopathology. Metabolic acidosis was defined by HCO_{3-} <22 mmol/L, and decompensated metabolic acidosis was defined by pH <7.35 and HCO_{3-} <22 mmol/L (11). Child-Pugh score (21) and Model for End-stage Liver Disease (MELD) (22) were calculated according to the published formulas. According to the method by Gilfix et al. (12), BE subsets reflecting the contributions of albumin (BE-Alb), lactate (BE-Lac), sodium (BE-Na), chloride (BE-Cl), and unmeasured anions (BE-UMA) were computed.

All patients with a diagnosis of liver cirrhosis were enrolled in the study. Patients with malignancy, acquired immune deficiency syndrome, post-organ transplant, and incomplete medical records were excluded from the study (Figure 1). For patients who were repeatedly admitted to the hospital, only data for the first admission were extracted. Death was assessed by matching the patient to the social security master death index.

Data collection

On ICU admission, parameters for the assessment of acid-base status and arterial blood samples were measured. A complete blood gas analysis includes pH, partial pressure of arterial oxygen (PaO_2), partial pressure of carbon dioxide (PCO_2), sodium (Na^+), potassium (K^+), ionized calcium (Ca^{2+}), magnesium, chloride (Cl^-), inorganic phosphate, bicarbonate (HCO_{3-}), BE, and lactate. Moreover, the levels of albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), activated partial thromboplastin time, blood urea nitrogen (BUN), creatinine, glucose, hemoglobin, hematocrit, international normalized ratio (INR), platelet, prothrombin time, and

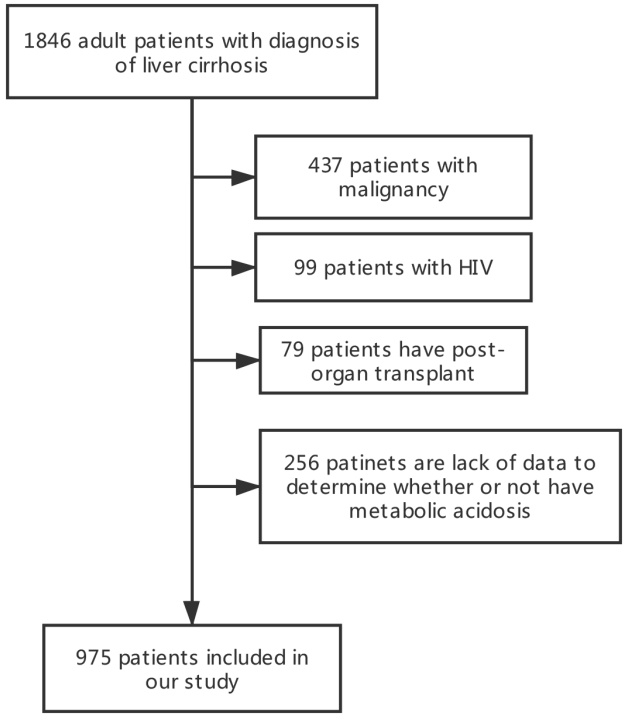

Figure 1. *A flow diagram of the study participants.*

white blood cell (WBC) were derived from the samples of separated plasma. Vital signs were recorded from the hospital's clinical information system, which archived and displayed clinical data at the bedside. All parameters were derived 24 h before and after ICU admission. In addition, all patients were followed up for at least 28 days.

Statistical analysis

Statistical Package for Social Sciences (version 23.0; IBM Corp., Armonk, NY, USA), R statistical package 2.14.0, and MedCalc (version 15.2.2; Ostend, Belgium) were used for statistical analyses. The Kolmogorov-Smirnov test was used to assess the distribution of the variables according to normal or non-normal distribution and compared with Student's t-test or Mann-Whitney U test, respectively. The chi-square test or Fisher's exact test was used for categorical variables. Data were presented as mean±standard derivation or median with interquartile range (IQR) according to normal or non-normal distribution for continuous variables and frequencies for categorical variables. Cox regression was used for univariate and multivariate analyses. The results were presented as hazard ratio (HR) with 95% confidence interval (CI). Survival curves were constructed by Kaplan-Meier estimates, and comparisons were performed using the log-rank test. Random forest analysis, a type of machine-learning algorithm that can build classification prediction models, was used to identify the importance of different risk factors associated with the 28-day mortality risk (23). A p value <0.05 was considered statistically significant.

RESULTS

Patients' characteristics

After the exclusion criteria were applied, 975 critically ill patients with cirrhosis were identified. The median age of the patients was 55.6 years, and the median MELD score was 17 (IQR: 10-25). Most patients were male (65%) and White (73%). Child-Pugh class A, B, and C patients accounted for 11% (107/975), 47% (456/975), and 42% (412/975), respectively. The incidence of metabolic acidosis in our patient population with cirrhosis was 52% (506/975) at ICU admission. Among them, 257 (51%) patients had decompensated metabolic acidosis. Therefore, the morbidity of decompensated metabolic acidosis was 26%. The 7-day, 28-day, and in-hospital mortality were 16% (161/975), 32% (315/975), and 32% (311/975) in critically ill patients with cirrhosis, 23% (118/506), 41% (206/506), and 42% (211/506) in patients with metabolic acidosis, and 29% (75/257), 44% (114/257), and 47% (120/257) in patients with decompensated metabolic acidosis, respectively.

