Original Article

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 BE_{UMA} 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 BE_{UMA}, novel markers of acid-base disorders, show promise in predicting mortality rate of CICPs with AKI.

Citation of this article: Sun DQ, Zhang L, Zheng CF, Liu WY, Zheng KI, Chen XM, *et al.* Metabolic acidosis in critically ill cirrhotic patients with acute kidney injury. J Clin Transl Hepatol 2019;7(2):112–121. doi: 10.14218/JCTH.2019.00013.

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 hypoalbuminemic 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 (HCO^{3-}), 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 morality.

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; HCO^{3-}, 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-apparent; SIDe, strong ion difference-effective; SIG, strong ion gap.

Received: 22 March 2019; Revised: 20 April 2019; Accepted: 22 April 2019

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concentration; changes in protein charges (mainly albumin); and presence of unmeasured organic anions.[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,[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.[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.[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.[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^{3-}, standard bicarbonate (HCO^{3-}_{st}), base excess (BE) and standard base excess measurements were carried out according to Henderson-Hasselbach and Siggaard-Andersen equations respectively.[19] In the present study, pH <7.35 was defined as acidemia, pH >7.45 as alkalemia, HCO^{3-} <22 mmol/L as net metabolic acidosis, HCO^{3-} >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.[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_2, albumin, and phosphate) in the balance of electrical charges in plasma.

Calculated acid-base variables

1) BE caused by free water effect (BE_{Na}) = 0.3 × ($Na–Na_{normal}$); Na_{normal} = 140 mmol/L, BE_{Na} <−5 mmol/L was defined as dilutional acidosis, and BE_{Na} > +5 mmol/L as concentrational alkalosis, respectively.
2) $Cl_{Na\text{-}corrected}$ = Cl × Na_{normal}/Na; BE_{Cl} = Cl_{normal}–$Cl_{Na\text{-}corrected}$ BE_{Cl} <−5 mmol/L was defined as hyperchloremic acidosis, and BE_{Cl} > +5 mmol/L as hypochloremic alkalosis.
3) BE_{Lac} = $lactate_{normal}$–$lactate_{measured}$; $Lactate_{normal}$ = 0.8 mmol/L
4) BE_{Alb} = (0.148 × pH-0.818) × ($albumin_{normal}$ –$albumin_{measured}$) BE_{Alb} > +5 mmol/L was defined as hypoalbuminemic alkalosis.
5) BE_{UMA} = BE – (BE_{Na} + BE_{Cl} + BE_{Alb} + BE_{Lac}) BE_{UMA} <−5 mmol/L was defined as metabolic acidosis due to unmeasured anions.
6) BE = BE_{Na} + BE_{Cl} + BE_{Alb} + BE_{Lac} + BE_{UMA}
7) AG = $[Na^+]$ + $[K^+]$ − $[Cl^-]$ − $[HCO^{3-}]$
8) $AG_{corrected}$ = AG + 0.25 × (45 − observed albumin in g/L)
9) Strong ion difference-apparent (SIDa) = $[Na^+]$ + $[K^+]$ + $[Ca^{2+}]$ + $[Mg^{2+}]$ − $[Cl^-]$ − lactate
10) Strong ion difference-effective (SIDe) = partial pressure of carbon dioxide × 2.46 × $10^{\text{pH-8}}$ + albumin × (0.123 × pH − 0.631) + 2 × phosphate × (0.309 × 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^2-test was performed for categorical variables. Data were compared by

χ^2-test for categorical variables and a one-way analysis of variance for continuous variables. Multivariate analysis was carried by Cox regression to test the association between acid-base state and ICU 30-day mortality.

The diagnostic performance was examined by area under the receiver operating characteristic curve (AUROC). The cut-off point was calculated according to the max value of Youden index, and the specificity, positive likelihood ratio, negative likelihood ratio, corresponding sensitivity, positive predictive value, and negative predictive value for relevant cut-offs were also calculated. All patients were enrolled for a comparison of diagnostic performance of the CLIF-SOFA, lactate, BE_{UMA}, CLIF-SOFA + LAC, CLIF-SOFA + BE_{UMA} and CLIF-SOFA + LAC + BE_{UMA} for predicting 30-day mortality rate. Statistical analyses were performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) and MedCalc version 12.7 (MedCalc Software, Ostend, Belgium). A two-tailed $p < 0.05$ was considered to be statistically significant.

