Metabolic Acidosis in Critically Ill Cirrhotic Patients with Acute
Kidney Injury

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Abstract

Background and Aims: The metabolic acid-base disorders have a high incidence of acute kidney injury (AKI) in critically ill cirrhotic patients (CICPs). The aims of our study were to ascertain the composition of metabolic acidosis of CICPs with AKI and explore its relationship with hospital mortality.

Methods: Three-hundred and eighty consecutive CICPs with AKI were eligible for the cohort study. Demographic, clinical and laboratory parameters were recorded and arterial acid-base state was analyzed by the Stewart and Gilfix methodology.

Results: Net metabolic acidosis, lactic acidosis, acidosis owing to unmeasured anions, acidemia, and dilutional acidosis were less frequent in the non-survival group compared to the survival group of CICPs. The presence of acidemia, acidosis owing to unmeasured anions, and lactic acidosis were independently associated with increased risk of intensive care unit 30-day mortality, with hazard ratios of 2.11 (95% confidence interval (CI): 1.43–3.12), 3.38 (95% CI: 2.36–4.84), and 2.16 (95% CI: 1.47–3.35), respectively. After full adjustment for confounders, the relationship between acidosis owing to unmeasured anions with hospital mortality was still significant, with hazard ratio of 2.29 (95% CI: 1.22–4.30). Furthermore, arterial lactate concentration in combination with chronic liver failure-sequential organ failure assessment and BEUMA had the strongest ability to differentiate 30-day mortality (area under the receiver operating characteristic curve: 0.79, 95% CI: 0.74–0.83).

Conclusions: CICPs with AKI exhibit a complex metabolic acidosis during intensive care unit admission. Lactic acidosis and BEUMA, novel markers of acid-base disorders, show promise in predicting mortality rate of CICPs with AKI.

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Introduction

Acute kidney injury (AKI) is defined by rapid kidney function decline, over several hours to days, with contradistinction to chronic kidney disease.1 It is a common complication of critically ill cirrhotic patients (CICPs) and is a common reason for which CICPs are admitted to the intensive care unit (ICU).2,3 In patients with stable cirrhosis, studies have found that hyperammonemic alkalosis, dilutional acidosis and hyperchloremic acidosis work together to achieve a compensatory effect, in which alkalizing and acidifying acid-base disturbances can achieve an equilibrium that eventually results in a stable metabolic acid-base state.4,5 No data to date is available for disorders of acid-base homeostasis in CICPs with AKI. Acid-base data have been interpreted by traditional methods that contain the parameters of standard base excess, bicarbonate (HCO3−), anion gap (AG), and pH.6 The standard base excess, a calculated data value, assumes normal plasma protein and electrolyte content.7 The observed AG also ignores the role of major non-bicarbonate buffers in blood plasma, such as plasma proteins and inorganic phosphate.8 However, CICPs with AKI always present with electrolyte and protein abnormalities. Thus, the physicochemical approach performed by Stewart for acid-base disturbances has been applied in clinical practice, particularly for critically ill patients.9

In addition, the Gilfix methodology, a simple bedside approach based on the fundamental principles of the Stewart method, can be used to analyze base excess compounds.10 The Gilfix method proposed that non-respiratory acid–base disturbance may be attributed to the following: changes in strong ions due to free water deficit or excess, determined by changes in sodium concentration, and changes in chloride.

Keywords: Metabolic acidosis; Critically ill cirrhotic patients; Acute kidney injury; Hospital mortality; Abbreviations: AKI, acute kidney injury; AG, anion gap; AUROC, area under the receiver operating characteristic curve; BE, base excess; CI, confidence interval; CICPs, critically ill cirrhotic patients; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; HCO3−, bicarbonate; ICU, intensive care unit; KDIGO, kidney disease improving global outcomes; MIMIC-III v3.0, Multiparameter Intelligent Monitoring in Intensive Care Database III version 3.0; SAPS, simplified acute physiology score; SCr, serum creatinine; SIDa, strong ion difference-effective; SIDe, strong ion difference-effective; SIG, strong ion gap.

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concentration; changes in protein charges (mainly albumin); and presence of unmeasured organic anions.\textsuperscript{11,12} Although the Stewart model theory and the Gilfix method have been used previously to better understand acid-base homeostasis in critically ill patients,\textsuperscript{13,14} there has been no report to evaluate their ability to predict mortality in CICPs with AKI.