Comparison between patients with and without metabolic acidosis

Patients with metabolic acidosis had a significantly higher proportion of alcoholic liver cirrhosis (55.1% vs. 45.6%, p=0.008), bacterial infection (76.7% vs. 64.8%, p<0.001), hepatorenal syndrome (24.5% vs. 15.4%, p<0.001), acute-on-chronic liver failure (ACLF; 61.5% vs. 48.0%, p<0.001), ascites (29.4% vs. 23%, p=0.023), hepatic encephalopathy (29.4% vs. 22%, p=0.008), and vasopressors used (51.6% vs. 39.7%, p<0.001); a significantly lower proportion of mechanical ventilation (59.1% vs. 67.4%, p=0.007); a significantly higher BUN (33.0 vs. 22.5 mg/dL, p<0.001), creatinine (1.5 vs. 1.0 mg/dL, p<0.001), phosphorus (4.0 vs. 3.7 mmol/L, p<0.001), strong ion gap (24.5 vs. 22.8, p<0.001), WBC (10.0×10^9/L vs. 9.3×10^9/L, p=0.012), INR (1.8 vs.1.6, p<0.001), ALT (35 vs. 28 IU/L, p<0.001), AST (69 vs. 57 IU/L, p<0.001), and MELD (19.4 vs. 14.8, p<0.001) levels; and a significantly lower temperature (36.6 vs. 36.8 °C, p=0.003), mean arterial pressure (72 vs. 75 mm Hg, p<0.001), PaO_2 (116 vs. 137 mm Hg, p<0.001), PCO_2 (33 vs. 41 mm Hg, p<0.001), HCO_{3-} (18.0 °C vs. 25.8 mEq/L, p<0.001), Ca^{2+} (8.1 vs. 8.5 mEq/L, p<0.001), 24-hour urine output (900 vs. 1272 mL, p<0.001), pH (7.3 vs. 7.4, p<0.001), BE (-5.0 vs. 1.0, p<0.001), BE-Cl (-7.1 vs. -3.3, p<0.001), BE-Lac (-2.2 vs. -1.2, p<0.001), BE-UMA (0.4 vs. 2.9, p<0.001), SIDe (26.7 vs. 33.9 mEq/L, p<0.001), and SIDa (51.4 vs. 57.9 mEq/L, p<0.001) levels than patients without metabolic acidosis. Baseline characteristics among the two groups are presented in Tables 1 and 2.

Patients with decompensated metabolic acidosis had a significantly higher proportion of renal replacement therapy (13.6% vs. 8.3%, p=0.024) and higher K^+ (4.4 vs. 4.1 mEq/L, p<0.001) than patients without metabolic acidosis. However, there were no significant differences with or without hepatic encephalopathy (24.1% vs. 22.0%, p=0.506) and mechanical ventilation (65.8% vs. 67.4%, p=0.658) among the two groups. More detailed baseline characteristics among the two groups are presented in Tables 1 and 2. Moreover, patients with ACLF were found to have higher proportion of metabolic acidosis and decompensated metabolic acidosis than those without (58.0% (311/536) vs. 44.4% (195/439), p<0.001 and 43.8% (175/400) vs. 25.2% (82/326), p<0.001).

Risk factors for the 28-day mortality of critically ill patients with cirrhosis with metabolic acidosis

Through Cox hazard univariate and multivariate analyses, bilirubin (HR: 1.023, 95% CI: 1.011-1.036), INR (HR: 1.527, 95% CI: 1.332-1.750), pH (HR: 0.173, 95% CI: 0.047-

Table 1. Characteristics of the study population.