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, HCO^{3-}, 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, HCO^{3-}, 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*)

Table 1. (*continued*)

Variable	Survivors, *n* = 254	Non-survivors, *n* = 126	*p*
Vasopressin used, *n* (%)	96 (37.80%)	84 (66.67%)	<0.001
Laboratory parameters			
Glucose in mg/dL	141.28 ± 76.54	123.60 ± 62.12	0.025
White blood cell as 10^9/L	10.58 ± 6.23	12.28 ± 7.65	0.021
Platelet as 10^9/L	159.56 ± 108.66	119.43 ± 72.71	<0.001
INR	1.65 ± 0.57	2.45 ± 1.69	<0.001
Bilirubin in mg/dL	3.46 ± 5.32	8.09 ± 10.03	<0.001
Urine output in mL	1560.17 ± 2188.48	1332.92 ± 1868.41	0.319
pH	7.39 ± 0.08	7.35 ± 0.11	<0.001
$PaCO_2$ in mmHg	38.11 ± 9.09	35.95 ± 8.86	0.029
HCO^{3-} in mmol/L	22.53 ± 4.96	19.54 ± 5.67	<0.001
BE in mmol/L	−1.20 ± 4.62	−4.70 ± 6.25	<0.001
Na^+ in mmol/L	138.49 ± 4.94	135.54 ± 6.98	<0.001
Cl^- in mmol/L	106.16 ± 6.08	102.60 ± 8.23	<0.001
K^+ in mmol/L	4.11 ± 0.73	4.52 ± 0.87	<0.001
Ca^{2+} in mmol/L	1.11 ± 0.13	1.04 ± 0.14	<0.001
Mg^{2+} in mmol/L	0.78 ± 0.20	0.85 ± 0.19	0.001
Pi in mmol/L	1.13 ± 0.48	1.62 ± 0.73	<0.001
Alb in g/L	29.58 ± 6.44	25.71 ± 6.01	<0.001
Lactate, mmol/L	2.80 ± 2.26	4.77 ± 3.81	<0.001
Creatinine in mg/dL	2.31 ± 1.78	2.12 ± 1.77	0.343
eGFR in mL/min/1.73m^2	48.40 ± 33.04	50.49 ± 31.72	0.556
BUN in mmol/L	26.52 ± 21.44	42.62 ± 29.69	<0.001
SBE in mmol/L	−2.44 ± 5.54	−6.11 ± 6.93	<0.001
AG in mmol/L	13.92 ± 4.76	17.92 ± 7.13	<0.001
AGcorr in mmol/L	19.17 ± 5.49	23.45 ± 7.48	<0.001
SIDa in mEq/L	35.47 ± 4.92	34.40 ± 5.23	0.053
SIDe in mEq/L	31.69 ± 6.41	29.06 ± 6.10	<0.001
SIG in mEq/L	3.78 ± 5.47	5.28 ± 4.77	0.011
Clinical scores			
CLIF-SOFA	8.80 ± 3.21	12.01 ± 3.57	<0.001
MELD	14.93 ± 8.86	25.26 ± 12.38	<0.001
SAPSII	44.50 ± 13.84	53.10 ± 14.53	<0.001
SOFA	7.59 ± 3.09	10.35 ± 3.47	<0.001

Abbreviations: CLIF-SOFA, chronic liver failure-sequential organ failure assessment score; DBP, diastolic blood pressure; INR, international normalized ratio; MELD, model for end-stage liver disease; SBP, systolic blood pressure; MAP, mean arterial pressure; SAPSII, simplified acute physiology score; BUN, blood urea nitrogen; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; FIO_2, fraction of inspiration O_2; BE, base excess; SBE, standard base excess; Na^+, sodium; Cl^-, chloride; Alb, albumin; Ca^{2+}, ionized calcium; Pi, inorganic phosphate; Mg^{2+}, magnesium; AG, anion gap; SID, strong ion difference; SIDa, the apparent SID; SIDe, the effective SID; UMA, unmeasured anions; AGcorr, anion gap corrected for albumin; eGFR, evaluated glomerular filter rate; AKI, acute kidney injury.

