Metabolic acidosis as a risk factor for the development of acute kidney injury and hospital mortality

JIACHANG HU[1-3*], YIMEI WANG[1-3*], XUEMEI GENG[1-3], RONGYI CHEN[1-3],
XIALIAN XU[1-3], XIAOYAN ZHANG[1-3], JING LIN[1-3], JIE TENG[1-3] and XIAOQIANG DING[1-3]

[1]Division of Nephrology, Zhongshan Hospital, Shanghai Medical College, Fudan University; [2]Shanghai Institute of Kidney and Dialysis; [3]Shanghai Key Laboratory for Kidney and Blood Purification, Shanghai 200032, P.R. China

Abstract. Metabolic acidosis has been proved to be a risk factor for the progression of chronic kidney disease, but its relation to acute kidney injury (AKI) has not been investigated. In general, a diagnosis of metabolic acidosis is based on arterial blood gas (ABG) analysis, but the diagnostic role of carbon dioxide combining power (CO_2CP) in the venous blood may also be valuable to non-respiratory patients. This retrospective study included all adult non-respiratory patients admitted consecutively to our hospital between October 01, 2014 and September 30, 2015. A total of 71,089 non-respiratory patients were included, and only 4,873 patients were evaluated by ABG analysis at admission. In patients with ABG, acidosis, metabolic acidosis, decreased HCO_3^- and hypocapnia at admission was associated with the development of AKI, while acidosis and hypocapnia were independent predictors of hospital mortality. Among non-respiratory patients, decreased CO_2CP at admission was an independent risk factor for AKI and hospital mortality. ROC curves indicated that CO_2CP was a reasonable biomarker to exclude metabolic acidosis, dual and triple acid-base disturbances. The effect sizes of decreased CO_2CP on AKI and hospital mortality varied according to age and different underlying diseases. Metabolic acidosis is an independent risk factor for the development of AKI and hospital mortality. In non-respiratory patient, decreased CO_2CP is also an independent contributor to AKI and mortality and can be used as an indicator of metabolic acidosis.

Correspondence to: Dr Xiaoqiang Ding, Division of Nephrology, Zhongshan Hospital, Shanghai Medical College, Fudan University, 80 Fenglin Road, Xuhui, Shanghai 200032, P.R. China
E-mail: ding.xiaoqiang@zs-hospital.sh.cn

*Contributed equally

Introduction

Acidosis is the most common acid-base disturbance, with metabolic acidosis potentially indicating a more severe course and worse outcome. The actual incidence and prevalence of metabolic acidosis have not been established in critically ill and general patients. Often this disorder is a marker for underlying pathology, and the most commonly encountered causes of metabolic acidosis are renal insufficiency, sepsis, and diabetic ketoacidosis. Although recent studies showed that metabolic acidosis is associated with high mortality and increased the length of stay in the hospital and ICU (1,2), it remains uncertain whether or not there is a true cause relationship between metabolic acidosis and adverse clinical outcomes.

The kidney is a principally responsible organ for retention and excretion of electrolytes and maintaining acid-base homeostasis in healthy individuals (3). Both acute kidney injury (AKI) and chronic kidney disease (CKD) can cause metabolic acidosis. But on the other hand, accumulating evidence identifies metabolic acidosis not only as a consequence of but as a contributor to, the progression of kidney dysfunction in patients with CKD (4). The mechanisms may be that metabolic acidosis can reduce renal blood flow in healthy human volunteers (5) and increase inflammatory mediator release (6). A recent experimental study proved that metabolic acidosis exacerbates ischemia/reperfusion-induced AKI (7). However, Limited data exist about the harmful effect of metabolic acidosis on the development of AKI.

In general, a diagnosis of metabolic acidosis is based on arterial blood gas (ABG) analysis after an arterial puncture which may lead to local hematoma and other complications. Carbon dioxide combining power (CO_2CP) in the venous blood which is a measure of the alkali reserve, can help in the diagnosis of the metabolic types of acidosis and alkalosis. Even though CO_2CP does not give any idea of the ratio between carbonic acid and bicarbonate, it enables timely diagnosis and proper corrective therapy in metabolic acidosis if respiratory types of acid-base disturbances do not exist.