Variable	Metabolic acidosis (n=506)	Decompensated metabolic acidosis (n=257)	No metabolic acidosis (n=469)	p	p*
Demographic parameters					
Age, year	55.6 (49.4-63.1)	56.0 (49.7-63.2)	55.9 (49.2-65.1)	0.585	0.966
Sex, male, n (%)	332 (65.6%)	83 (32.3%)	305 (65.0%)	0.849	0.467
Height, cm	173 (165-180)	175 (165-180)	170 (163-178)	0.036	0.016
Weight, kg	83.2 (71.0-96.8)	87.0 (74.5-99.2)	83.5 (69.5-99.0)	0.791	0.137
Ethnicity					
White, n (%)	358 (70.8%)	176 (68.5%)	355 (75.7%)	0.199	0.105
Black, n (%)	48 (9.5%)	26 (10.1%)	34 (7.2%)		
Others, n (%)	100 (19.8%)	55 (21.4%)	80 (17.1%)		
Etiologies					
Alcoholic, n (%)	279 (55.1%)	140 (54.5%)	214 (45.6%)	0.008	0.049
Biliary, n (%)	13 (2.6%)	7 (2.7%)	10 (2.1%)		
Others, n (%)	214 (42.3%)	110 (42.8%)	245 (52.5%)		
Vital signs					
Heart rate, beats/min	92 (80-103)	90 (78-104)	85 (75-99)	<0.001	0.012
Respiratory rate, breaths/min	19 (16-23)	20 (17-23)	18 (15-20)	<0.001	<0.001
Temperature, °C	36.6 (36.2-37.1)	36.6 (36.1-37.0)	36.8 (36.4-37.2)	0.003	<0.001
SBP, mm Hg	108 (100-120)	106 (98-116)	114 (104-127)	<0.001	<0.001
DBP, mm Hg	57 (51-64)	56 (50-63)	60 (52-67)	0.003	<0.001
MAP, mm Hg	72 (67-81)	71 (65-78)	75 (68-85)	<0.001	<0.001
24-hour urine output, mL	900 (408-1763)	752 (263-1596)	1272 (684-2151)	<0.001	<0.001
Vasopressors, n (%)	261 (51.6%)	159 (61.9%)	186 (39.7%)	<0.001	<0.001
Laboratory parameters					
Glucose, mg/dL	127 (105-164)	129 (103-169)	131 (110-158)	0.411	0.619
WBC, 10^9/L	10.0 (6.6-15.2)	10.7 (6.7-15.6)	9.3 (6.3-13.2)	0.012	0.004
Hematocrit, %	29.6 (26.9-32.9)	29.4 (27.0-33.0)	29.4 (27.0-33.0)	0.702	0.696
Hemoglobin, mg/dL	10.1 (9.0-11.1)	9.9 (9.1-11.1)	9.9 (9.1-11.1)	0.678	0.471
PLT, 10^9/L	101 (73-148)	101 (73-155)	108 (77-163)	0.091	0.309
Potassium, mEq/L	4.2 (3.7-4.7)	4.4 (3.8-5.0)	4.1 (3.7-4.6)	<0.001	<0.001
Calcium, mEq/L	8.1 (7.4-8.9)	8.0 (7.2-8.8)	8.5 (7.9-9.1)	<0.001	<0.001
Magnesium, mEq/L	1.9 (1.6-2.2)	1.9 (1.6-2.2)	1.9 (1.7-2.2)	0.817	0.496
Phosphorus, mEq/L	4.0 (3.1-5.3)	4.7 (3.5-6.1)	3.7 (3.0-4.5)	<0.001	<0.001
PaO_2, mm Hg	116 (87-163)	116 (88-164)	137 (90-194)	<0.001	0.006
PCO_2, mm Hg	33.0 (27.0-38.0)	37.0 (31.0-43.0)	41.0 (37.0-47.0)	<0.001	<0.001
PaO_2/FiO_2	240 (154-319)	216 (147-311)	255 (181-357)	<0.001	<0.001
SpO_2/FiO_2	1.9 (1.5-2.2)	1.7 (1.4-2.1)	2.0 (1.7-2.2)	<0.001	<0.001
SIG	24.5 (21.6-28.3)	23.7 (20.9-27.6)	22.8 (19.6-26.6)	<0.001	0.059
SIDe	26.7 (23.7-29.4)	26.4 (22.8-29.4)	33.9 (31.6-36.6)	<0.001	<0.001
SIDa	51.4 (47.5-55.3)	50.0 (45.9-54.6)	57.9 (53.8-62.2)	<0.001	<0.001
BE	-5.0 (-9.0 to -3.0)	-9.0 (-12.0 to -6.0)	1.0 (0.0-4.0)	<0.001	<0.001

Table 1. Characteristics of the study population (Continued).