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, HCO^{3-}, BE, BE_{UMA}, 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

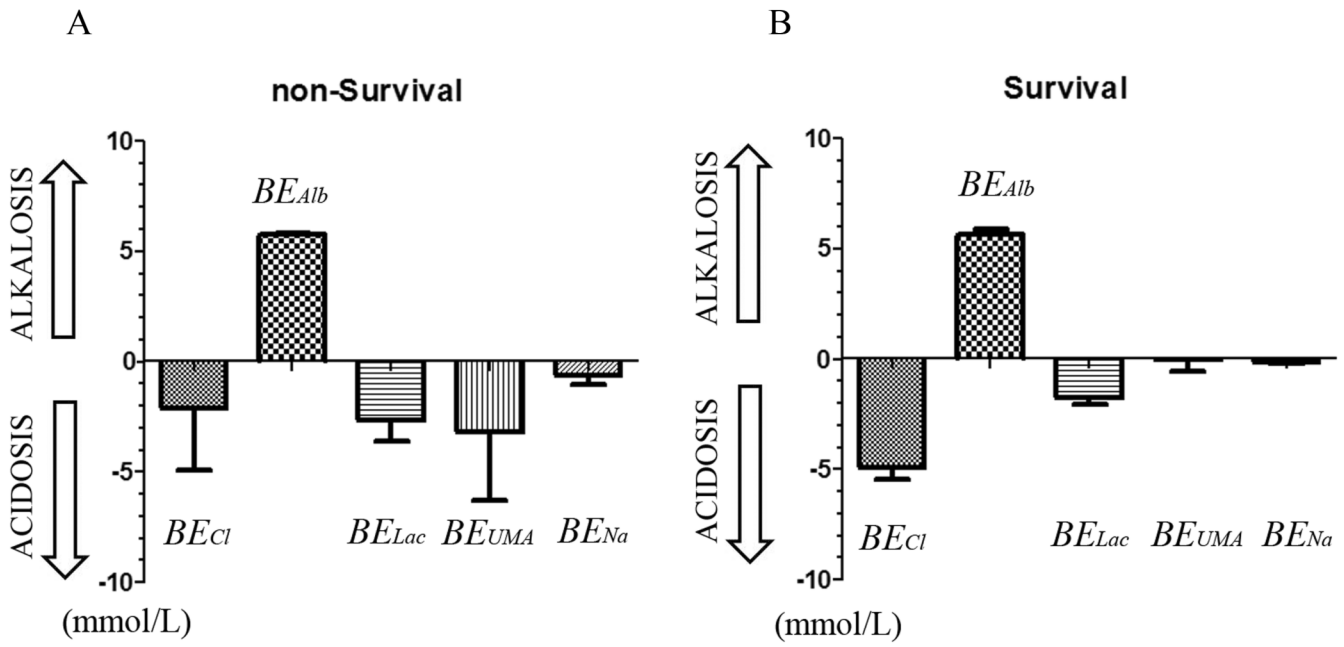

Fig. 1. Disequilibrium of metabolic acid-base disorders in CICPs with AKI between non-survivors and survivors. Acidosis owing to unmeasured anions and lactate, hyperchloremic acidosis and dilutional acidosis outweigh hypoalbuminemic alkalosis, resulting in net metabolic acidosis. Metabolic acid-base analysis was performed applying Gilfix methodology, based on the concept that net base excess (BE) is determined by effect of free water excess (BE_{Na}), changes in concentrations of chloride (BE_{Cl}), albumin (BE_{Alb}), lactate (BE_{Lac}) and the accumulation of unmeasured anions (BE_{UMA}): $BE = BE_{Na} + BE_{Cl} + BE_{Alb} + BE_{Lac} + BE_{UMA}$.

from the reduction of pyruvate by enzyme lactate dehydrogenase, with lactate levels maintained at <2 mmol/L.[21] 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.[22–24] 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.[22,25] 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.[16]

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 BE_{UMA} value became lower than -4.14 mmol/L. Some unmeasured anions might be the result of retained organic anions, attributed to AKI, during BE_{UMA} evaluation.[26] Furthermore, among the examined acid-base parameters, BE_{UMA} had the best discrimination and did not differ significantly with CLIF-SOFA. Thus, BE_{UMA} 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