In this study, we hypothesized that metabolic acidosis might be associated with the development of AKI and hospital mortality, and decreased CO_2CP can be used to an indicator of metabolic acidosis in non-respiratory patients. The study was aimed at identifying the variables in acid-base status

at admission which were associated with the occurrence of renal dysfunction and hospital mortality. The secondary aims were to determine the relationship between CO_2CP and other variables in the electrolyte and acid-base status and to screen high-risk patients of AKI and hospital mortality when decreased CO_2CP occurs.

Materials and methods

Study population and data collection. This retrospective study included all adult patients admitted consecutively to Zhongshan Hospital, Fudan University in Shanghai, China, between October 01, 2014 and September 30, 2015. This study was approved by the institutional review board of the ethics committee, Zhongshan Hospital, Fudan University, Shanghai China. The requirement for informed consent was waived for this observational survey. The patient records and information were anonymized and de-identified before analysis.

Exclusion criteria were the following: Age of fewer than 18 years, serum creatinine (SCr) at admission >115 μmol/l, CO_2CP at admission >29 mmol/l, history of CKD and respiratory diseases, hospital admissions for respiratory diseases. The respiratory diseases included inflammatory lung diseases, restrictive lung diseases, respiratory tract infections, lung tumors, pleural cavity diseases and pulmonary vascular diseases.

All the data were collected from an electronic medical record database. The data included demographics, categories of underlying diseases, mean blood pressure (MBP) and laboratory values at admission. However, we focused on the data of electrolyte and acid-base status in all included patients. The incidence of AKI, hospital mortality, hospital stay, and costs was also recorded.

Definitions and calculation. AKI was defined using Kidney Disease: Improving Global Outcomes criteria (8) as an increase in serum creatinine (SCr) ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h, or an increase in SCr to ≥1.5 times baseline known or presumed to have occurred within the prior seven days. The patients who developed AKI during the following hospitalization were divided into AKI group, while those who did not be split into the non-AKI group.

All samples were analyzed in the central laboratory of the Institution. Anion gap (AG) was calculated by the standard formula (9): $AG=[Na^+]-[Cl^-]-[HCO_3^-]$, with an elevated AG defined as greater than or equal to 16 mmol/l. Strong ion difference (SID) is the sum of strong cations minus the sum of strong anions. Strong ion gap (SIG) is the difference between the apparent SID (SIDa) and the effective SID (SIDe). SIG represents the sum of any unmeasured strong positive and negative ions with an elevated SIG defined as greater than 2 mmol/l. $SIDa=[Na^+]+[K^+]+[Ca^{2+}]+[Mg^{2+}]-[Cl^-]$. $SIDe=[HCO_3^-]+(0.123xpH-0.631)x[Alb]+(pH-0.469)x[P_i]$. $SIG=SIDa-SIDe$ (10). Calculated osmolality=$2x[Na^+]+[glucose]+[urea]$, with the normal range from 280 to 310 mOsm/l. Hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hyperchloremia, hypochloremia, hypercalcemia, hypocalcemia, hyperphosphatemia, hypophosphatemia, hypermagnesemia, hypomagnesemia, hyperuricemia and hypouricemia were defined according

to the reference ranges provided by the central laboratory. Metabolic acidosis includes simple and complex metabolic acidosis, and the latter may exist in dual or triple acid-base disturbances. Simple, dual and triple acid-base disturbances were diagnosed according to the flow diagrams described by Milford Fulop (11). Decreased CO_2CP was defined when it was lower than 23 mmol/l (normal range: 23-29 mmol/l).