It is generally understood that one cannot separate acid-base effects of CICPs from AKI; therefore, comprehending the contribution of AKI to acid-base disorders becomes essential to opening avenues for novel screening methods that may provide better physiological diagnosis and prognosis. This study aims to identify and describe the composition of metabolic acidosis in CICPs with AKI and their relationship with hospital mortality.

Methods

The database and patients

The data for this study was extracted from the Medical Information Mart for Intensive Care version 3.0 (MIMIC-III v3.0), a comprehensive and free database. With permission, we were allowed access to medical records of patients treated in the ICU from 2001 to 2012 at Beth Israel Deaconess Medical Center (our certification number: 1605699). The data used were non-patient identifiable and anonymous; detailed descriptions have been reported in our previous studies.\textsuperscript{15,16}

In this study, we extracted a total of 1460 consecutive CICPs from the MIMIC-III v3.0 database. Ultimately, 380 in-hospital patients in the ICU were deemed eligible for study inclusion. Criteria for inclusion were as follows: diagnosis of liver cirrhosis and older than 18 years; diagnosis of AKI followed-up for at least 30 days; no history of liver transplantation; no history of end-stage renal disease; no regular renal replacement therapy; and admitted to the hospital for more than 24 h.

CICPs, defined as patients with critically ill cirrhosis, were enrolled in our study when admitted to the ICU. The criteria of liver cirrhosis and AKI in the present study were described in our previous studies.\textsuperscript{15-17} For patients without a serum creatinine (SCR) value prior to hospitalization, we used the first SCR value measured during hospitalization as the baseline SCR, in compliance with recommendations of the International Club of Ascites.\textsuperscript{18} In addition, the models for end-stage liver disease (commonly known as MELD), chronic liver failure-sequential organ failure assessment (CLIF-SOFA), simplified acute physiology score (commonly known as SAPS II), SOFA score, and kidney disease improving global outcomes (commonly known as KDIGO) criteria were calculated to evaluate the severity of CICPs with AKI.

Sampling and blood analysis

Our investigators extracted detailed patient records, typically containing demographic and laboratory parameters as well as survival time. The clinical parameters were derived from the hospital’s online information systems. The laboratory parameters from routine tests on admission were extracted into a relational database. Patient arterial blood was collected on admission. SCr was evaluated upon admission and at least once every 24-h interval. The urine output was calculated for the first 24 h after ICU admission, recorded at least 6 h intervals. Social Security Death Records from the USA government provided the time of death. Patient data was obtained using Oracle Structured Query Language Developer version 3.0 (Oracle Corporation, Redwood Shores, CA, USA).

Acid-base analysis

Arterial HCO\textsubscript{3}\textsuperscript{−}, standard bicarbonate (HCO\textsubscript{3}\textsuperscript{−},\textsubscript{a}), base excess (BE) and standard base excess measurements were carried out according to Henderson-Hasselbalch and Siggaard-Andersen equations respectively.\textsuperscript{19} In the present study, pH <7.35 was defined as acidemia, pH >7.45 as alkalemia, HCO\textsubscript{3}\textsuperscript{−} <22 mmol/L as net metabolic acidosis, HCO\textsubscript{3}\textsuperscript{−} >26 mmol/L as alkalosis, and lactate >2.2 mmol/L as lactic acidosis.

Acid-base analysis was performed using Stewart equations and the Gilfix methodology. In the Gilfix methodology, lactate levels, unmeasured anions, hypoalbuminemia, chloride levels, and changes of plasma can influence BE. Based on this concept, we calculated the BE compounds in comparison with the effects of electrolytes, albumin, lactate and unmeasured anions.\textsuperscript{10,14} The means of reference values were used as normal values. The effective strong ion difference was necessary for the role of weak acids (CO\textsubscript{2}, albumin, and phosphate) in the balance of electrical charges in plasma.

Calculated acid-base variables

1) BE caused by free water effect (BE\textsubscript{Na}) = 0.3 \times (Na–Na\textsubscript{normal}); Na\textsubscript{normal} = 140 mmol/L, BE\textsubscript{Na} <−5 mmol/L was defined as dilutional acidosis, and BE\textsubscript{Na} > +5 mmol/L as concentrational alkalosis, respectively.