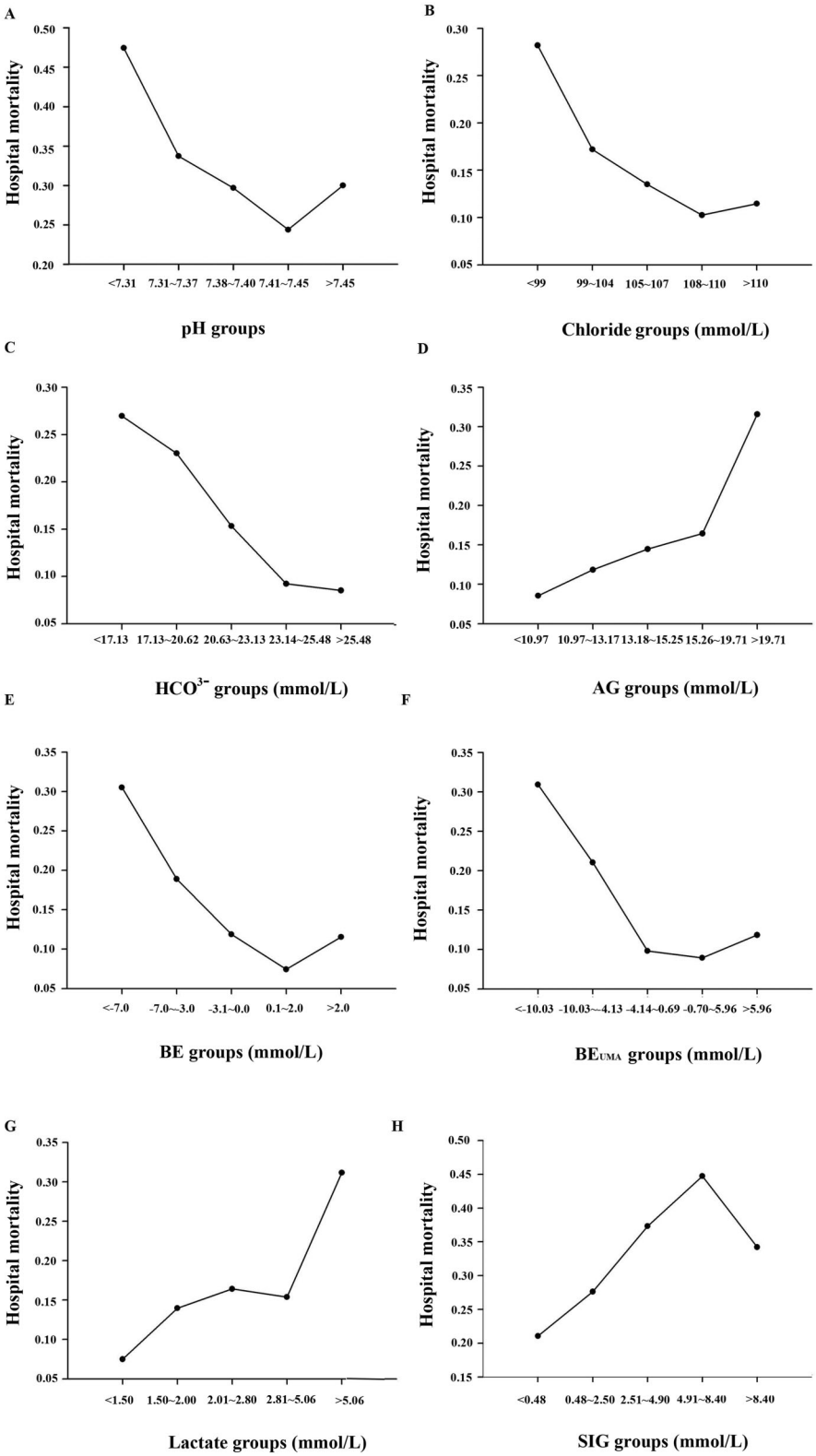

Fig. 2. The 30-day hospital mortality of the associated acid-base marker in different intervals.

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.

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 BE_{UMA} 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 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		12.00	49.21	87.01	3.79	0.58	65.30	77.50
LAC	0.68	0.63–0.73	0.008	2.50	62.61	65.37	1.81	0.57	47.40	77.80
BE_{UMA}	0.69	0.64–0.74	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	0.049	3.79	56.80	83.46	3.44	0.52	62.80	79.70
CLIF-SOFA + BE_{UMA}	0.76	0.71–0.80	0.731	0.78	68.80	77.95	3.12	0.40	60.60	83.50
CLIF-SOFA + LAC + BE_{UMA}	0.79	0.74–0.83	<0.001	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.