BE-Na	-0.6 (-1.8-0.6)	-0.6 (-1.8-0.6)	-0.3 (-1.2-0.6)	0.127	0.362
BE-Cl	-7.1 (-9.8 to -3.5)	-7.2 (-10.2 to -4.5)	-3.3 (-5.5-0.4)	<0.001	<0.001
BE-Alb	4.3 (3.4-5.3)	4.1 (3.0-5.2)	4.3 (3.5-5.1)	0.688	0.316
BE-Lac	-2.2 (-3.6 to -1.0)	-2.2 (-4.7 to -1.0)	-1.2 (-2.2 to -0.6)	<0.001	<0.001
BE-UMA	0.4 (-3.5-3.1)	-1.9 (-6.2-1.3)	2.9 (0.2-4.8)	<0.001	<0.001
PH	7.3 (7.3-7.4)	7.3 (7.2-7.3)	7.4 (7.4-7.5)	<0.001	<0.001
Bicarbonate, mEq/L	18.0 (15.0-20.1)	16.3 (13.0-19.3)	25.5 (23.7-28.1)	<0.001	<0.001
Creatinine, mg/dL	1.5 (1.0-2.9)	1.9 (1.1-3.3)	1.0 (0.7-1.7)	<0.001	<0.001
BUN, mg/dL	33.0 (20.5-56.5)	35.2 (23.2-59.7)	22.5 (14.8-38.0)	<0.001	<0.001
INR	1.8 (1.5-2.3)	1.8 (1.5-2.4)	1.6 (1.4-1.9)	<0.001	<0.001
Bilirubin, mg/dL	3.3 (1.6-8.3)	3.1 (1.4-7.9)	3.5 (1.5-7.4)	0.256	0.999
ALT, U/L	35 (20-63)	34 (20-61)	28 (17-53)	<0.001	0.001
AST, U/L	69 (41-132)	68 (39-138)	57 (28-112)	<0.001	0.005
Clinical scores					
Child-Pugh class					
A, n (%)	47 (9.3%)	26 (10.1%)	60 (12.8%)	<0.001	<0.001
B, n (%)	208 (41.1%)	102 (39.7%)	248 (52.9%)		
C, n (%)	251 (49.6%)	129 (50.2%)	161 (34.3%)		
MELD	19.4 (12.1-27.9)	23.3 (13.7-32.7)	14.8 (9.2-22.0)	<0.001	<0.001
RRT, n (%)	55 (10.9%)	35 (13.6%)	39 (8.3%)	0.177	0.024
Ventilator, n (%)	299 (59.1%)	169 (65.8%)	316 (67.4%)	0.007	0.658
Mortality, n (%)					
In-hospital	211 (41.7%)	120 (46.7%)	100 (21.3%)	<0.001	<0.001
7 days	118 (23.3%)	257 (100.0%)	43 (9.2%)	<0.001	<0.001
14 days	162 (32.0%)	93 (36.2%)	74 (15.8%)	<0.001	<0.001
28 days	206 (40.7%)	114 (44.4%)	109 (23.2%)	<0.001	<0.001

p: metabolic acidosis versus no metabolic acidosis; p*: decompensated metabolic acidosis versus no metabolic acidosis.
Alb: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BE: base excess; BUN: blood urine nitrogen; Cl: chloride; DBP: diastolic blood pressure; FiO_2: fraction of inspired oxygen; INR: international normalized ratio; Lac: lactate; MAP: mean arterial pressure; MELD: Model for End-stage Liver Disease; Na: sodium; PaO_2: partial pressure of arterial oxygen; PCO_2: partial pressure of arterial carbon dioxide; PH: potential of hydrogen; PLT: platelet; RRT: renal replacement therapy; SBP: systolic blood pressure; SIG: strong ion gap; SIDe: effective strong ion difference; SIDa: apparent strong ion difference; SpO_2: pulse oxygen saturation; UMA: unmeasured anions; WBC: white blood cell.

0.640), BE-Lac (HR: 0.907, 95% CI: 0.868-0.948), and BE-Na (HR: 0.923, 95% CI: 0.859-0.991) were considered as independent prognostic parameters for 28-day mortality (Table 3). After calculating the maximum Youden index, optimal cut-off points were found. Subgroup analysis demonstrated that patients with bilirubin ≥4.2 mg/dL, INR≥1.8, BE-Lac ≤-2.1, BE-Na ≤-1.4, and pH ≤7.2 had a poorer survival probability (Figure 2).

Machine-learning algorithm was used to identify the significance of different risk factors

Random forest algorithms using components were used to identify the significance of risk factors in patients with cirrhosis with metabolic acidosis who died during hospitalization. The proportional importance of each input variable in the random forest model is shown in Figure 3. Furthermore, the most crucial variables in patients who died were as follows: INR, BE-Lac, bilirubin, BE-Na, and pH.

Rebuild model for end-stage liver disease

Through univariate and multivariate analyses, bilirubin, INR, potential of hydrogen (PH), BE-Na, and BE-Lac were demonstrated as independent prognostic parameters for 28-day mortality. Through machine-learning algorithm, lactic acidosis was considered as the worst prognosis of all types of metabolic acidosis. Therefore,

Table 2. Complications of cirrhosis.

Variable, n (%)	Metabolic acidosis (n=506)	Decompensated metabolic acidosis (n=257)	No metabolic acidosis (n=469)	p	p*
Hepatic encephalopathy	149 (29.4%)	62 (24.1%)	103 (22.0%)	0.008	0.506
Ascites	149 (29.4%)	77 (30.0%)	108 (23.0%)	0.023	0.040
Bacterial infection	388 (76.7%)	196 (76.3%)	304 (64.8%)	<0.001	0.001
Variceal bleeding	176 (34.8%)	87 (33.9%)	135 (28.8%)	0.045	0.156
Hepatorenal syndrome	124 (24.5%)	68 (26.5%)	72 (15.4%)	<0.001	<0.001
Spontaneous bacterial peritonitis	60 (11.9%)	32 (12.5%)	38 (8.1%)	0.051	0.058
Acute-on-chronic liver failure					
None	195 (38.5%)	82 (31.9%)	244 (52.0%)	<0.001	<0.001
Grade A	71 (14.0%)	36 (14.0%)	71 (15.1%)		
Grade B	124 (24.5%)	59 (23.0%)	98 (20.9%)		
Grade C	116 (22.9%)	80 (31.1%)	56 (11.9%)		

p: metabolic acidosis versus no metabolic acidosis. p*: decompensated metabolic acidosis versus no metabolic acidosis.