Statistical methods. The data were analyzed using SPSS version 24.0 software (SPSS, Chicago, IL, USA). Continuous variables are presented as mean ± SD if they were statically normally distributed and categorical variables as numbers and percentages. Moreover, they were compared using the Student *t*-test for continuous variables and the χ^2 test for categorical variables. Medians and interquartile ranges are presented when variables are not normally distributed, and they were compared using Mann-Whitney U test. Multiple regression binary logistic regression with the Wald forward stepwise method was performed to evaluate the independent risk factors for the occurrence of AKI and hospital mortality, and the results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). We also used Cox proportional hazard model with the Wald forward stepwise method to analyze the independent predictors of AKI and hospital mortality after propensity scores matching, and the results are presented as hazard ratios (HRs) and 95% CIs. The significant acceptance and removal levels for a covariate were set at 0.05 and 0.1, respectively. Multiple linear regression analysis with the stepwise method was used to determine the relationship of CO_2CP and other variables. The ability of CO_2CP to predict AKI and hospital mortality, and to diagnose acid-base disturbances was assessed by plotting the receiver operating characteristic (ROC) curves and further reported as areas under the curve (AUC) with 95% CIs. An AUC-ROC value of >0.7 was taken to indicate reasonable biomarker performance (12). ROC curve optimal cut-off values were defined as the point that maximized the Youden index, defined as (sensitivity + specificity)-1 (13). A P-value <0.05 was considered to indicate statistical significance.

Propensity score matching. To reduce the impact of potential confounding factors in an observational study, we also performed propensity score matching for each AKI using a multivariable logistic regression analysis model based on the following covariates: Age, sex, SCr and BUN at admission. Propensity scores were then employed using the nearest neighbor matching algorithm. Matching was performed with a computer application implemented in SPSS 24.0 and R software version 3.2.2 to select for the most similar propensity scores and to create 1:2 matched pairs (matching the non-AKI to AKI). To identify independent risk factors of AKI and hospital mortality in patients with ABG, we conducted three Cox proportional hazard models. We included all potential factors associated with AKI and hospital mortality in model 1, the level of HCO_3^- was not included in model 2, and $PaCO_2$ was not considered in model 3.