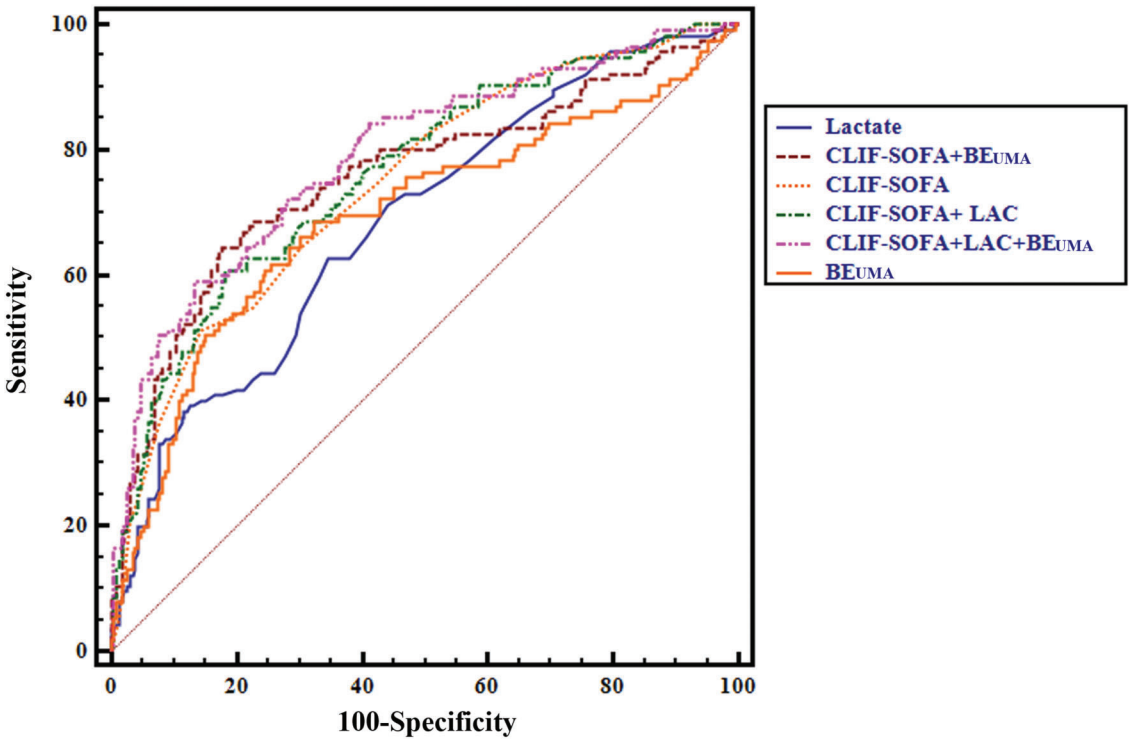

Fig. 3. Area under the receiver operating characteristic curve analysis of different models in predicting 30-day mortality. Chronic liver failure-sequential organ failure assessment (CLIF-SOFA) showed improvement in discriminative ability by combining lactate and BE_{UMA}, as compared with CLIF-SOFA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

Acknowledgment

This work was supported by grants from the General Program of Science and Technology Development Foundation of Nanjing Medical University (2017NJMU168) and the Zhejiang Engineering Research Center of Intelligent Medicine (2016E10011), The First Affiliated Hospital of Wenzhou Medical University.

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.

References

[1] Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, *et al*. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol 2017;13:241–257. doi: 10.1038/nrneph.2017.2.

[2] Ferrarese A, Feltracco P, Barbieri S, Cillo U, Burra P, Senzolo M. Outcome of critically ill cirrhotic patients admitted to the ICU: The role of ACLF. J Hepatol 2019;70:801–803. doi: 10.1016/j.jhep.2018.09.015.

[3] Nadim MK, Durand F, Kellum JA, Levitsky J, O'Leary JG, Karvellas CJ, *et al*. Management of the critically ill patient with cirrhosis: A multidisciplinary perspective. J Hepatol 2016;64:717–735. doi: 10.1016/j.jhep.2015.10.019.

[4] Drolz A, Horvatits T, Roedl K, Rutter K, Brunner R, Zauner C, *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. doi: 10.1186/s13613-018-0391-9.

[5] Scheiner B, Lindner G, Reiberger T, Schneeweiss B, Trauner M, Zauner C, *et al*. Acid-base disorders in liver disease. J Hepatol 2017;67:1062–1073. doi: 10.1016/j.jhep.2017.06.023.

[6] Mallat J, Michel D, Salaun P, Thevenin D, Tronchon L. Defining metabolic acidosis in patients with septic shock using Stewart approach. Am J Emerg Med 2012;30:391–398. doi: 10.1016/j.ajem.2010.11.039.

[7] Morgan TJ. Partitioning standard base excess: a new approach. J Clin Monit Comput 2011;25:349–352. doi: 10.1007/s10877-011-9324-y.