Table 3. Univariate and multivariate analyses of the association between clinical parameters and 28-day mortality in patients with cirrhosis with metabolic acidosis.

	Univariate analysis			Multivariate analysis*		
Variables	HR	95% CI	p	HR	95% CI	p
Bilirubin (mg/dL)	1.029	(1.018-1.041)	<0.001	1.023	(1.011-1.036)	<0.001
Creatinine (mg/dL)	1.111	(1.047-1.180)	<0.001	-	-	-
INR	1.665	(1.499-1.848)	<0.001	1.527	(1.332-1.750)	<0.001
PH	0.055	(0.017-0.175)	<0.001	0.173	(0.047-0.640)	0.009
BE-Na	0.915	(0.853-0.982)	0.014	0.923	(0.859-0.991)	0.027
BE-Cl	1.071	(1.042-1.100)	<0.001	-	-	-
BE-Lac	0.875	(0.846-0.906)	<0.001	0.907	(0.868-0.948)	<0.001
BE-Alb	1.028	(0.948-1.116)	0.502	-	-	-
BE-UMA	0.947	(0.925-0.969)	<0.001	-	-	-
Ascites	1.201	(0.898-1.605)	0.217	-	-	-
Hepatic encephalopathy	0.877	(0.649-1.187)	0.396	-	-	-

*Adjusted for bilirubin, creatinine (mg/dL), INR, PH, BE-Na, BE-Cl, BE-Lac, BE-Alb, BE-UMA, ascites, and hepatic encephalopathy.
BE-Alb: base excess due to the alkalinizing effect of hypoalbuminemia; BE-UMA: base excess due to the acidifying effect of unmeasured anions; BE-Na: base excess due to the acidifying effect of plasma dilution by free water; BE-Cl: base excess due to the acidifying effect of hyperchloremia; BE-Lac: base excess due to the acidifying effect of elevated lactate; INR: international normalized ratio; PH: potential of hydrogen.

creatinine was replaced with lactate, and INR and bilirubin were retained in the final model. These variables are transformed to their natural logarithms. The improved prognostic model was named as Model for End-stage Liver Disease and metabolic acidosis (MELD-MA). The final model was represented as follows: R=1.5×loge (bilirubin (mg/dL))+9.6×loge (INR)+2.8×loge (lactate (mg/dL))+1.4×(decompensated metabolic acidosis: 1 yes, 0 no). MELD-NA performed significantly higher area under the receiver operating characteristic curve than MELD and Child-Pugh score (Figure 4).

DISCUSSION

Metabolic acidosis is a common complication in patients with cirrhosis at the ICUs. Our study demonstrated that the prevalence of metabolic acidosis in critically ill patients with cirrhosis was 52%, and that the 28-day mortality was 40.7%. The prevalence of decompensated