2) Cl\textsubscript{Na-corrected} = Cl \times Na\textsubscript{normal}/Na; BE\textsubscript{Cl} = Cl\textsubscript{normal}–Cl\textsubscript{Na-corrected} <−5 mmol/L was defined as hyperchloremic acidosis, and BE\textsubscript{Cl} > +5 mmol/L as hypochloremic alkalosis.

3) BE\textsubscript{Lac} = lactate\textsubscript{normal}−lactate\textsubscript{measured}; Lactate\textsubscript{normal} = 0.8 mmol/L

4) BE\textsubscript{AI} = (0.148 \times \text{pH–0.818}) \times (albumin\textsubscript{normal}–albumin\textsubscript{measured}) BE\textsubscript{AI} > +5 mmol/L was defined as hypoalbuminemic alkalosis.

5) BE\textsubscript{UMA} = BE (BE\textsubscript{Na} + BE\textsubscript{Cl} + BE\textsubscript{AID} + BE\textsubscript{LAC}) BE\textsubscript{UMA} <−5 mmol/L was defined as metabolic acidosis due to unmeasured anions.

6) BE = BE\textsubscript{Na} + BE\textsubscript{Cl} + BE\textsubscript{AI} + BE\textsubscript{LAC} + BE\textsubscript{UMA}

7) AG = [Na\textsuperscript{+}] + [K\textsuperscript{+}] – [Cl\textsuperscript{−}] – [HCO\textsubscript{3}\textsuperscript{−}]

8) AG\textsubscript{corrected} = AG + 0.25 \times (45 – observed albumin in g/L)

9) Strong ion difference-apparent (SIDa) = [Na\textsuperscript{+}] + [K\textsuperscript{+}] + [Ca\textsuperscript{2+}] + [Mg\textsuperscript{2+}] – [Cl\textsuperscript{−}] – lactate

10) Strong ion difference-effective (SIDe) = partial pressure of carbon dioxide \times 2.46 \times 10^{-9} + albumin \times (0.123 \times pH – 0.631) + 2 \times phosphate \times (0.309 \times pH – 0.469)

11) Strong ion gap (SIG) = SIDa – SIDe

Statistical analysis

In the present study, continuous variables were presented as means (standard derivations) if data were normally distributed, and categorical variables were expressed by frequencies (percentages). For comparisons, the Student’s t-test and the Mann-Whitney test was used for continuous baseline characteristics of each group for continuous variables with or without normal distribution, respectively. The χ\textsuperscript{2}-test was performed for categorical variables. Data were compared by
Results

Baseline characteristics of CICPs with AKI

In this study, we found that the mean age of 380 CICPs with AKI was 57 years and 71.05% (270 of 380) were male. Both survivors (n = 254, 66.84%) and non-survivors (n = 126, 33.16%) had similar respective age (56.95 ± 10.58 vs. 57.74 ± 11.59) as well as sex (70.47% vs. 72.22% males). The cause, complication and comorbidity of cirrhosis, clinical scores, as well as demographic, clinical and laboratory parameters were collected for both survivors and non-survivors. The patients in the non-survival group had higher morbidity rate for sepsis than those in the survival group. Other complications of individuals did not differ significantly. There is no significant difference in the demographic data and comorbidities of CICPs with AKI between the two groups.

Moreover, the etiology of AKI was determined for the survival and non-survival groups. We found that gastrointestinal bleeding predominately contributed to AKI in CICPs. Patients in the non-survival group were older, more likely to engage in alcohol abuse, and had higher mean parameters for serum lactate, bilirubin, CLIF-SOFA, MELD, SAPS II, and SOFA score than those in the survival group. The mean arterial pressure levels were lower and vasopressin use ratio was higher in the non-survivors than results in survivors.

In addition, calculations of SIDA and SIDe suggest that non-survivors had elevated SIG in comparison with survivors (p < 0.001). A positive value for the SIG also represented increased unmeasured anions. Furthermore, there was significant difference in the acid-base and electrolyte value for the study population between the two groups (Table 1).

Disequilibrium of acid-base disorders in CICPs with AKI

Net metabolic acidosis, compensated by respiratory alkalosis, was attributed to acidosis caused by unmeasured anions, hyperchloremic, lactic acidosis, and mild dilutional acidosis. In contrast, hypoalbuminemia was the only alkalinizing element that contributed to alkalosis in both groups. As illustrated in Fig. 1, non-survivors had more severe metabolic acid-base disorders than the survival group. The mean levels of BE_{lac}, BE_{uma}, and BE_{na} were remarkably decreased in the survival group.