[8] Figge J, Rossing TH, Fencl V. The role of serum proteins in acid-base equilibria. J Lab Clin Med 1991;117:453–467.

[9] Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444–1461.

[10] 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;8:187–197. doi: 10.1016/0883-9441(93)90001-2.

[11] Lim HS, Howell N. Cardiogenic shock due to end-stage heart failure and acute myocardial infarction: Characteristics and outcome of temporary mechanical circulatory support. Shock 2018;50:167–172. doi: 10.1097/SHK.0000000000001052.

[12] Ortner CM, Combrinck B, Allie S, Story D, Landau R, Cain K, *et al*. Strong ion and weak acid analysis in severe preeclampsia: potential clinical significance. Br J Anaesth 2015;115:275–284. doi: 10.1093/bja/aev221.

[13] Ho KM, Lan NS, Williams TA, Harahsheh Y, Chapman AR, Dobb GJ, *et al*. A comparison of prognostic significance of strong ion gap (SIG) with other acid-base markers in the critically ill: a cohort study. J Intensive Care 2016;4:43. doi: 10.1186/s40560-016-0166-z.

[14] Funk GC, Doberer D, Kneidinger N, Lindner G, Holzinger U, Schneeweiss B. Acid-base disturbances in critically ill patients with cirrhosis. Liver Int 2007;27:901–909. doi: 10.1111/j.1478-3231.2007.01510.x.

[15] Sun DQ, Zheng CF, Liu WY, Van Poucke S, Mao Z, Shi KQ, *et al*. AKI-CLIF-SOFA: a novel prognostic score for critically ill cirrhotic patients with acute kidney injury. Aging (Albany NY) 2017;9:286–296. doi: 10.18632/aging.101161.

[16] Sun DQ, Zheng CF, Lu FB, Van Poucke S, Chen XM, Chen YP, *et al*. Serum lactate level accurately predicts mortality in critically ill patients with cirrhosis with acute kidney injury. Eur J Gastroenterol Hepatol 2018;30:1361–1367. doi: 10.1097/MEG.0000000000001189.
[17] Lameire N, Kellum JA. Contrast-induced acute kidney injury and renal support for acute kidney injury: a KDIGO summary (Part 2). Crit Care 2013;17:205. doi: 10.1186/cc11455.
[18] Rosi S, Piano S, Frigo AC, Morando F, Fasolato S, Cavallin M, *et al*. New ICA criteria for the diagnosis of acute kidney injury in cirrhotic patients: can we use an imputed value of serum creatinine? Liver Int 2015;35:2108–2114. doi: 10.1111/liv.12852.
[19] Siggaard-Andersen O, Wimberley PD, Fogh-Andersen N, Gøthgen IH. Measured and derived quantities with modern pH and blood gas equipment: Calculation algorithms with 54 equations. Scandinavian Journal of Clinical and Laboratory Investigation 1988;48:7–15, doi: 10.1080/00365518809168181.
[20] Antonogiannaki EM, Mitrouska I, Amargianitakis V, Georgopoulos D. Evaluation of acid-base status in patients admitted to ED-physicochemical vs traditional approaches. Am J Emerg Med 2015;33:378–382. doi: 10.1016/j.ajem.2014.12.010.
[21] Philp A, Macdonald AL, Watt PW. Lactate–a signal coordinating cell and systemic function. J Exp Biol 2005;208:4561–4575. doi: 10.1242/jeb.01961.
[22] Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na+ K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet 2005;365:871–875. doi: 10.1016/S0140-6736(05)71045-X.
[23] Aramburo A, Todd J, George EC, Kiguli S, Olupot-Olupot P, Opoka RO, *et al*. Lactate clearance as a prognostic marker of mortality in severely ill febrile children in East Africa. BMC Med 2018;16:37. doi: 10.1186/s12916-018-1014-x.
[24] Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med 2019;45:82–85. doi: 10.1007/s00134-018-5213-x.
[25] Levy B, Sadoune LO, Gelot AM, Bollaert PE, Nabet P, Larcan A. Evolution of lactate/pyruvate and arterial ketone body ratios in the early course of catecholamine-treated septic shock. Crit Care Med 2000;28:114–119. doi: 10.1097/00003246-200001000-00019.
[26] Rocktaeschel J, Morimatsu H, Uchino S, Goldsmith D, Poustie S, Story D, *et al*. Acid-base status of critically ill patients with acute renal failure: analysis based on Stewart-Figge methodology. Crit Care 2003;7:R60. doi: 10.1186/cc2333.