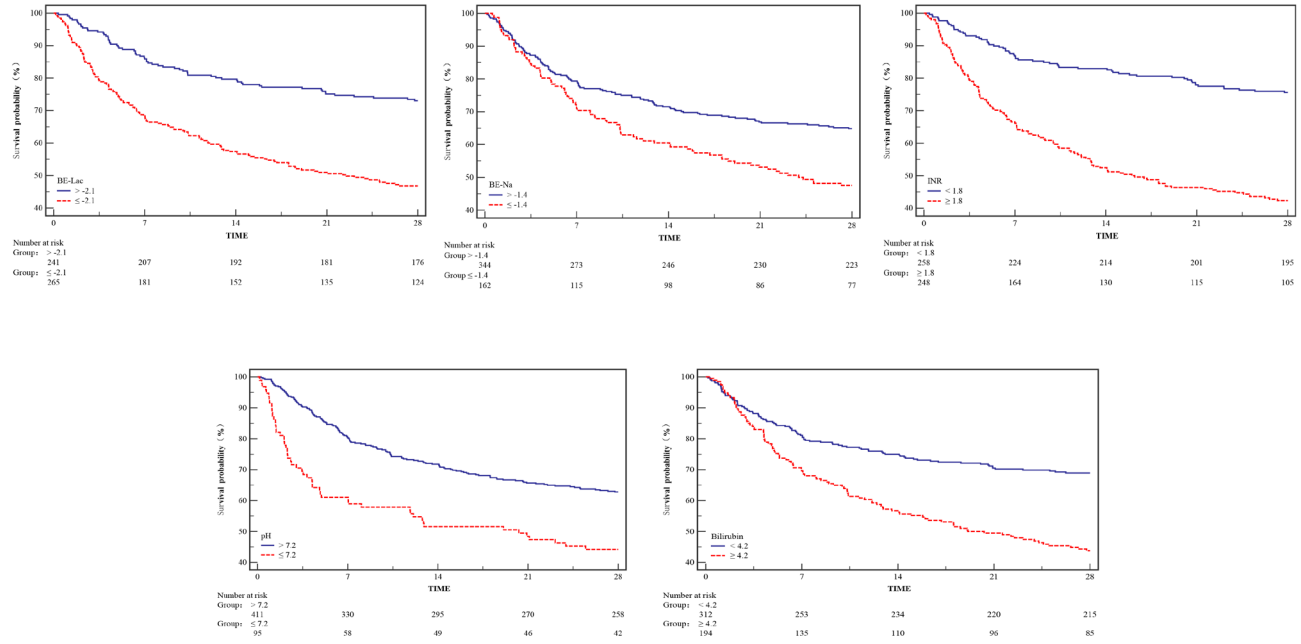

Figure 2. *Kaplan-Meier curves stratified by BE-Lac, BE-Na, INR, pH, and bilirubin, respectively (all p<0.05).*

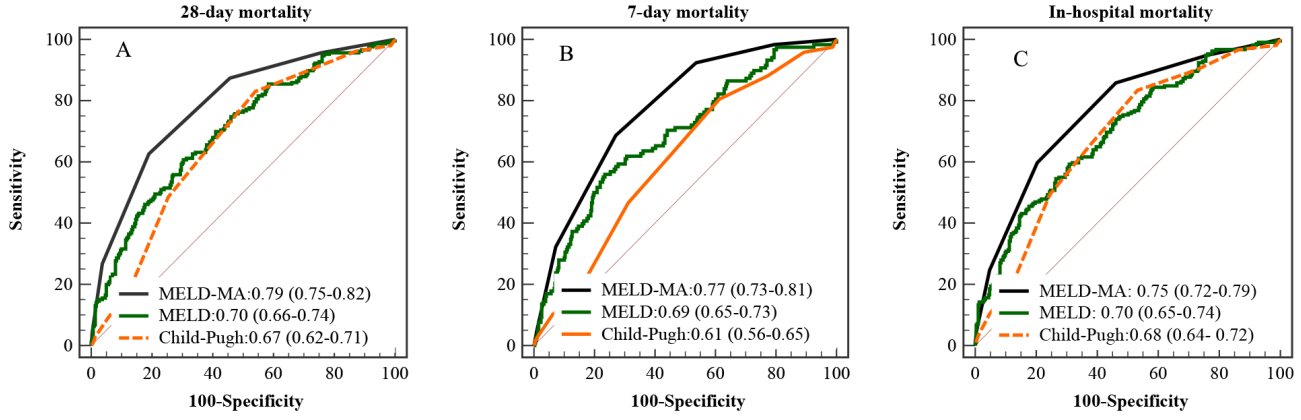

Figure 3. *Area under the receiver operating characteristic curve of the predictive ability of MELD-MA and other scoring models to predict (A) 28-day, (B) 7-day, and (C) in-hospital mortality of patients with cirrhosis with metabolic acidosis (all p<0.05).*

metabolic acidosis in critically ill patients with cirrhosis was 26%, and the 28-day mortality was 44.4%. This suggests that in the ICU, patients with cirrhosis have a high prevalence and mortality of metabolic acidosis.

Our study indicated that patients with cirrhosis with metabolic acidosis were associated with temperature, blood pressure, PaO_2, Cl^-, albumin, lactate, bilirubin, creatine, ALT, ASR, INR, BUN, WBC, 24-hour urine output, alcoholic cirrhosis, ascites, vasopressor used, ventilator used, and the score of prognostic models. Bilirubin, ALT, AST, INR, ascites, and the score of prognostic models are associated with the severity of liver dysfunction. Creatine, BUN, and 24-hour urine output represent the function of the kidney. Blood pressure and vasopressors used represent the health of the cardiovascular system (24). Low PaO_2 and ventilator used are related with respiratory failure (25). These indicate that metabolic acidosis may be the

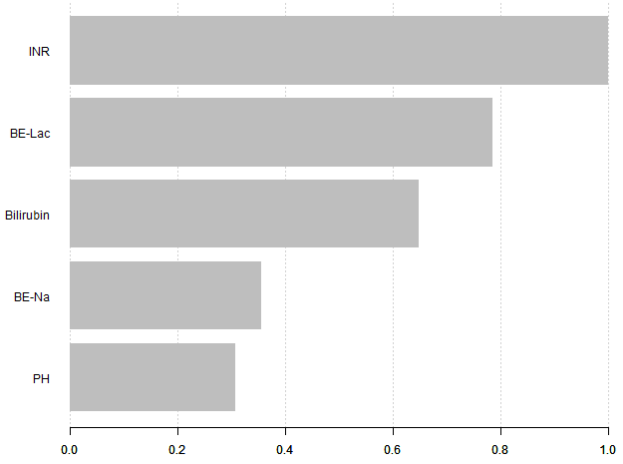

Figure 4. *The importance of different risk factors in patients with metabolic acidosis who died during 28 days.*

sign of multiple organ failure in critically ill patients with cirrhosis.