Acid-base state and hospital mortality in CICPs with AKI

Mean parameters of pH, HCO3−, and BE were reduced, whereas that of AG was elevated in non-survivors because of elevated lactate and unmeasured anions. The composition frequencies of acidemia, net metabolic acidosis, lactic acidosis, acidosis based on unmeasured anions, and dilutional acidosis were significantly different between the two groups (Table 2). In a subgroup analysis, scatter plots showed observed hospital 30-day mortality rate for patients to be associated with the value of the associated acid-base marker in admission to ICU. We found a positive correlation between hospital mortality and acid-base parameters at different intervals rather than a linear trend; this suggests that fluctuation of acidotic markers may have a contributing role in hospital mortality and that maintaining these markers in the normal range could potentially reduce mortality (Fig. 2).

Moreover, hospital mortality rate was further assessed by comparing the hazard ratio in univariate and multivariate analyses. In these analyses, the presence of acidemia, acidosis owing to unmeasured anions, as well as lactic acidosis were each associated with increased ICU 30-day mortality rate with hazard ratio of 2.11 (95% CI: 1.43–3.12), 3.38 (95% CI: 2.36–4.84), and 2.16 (95% CI: 1.47–3.35), respectively (Table 3). After adjusting traditional confounders in model 3, the relationship between acidosis owing to unmeasured anions with mortality rate was still significantly positive. Furthermore, the diagnostic accuracy of arterial lactate and BE_{uma} concentrations in predicting mortality rate is sound, with a relatively linear correlation to risk of observed mortality.

The ability to predict hospital mortality by CLIF-SOFA (with lactate: AUROC of 0.76, 95% CI: 0.71–0.81; without lactate: AUROC of 0.74, 95% CI: 0.70–0.79) showed similar strength as CLIF-SOFA + BE_{uma} (AUROC of 0.76, 95% CI 0.71–0.80). Overall, arterial lactate concentration in combination with the CLIF-SOFA and BE_{uma} had the strongest ability to predict 30-day mortality (AUROC of 0.79, 95% CI: 0.74–0.83) (Table 4 and Fig. 3).

Discussion

Mounting evidence suggests that applying Stewart equations and the Gilfix methodology to acid-base can easily and accurately identify crucial metabolic acid-base abnormalities.20 This method has high application in critically ill patients, but few reports on its usefulness in CICPs with AKI exist in the literature. In this study, we performed a retrospective analysis of 380 CICPs with AKI in the ICU and demonstrated that these types of patients had imbalance of metabolic acid-base.

Several significant findings emerged from our investigation. Firstly, our study showed metabolic acid-base abnormalities in non-survival and survival groups. Mean parameters of pH, HCO3−, and BE were reduced, while that of AG was elevated in non-survivors because of increased lactate and unmeasured anions. Secondly, the SIG plays an important effect on Stewart’s acid-base physiology. It is shown that an increase in SIG of non-survivors partly counteracted the decrease in partial pressure of carbon dioxide and other weak acids. Although SIG was higher in non-survivors than in survivors, it was not...
Table 1. Characteristics of critically ill cirrhotic patients with acute kidney injury on the first day of admission, stratified by mortality

| Variable                          | Survivors, \( n = 254 \) | Non-survivors, \( n = 126 \) | \( p \)  |
|-----------------------------------|---------------------------|-------------------------------|-------|
| **Demographic parameters**        |                           |                               |       |
| Age in years                      | 56.95 ± 10.58             | 57.74 ± 11.59                 | <0.001|
| Sex: male, \( n \) (%)            | 179 (70.47%)              | 91 (72.22%)                   | 0.723 |
| Height in cm                      | 172.50 ± 8.88             | 170.77 ± 10.58                | 0.199 |
| Weight in kg                      | 83.67 ± 22.08             | 83.75 ± 19.53                 | 0.973 |
| **Survival time in days**         |                           |                               |       |
| Death time after admission        | 30.00 ± 0.00              | 10.39 ± 8.12                  | <0.001|
| **Etiology of cirrhosis, \( n \) (%)** |                       |                               |       |
| Alcoholic cirrhosis               | 104 (40.94%)              | 72 (57.14%)                   | 0.030 |
| Non-alcoholic cirrhosis           | 138 (54.33%)              | 50 (39.68%)                   | 0.005 |
| Biliary cirrhosis                 | 8 (3.14%)                 | 3 (2.38%)                     | 0.674 |
| Viral cirrhosis                   | 4 (1.57%)                 | 1 (0.79%)                     | 0.529 |
| **Etiology of AKI, \( n \) (%)**  |                           |                               |       |
| Sepsis                            | 37 (14.57%)               | 50 (39.68%)                   | <0.001|
| Heart failure                     | 12 (4.72%)                | 6 (4.76%)                     | 0.987 |
| Gastrointestinal bleeding         | 88 (34.65%)               | 48 (38.10%)                   | 0.509 |
| Respiratory failure               | 10 (3.93%)                | 5 (3.97%)                     | 0.988 |
| Hepatology renal syndrome         | 76 (29.92%)               | 45 (35.71%)                   | 0.224 |
| Obstructive kidney disease        | 2 (0.79%)                 | 1 (0.79%)                     | 0.995 |
| **Complication**                  |                           |                               |       |
| Sepsis                            | 37 (14.57%)               | 50 (39.68%)                   | <0.001|
| Gastrointestinal bleeding         | 88 (34.65%)               | 48 (38.10%)                   | 0.509 |
| Hepatic coma                      | 22 (8.67%)                | 6 (4.76%)                     | 0.710 |
| Spontaneous peritonitis           | 1(0.39%)                  | 2 (1.59%)                     | 0.216 |
| Respiratory failure               | 10 (3.93%)                | 5 (3.97%)                     | 0.988 |
| **Comorbidity**                   |                           |                               |       |
| Cardiac arrhythmias               | 36 (14.17%)               | 21 (16.67%)                   | 0.522 |
| Chronic pulmonary disease         | 32 (12.60%)               | 22 (17.46%)                   | 0.201 |
| Lymphoma                          | 1 (0.39%)                 | 1 (0.79%)                     | 0.612 |
| Solid tumor                       | 55 (21.65%)               | 21 (16.67%)                   | 0.253 |
| Deficiency anemias                | 35 (13.78%)               | 16 (12.70%)                   | 0.771 |
| Hypertension                      | 76 (29.92%)               | 28 (22.22%)                   | 0.113 |
| Diabetes Mellitus                 | 68 (26.77%)               | 25 (19.84%)                   | 0.139 |
| **Ethnicity, \( n \) (%)**        |                           |                               |       |
| White                             | 192 (75.59%)              | 81 (64.29%)                   |       |
| African black                     | 17 (6.69%)                | 12 (9.52%)                    | 0.070 |
| Other                             | 45 (17.72%)               | 33 (26.19%)                   |       |
| **Clinical parameters**           |                           |                               |       |
| Heart rate, \( n \)              | 91.88 ± 18.93             | 94.25 ± 19.55                 | 0.257 |
| Respiratory rate                  | 41.57 ± 33.83             | 38.14 ± 32.06                 | 0.346 |
| Temperature in °C                 | 36.75 ± 0.82              | 36.36 ± 1.20                  |       |
| SBP in mmHg                       | 123.99 ± 24.30            | 112.49 ± 19.27                | 0.001 |
| DBP in mmHg                       | 65.45 ± 16.47             | 56.95 ± 14.90                 | <0.001|
| MAP in mmHg                       | 84.96 ± 17.22             | 75.47 ± 14.13                 | <0.001|

(continued)
a pivotal predictor of outcome in our study. Thirdly, the development of acidemia, mainly attributed to increased unmeasured anions and lactic acidosis, had a positive relationship, independently, with increased ICU 30-day mortality.

Our finding confirmed that CICPs with AKI is a state of metabolic acidosis. We found decreases in pH, $\text{HCO}_3^-$, BE, BEUMA, and chloride levels, as well as increases in lactate and SIG in the non-survival group. In addition, the components determining BE and the effect of changes in albumin, sodium, lactate and chloride levels were analyzed and quantified. We demonstrated that these parameters were positively correlated with hospital mortality and that the frequencies of net metabolic acidosis, acidosis owing to unmeasured anions, and lactic acidosis were higher in non-survivors. Thus, understanding lactic acidosis and components of unmeasured anions is crucial in these patients.