A high proportion of alcoholic liver cirrhosis was found in patients with metabolic acidosis or decompensated metabolic acidosis in comparison with those without. The relationship between alcoholic liver cirrhosis and development of metabolic acidosis should be prospectively validated. Hepatic encephalopathy can induce respiratory alkalosis, which is related to hyperventilation (26). Owing to long-term respiratory alkalosis, the kidneys will reduce the HCO_{3-} level. Lactulose, which is often used to treat hepatic encephalopathy, can also cause gastrointestinal Cl^- retention and HCO_{3-} excretion (18). These may explain why there was a significant relationship between hepatic encephalopathy and risk of metabolic acidosis in liver cirrhosis, but not found in patients with net metabolic acidosis. Patients who used ventilator had a lower prevalence of metabolic acidosis than patients without ventilator used. However, this phenomenon was not found in patients with net metabolic acidosis, and further studies may be necessary to explore whether or not ventilator used protects from the development of metabolic acidosis in patients with cirrhosis.

Our study demonstrated that the 28-day mortality was significantly higher in critically ill patients with cirrhosis with metabolic acidosis than in those without (40.7% (206/506) vs. 23.2% (109/469), p<0.001). The importance of metabolic acidosis in liver cirrhosis should be well recognized by medical staffs. Thus, the independent prognostic parameters for 28-day mortality were explored. Through univariate and multivariate Cox analyses, bilirubin, INR, BE-lactate, BE-Na, and PH were found to show a strong association with 28-day mortality. Bilirubin and INR are classic indicators of liver function (27). The high levels of bilirubin and INR are well recognized as markers of liver failure. Moreover, the presence of acidemia and lactic acidosis were related with liver dysfunction (10). The improved model (MELD-MA) performed significantly higher discrimination than MELD and Child-Pugh in predicting the mortality of critically ill patients with cirrhosis and metabolic acidosis.

Na^+, Cl^-, albumin, lactate, and unmeasured anions were considered as subcomponents of BE. Increased lactic acidosis not only plays the most important role in the occurrence of metabolic acidosis but also plays the most crucial role in death (28). Lactic acidosis in critically ill patients with cirrhosis results from both increased lactate production and decreased hepatic lactate disposal. Sepsis and bleeding are considered as common causes of hyperlactacidemia in critically ill patients with cirrhosis (29). Several studies found the complex disturbances of lactate metabolism in patients with acute and chronic liver diseases (15,16).

The liver is an important acid-base regulation organ. A recent study showed that there were 100% 28-day mortality when patients' arterial pH values were <7.1 on admission and 89% 28-day mortality when patients' HCO_{3-} values were <10 mmol/L (11). In our study, pH value <7.1 on admission was associated with 68% (15/22), and HCO_{3-} value <10 mmol/L was associated with 65% (15/23) 28-day mortality. The difference may be affected by the sample size. pH and HCO_{3-} as prognosis predictors for patients with cirrhosis are consistent with two studies.

There are certain limitations in our study. First, the research we conducted is a single-center retrospective study, and more multicenter researches are needed to externally validate the conclusion. Second, our study only focused on short-term mortality, and the risk factors of long-term mortality are also needed to be explored.

In conclusion, this is the largest study to evaluate epidemiology and short-term mortality risk factors for critically ill patients with cirrhosis with metabolic acidosis. Critically ill patients with cirrhosis have a high mortality rate and poor prognosis because of the high prevalence of metabolic acidosis. INR, BE-Lac, bilirubin, BE-Na, and pH are recognized as independent predictors of 28-day mortality in these patients. Lactic acidosis is the worst progno-

sis of all types of metabolic acidosis when cirrhosis is accompanied by critical illness. The new model (MELD-MA) performed well in predicting the mortality of critically ill patients with cirrhosis and metabolic acidosis.

Ethics Committee Approval: N/A.