In the normal physiologic state, a total amount of 1500 mmol of lactate is produced in the human body daily.
from the reduction of pyruvate by enzyme lactate dehydrogenase, with lactate levels maintained at <2 mmol/L. However, in pathological conditions exposed to tissue hypoxia and anaerobic state, pyruvate is promptly accumulated and its metabolism is almost entirely shifted to lactate production. In physiological conditions, the generation and consumption of lactate are strictly balanced. The liver and kidney are well known for lactate dehydrogenase dysfunction in the setting of CICPs with AKI. Therefore, hyperlactatemia is common in CICPs with AKI and elevated serum lactate can gradually increase hospital mortality. The elevation of lactate can result from both increased lactate production and decreased hepatic lactate elimination. Moreover, patients who suffer from sepsis might also partly interpret the production of lactate. In our previous study, we revealed that initial lactate concentration strongly and independently predicted short- and long-term hospital outcome in CICPs with AKI.

In our evaluation of components contributing to BE, we discovered that CICPs with AKI had significant hypoalbuminemic alkalosis in combination with acidosis owing to unmeasured anions, even after adjusting for confounders. In the non-survival group, acidosis secondary to unmeasured anions was found to be significant, and hospital mortality was notably higher as BEUMA value became lower than -4.14 mmol/L. Some unmeasured anions might be the result of retained organic anions, attributed to AKI, during BEUMA evaluation. Furthermore, among the examined acid-base parameters, BEUMA had the best discrimination and did not differ significantly with CLIF-SOFA. Thus, BEUMA in combination with lactate levels and CLIF-SOFA score have markedly reinforced our ability to predict mortality in CICPs.

Table 2. Frequencies of acid-base disorders with critically ill cirrhosis with AKI, stratified by mortality

|                  | Survivors, n = 254 | Non-survivors, n = 126 | p       |
|------------------|--------------------|------------------------|---------|
| Acidemia         | 70 (27.5%)         | 59 (46.82%)            | <0.001  |
| Alkalemia        | 58 (22.8%)         | 23 (18.3%)             | 0.674   |
| Net metabolic acidosis | 46 (18.11%)    | 52 (41.27%)            | <0.001  |
| Dilutional acidosis   | 3 (1.18%)         | 5 (3.97%)              | 0.075   |
| Net metabolic alkalosis | 17 (6.69%)      | 7 (5.56%)              | 0.733   |
| Hyperchloremic acidosis | 115 (45.28%)  | 37 (29.37%)            | 0.254   |
| Hypochloremic alkalosis | 30 (11.81%)     | 42 (33.33%)            | <0.001  |
| Acidosis owing to unmeasured anions | 64 (25.20%) | 77 (61.11%)            | <0.001  |
| Hypoalbuminemic alkalosis | 114 (44.88%) | 77 (61.11%)            | 0.003   |
| Lactic acidosis   | 124 (48.82%)       | 88 (69.84%)            | <0.001  |
Fig. 2. The 30-day hospital mortality of the associated acid-base marker in different intervals.
with AKI. As a secondary outcome, we found that decreased serum albumin was associated with abnormal liver function and expenditure, which might possibly indicate a need for nutrition assessment. All together, these observations emphasize that imbalance of the acid-base state reflects hospital mortality of CICPs with AKI.

A few potential limitations exist in our study. Firstly, we recognize that the results from a single center may not fully reflect all the subjects’ conditions. Secondly, sequential measurement of acid-base disorders may provide a better insight into the mechanisms of metabolic acidosis. Thirdly, specific treatments of acid-base disorders benefiting CICPs with AKI are yet to be defined.

In conclusion, this study confirmed that CICPs with AKI exhibit a complex metabolic acidosis during ICU admission. There was highly significant difference between the survivors and the non-survivors for lactate and BEUMA of acid-base state in the CICPs with AKI, which can be used to determine mortality outcome. This physiochemical methodology to assess acid-base disorders showed great value with important prognostic implication, thus highlighting the need to control metabolic acidosis.

Table 3. Association of acid-base state with ICU 30-day mortality in critically ill cirrhotic patients with AKI

|                      | Model 1             | p        | Model 2             | p        | Model 3             | p        |
|----------------------|---------------------|----------|---------------------|----------|---------------------|----------|
| Acidemia             | 2.11 (1.43–3.12)    | <0.001   | 1.67 (0.99–2.78)    | 0.051    | 0.98 (0.50–1.91)    | 0.948    |
| Alkalemia            | 1.11 (0.67–1.84)    | 0.684    | 0.73 (0.34–1.57)    | 0.422    | 1.64 (0.47–5.55)    | 0.424    |
| Net metabolic acidosis| 2.65 (1.84–3.81)   | <0.001   | 2.10 (1.26–3.49)    | 0.004    | 0.91 (0.48–1.75)    | 0.914    |
| Dilutional acidosis  | 2.18 (0.89–5.34)    | 0.088    | 1.20 (0.27–5.27)    | 0.811    | 1.38 (0.25–7.52)    | 0.711    |
| Hyperchloremic acidosis | 0.78 (0.51–1.20) | 0.263    | 0.66 (0.37–1.17)    | 0.154    | 0.68 (0.33–1.40)    | 0.680    |
| Hypochloremic alkalosis | 2.45 (1.61–3.71) | <0.001   | 1.57 (0.86–2.87)    | 0.141    | 1.19 (0.53–2.68)    | 0.670    |
| Acidosis owing to unmeasured anions | 3.38 (2.36–4.84) | <0.001   | 3.20 (1.96–5.24)    | <0.001   | 2.29 (1.22–4.30)    | 0.010    |
| Hypoalbuminemic alkalosis | 1.75 (1.22–2.50) | 0.002    | 1.81 (1.11–2.94)    | 0.017    | 0.80 (0.35–1.83)    | 0.598    |
| Lactic acidosis       | 2.16 (1.47–3.15)    | <0.001   | 1.58 (0.97–2.56)    | 0.065    | 0.85 (0.37–1.93)    | 0.691    |

Model 1 is univariate analysis. Model 2 includes Model 1 plus age, sex, height, weight and complication (hypertension, diabetes mellitus, cardiac arrhythmias, chronic pulmonary disease, lymphoma, solid tumor, and iron deficiency anemias). Model 3 includes Model 2 plus comorbidities (sepsis, gastrointestinal bleeding, respiratory failure, hepatic coma, and spontaneous peritonitis), cause of liver cirrhosis (alcoholic cirrhosis, non-alcoholic cirrhosis, biliary cirrhosis, and viral cirrhosis), laboratory parameters (eGFR, white blood cell, platelet, albumin, lactate, and hematocrit), and chronic liver failure-sequential organ failure assessment score.

Table 4. Performance of different prognostic models in predicting 30-day mortality using the optimal cut-off point

| Prognostic model | AUROC | 95% CI  | p (vs. CLIF-SOFA) | Cut-off | Sensitivity, % | Specificity, % | PLR | NLR | PPV | NPV |
|------------------|-------|---------|------------------|---------|----------------|----------------|-----|-----|-----|-----|
| CLIF-SOFA        | 0.74  | 0.70–0.79| <0.001           | 12.00   | 49.21          | 87.01          | 3.79| 0.58| 65.30| 77.50|
| LAC              | 0.68  | 0.63–0.73| <0.001           | 0.008   | 2.50           | 62.61          | 65.37| 1.81| 0.57| 47.40| 77.80|
| BEUMA            | 0.69  | 0.64–0.74| <0.001           | 0.171   | −4.63          | 62.40          | 74.41| 2.44| 0.51| 54.50| 80.10|
| CLIF-SOFA + LAC  | 0.76  | 0.71–0.81| <0.001           | 0.049   | 3.79           | 56.80          | 83.46| 3.44| 0.52| 62.80| 79.70|
| CLIF-SOFA + BEUMA| 0.76  | 0.71–0.80| <0.001           | 0.731   | 0.78           | 68.80          | 77.95| 3.12| 0.40| 60.60| 83.50|
| CLIF-SOFA + LAC + BEUMA | 0.79 | 0.74–0.83| <0.001           | 0.78   | 2.79           | 56.00          | 87.80| 4.59| 0.50| 69.30| 80.20|

Abbreviations: CLIF-SOFA, chronic liver failure-sequential organ failure assessment score; LAC, lactate; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.
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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Designed the study, interpreted the data, and wrote the manuscript (DQS, LZ, CFZ), performed the statistical analyses and collected the data (WYL), revised the manuscript (KIZ), designed the study, allocated the funding, reviewed the results, and finalized the manuscript (WJY, XMC), reviewed the results and finalized the manuscript (MHZ). All authors read and approved the final version of the paper.

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Fig. 3. Area under the receiver operating characteristic curve analysis of different models in predicting 30-day mortality. Chronic liver failure-sequential organ failure assessment (CLIF-SOFA) showed improvement in discriminative ability by combining lactate and BEUMA, as compared with CLIF-SOFA alone.
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