Informed Consent: The study is a retrospective observational study, and all the information about patients in the database was anonymous, informed consent was not necessary for this manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.F., L.M.T., H.Z.M.; Design - G.F., C.M.X., H.Z.M.; Supervision - H.Z.M.; Resources - H.Z.M.; Materials - H.Z.M.; Data Collection and/or Processing - G.F., L.M.T., X.W.; Analysis and/or Interpretation - G.F., X.W.; Literature Search - G.F., X.W., H.Z.M.; Writing Manuscript - G.F., N.H., Y.X.Y.; Critical Review - H.Z.M.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Langberg KM, Kapo JM, Taddei TH. Palliative care in decompensated cirrhosis: A review. Liver Int 2018; 38: 768-75. [CrossRef]
2. Germani G, Hytiroglou P, Fotiadu A, Burroughs AK, Dhillon AP. Assessment of fibrosis and cirrhosis in liver biopsies: an update. Semin Liver Dis 2011; 31: 82-90. [CrossRef]
3. Cohen RD. Roles of the liver and kidney in acid-base regulation and its disorders. Br J Anaesth 1991; 67: 154-64. [CrossRef] https://doi.org/10.1093/bja/67.2.154
4. Weiss L, Loffler G. Interrelationship between adipose tissue and liver: gluconeogenesis and ketogenesis. Horm Metab Res 1970; 2(Suppl 2): 196-20.
5. Samsel RW, Cherqui D, Pietrabissa A, Sanders WM, Roncella M, Emond JC, Schumacker PT. Hepatic oxygen and lactate extraction during stagnant hypoxia. J Appl Physiol 1991; 70: 186-93. [CrossRef]
6. Mazzeo AT, Maimone S. Acid-base disorders in liver disease. J Hepatol 2018; 68: 617-8. [CrossRef]
7. Scheiner B, Lindner G, Reiberger T, et al. Acid-base disorders in liver disease. J Hepatol 2017; 67: 1062-73. [CrossRef]
8. Funk GC, Doberer D, Kneidinger N, Lindner G, Holzinger U, Schneeweiss B. Acid-base disturbances in critically ill patients with cirrhosis. Liver Int 2007; 27: 901-9. [CrossRef]
9. Peck-Radosavljevic M, Angeli P, Cordoba J, Farges O, Valla D. Managing complications in cirrhotic patients. United European Gastroenterol J 2015; 3: 80-94. [CrossRef]
10. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, Bennett ED. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med 2001; 27: 74-83. [CrossRef]
11. Drolz A, Horvatits T, Roedl K, et al. Acid-base status and its clinical implications in critically ill patients with cirrhosis, acute-on-chronic liver failure and without liver disease. Ann Intensive Care 2018; 8: 48. [CrossRef]
12. Gilfix BM, Bique M, Magder S. A physical chemical approach to the analysis of acid-base balance in the clinical setting. J Crit Care 1993; 8: 187-97. [CrossRef]
13. Masevicius FD, Rubatto Birri PN, Risso Vazquez A, et al. Relationship of at Admission Lactate, Unmeasured Anions, and Chloride to the Outcome of Critically Ill Patients. Crit Care Med 2017; 45: e1233-e9. [CrossRef]
14. Oster JR, Perez GO. Acid-base disturbances in liver disease. J Hepatol 1986; 2: 299-306. [CrossRef]
15. John S, Thuluvath PJ. Hyponatremia in cirrhosis: pathophysiology and management. World J Gastroenterol 2015; 21: 3197-205. [CrossRef]
16. Sinha VK, Ko B. Hyponatremia in Cirrhosis--Pathogenesis, Treatment, and Prognostic Significance. Adv Chronic Kidney Dis 2015; 22: 361-7. [CrossRef]
17. Funk GC, Doberer D, Osterreicher C, Peck-Radosavljevic M, Schmid M, Schneeweiss B. Equilibrium of acidifying and alkalinizing metabolic acid-base disorders in cirrhosis. Liver Int 2005; 25: 505-12. [CrossRef]
18. Ahya SN, Jose Soler M, Levitsky J, Batlle D. Acid-base and potassium disorders in liver disease. Semin Nephrol 2006; 26: 466-70. [CrossRef]
19. Funk GC, Doberer D, Fuhrmann V, et al. The acidifying effect of lactate is neutralized by the alkalinizing effect of hypoalbuminemia in non-paracetamol-induced acute liver failure. J Hepatol 2006; 45: 387-92. [CrossRef]
20. Johnson AE, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. Sci Data 2016; 3: 160035. [CrossRef]
21. Albers I, Hartmann H, Bircher J, Creutzfeldt W. Superiority of the Child-Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. Scand J Gastroenterol 1989; 24: 269-76. [CrossRef]
22. Boone MD, Celi LA, Ho BG, et al. Model for End-Stage Liver Disease score predicts mortality in critically ill cirrhotic patients. J Crit Care 2014; 29: 881.e7-13. [CrossRef]
23. Singal AG, Mukherjee A, Elmunzer BJ, et al. Machine learning algorithms outperform conventional regression models in predicting development of hepatocellular carcinoma. Am J Gastroenterol 2013; 108: 1723-30. [CrossRef]
24. Russell JA, Fjell C, Hsu JL, et al. Vasopressin compared with norepinephrine augments the decline of plasma cytokine levels in septic shock. Am J Respir Crit Care Med 2013; 188: 356-64. [CrossRef]
25. Federspiel CK, Itenov TS, Thormar K, Liu KD, Bestle MH. Hypophosphatemia and duration of respiratory failure and mortality in critically ill patients. Acta Anaesthesiol Scand 2018. [CrossRef]
26. Karetzky MS, Mithoefer JC. The cause of hyperventilation and arterial hypoxia in patients with cirrhosis of the liver. Am J Med Sci 1967; 254: 797-804. [CrossRef]
27. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013; 144: 1426-37.e1-9. [CrossRef]
28. Kimmoun A, Novy E, Auchet T, Ducrocq N, Levy B. Hemodynamic consequences of severe lactic acidosis in shock states: from bench to bedside. Crit Care 2015; 19: 175. [CrossRef]
29. Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med 2019; 45: 82-5. [CrossRef]