Results

Patient characteristics. After screening, a total of 71,089 patients met the inclusion criteria, and there were
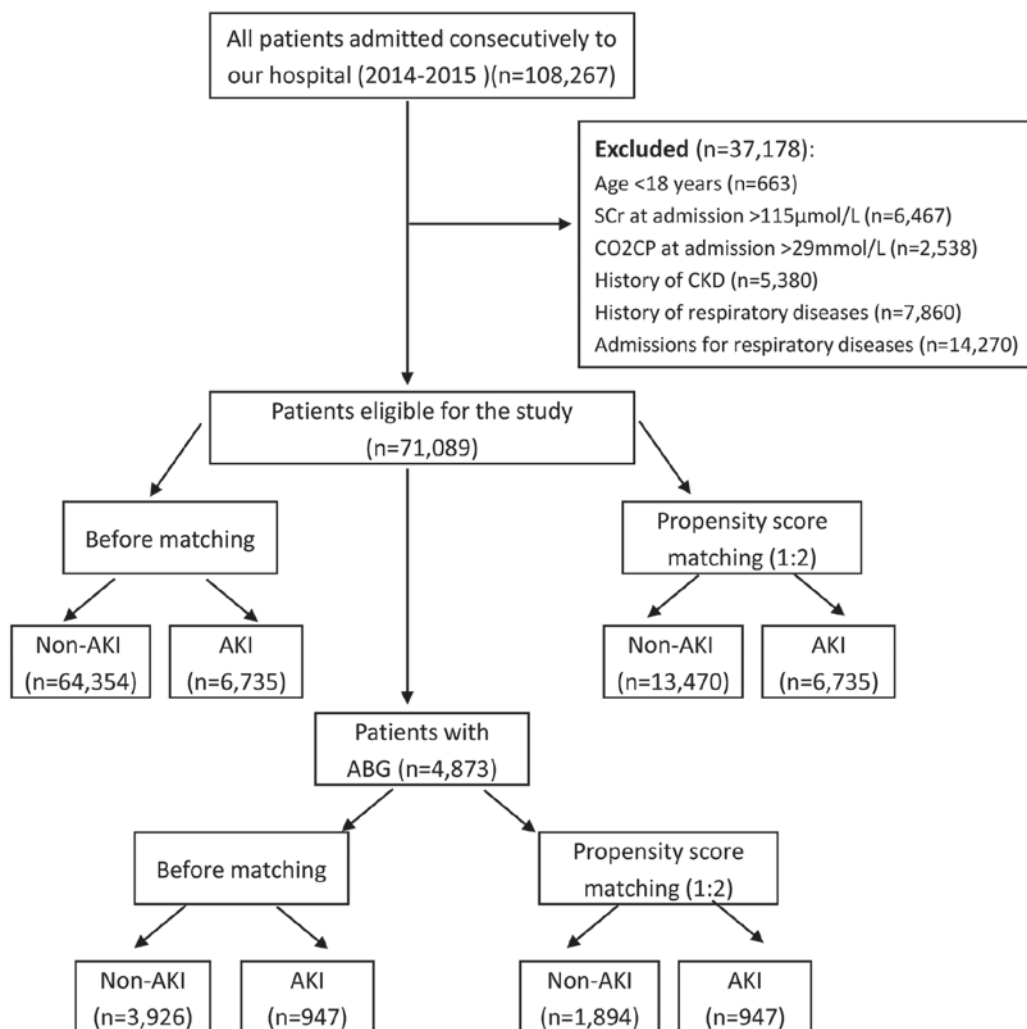
Figure 1. Flowchart of the study. All patients and patients with ABG were analyzed respectively, and propensity score matching was used to obtain more reliable conclusions. SCr, serum creatinine; CO_2CP, carbon dioxide combining power; AKI, acute kidney injury; ABG, arterial blood gas analysis; CKD, chronic kidney disease.

4,873 patients with ABG analysis. The flow-chart of this study was showed in Fig. 1. In all included patients, the incidence of AKI was 9.5%, and the hospital mortality was 0.7%, while the rates in patients with ABG were 19.4 and 1.6%, respectively. The top four underlying diseases with a high incidence of AKI were cardiothoracic surgery (40.7%), cancer (15.8%), general surgery (10.3%) and neurological diseases (10.1%), while the incidence of AKI in cardiovascular patients was 4.3%. Characteristics of all subjects before and after propensity score matching were listed in Table I, while the details of patients with ABG were showed in Table II. By the propensity score, patients in AKI group were successfully matched to patients in the non-AKI group with the ratio of 1:2 in all patients and patients with ABG. After propensity score matching, no statistically significant baseline characteristics in age, sex, SCr and BUN at admission between AKI and non-AKI groups were found. After propensity matching of all patients, the hospital mortality in AKI group was eight times higher than that in the non-AKI group (4.0 vs. 0.5%, respectively, P<0.001). The hospital stay was longer (P<0.001), and the cost was higher (P<0.001) in AKI group than these in the non-AKI group.

Clinical data at admission after propensity matching. In all included patients, the patients in AKI group had lower mean blood pressure, hemoglobin, albumin and a higher number of white blood cell and indexes of liver function (P<0.001). There was significant differences in the levels of Na (P<0.001), K (P=0.001), Cl (P<0.001), Mg (P<0.001), Ca (P<0.001), osmolality (P<0.001) and serum uric acid (P<0.001) between AKI and non-AKI group. Although the median of CO_2CP in these two groups was same, the lower interquartile was lower in AKI group than that in the non-AKI group, and there was a significant difference (P<0.001) (Table I).

In 4,873 patients with ABG, those in AKI group had still lower hemoglobin and albumin, higher indexes of liver function than these in the non-AKI group. There were significant differences in the levels of electrolytes, including Na (P=0.029), Cl (P=0.008), Mg (P<0.001), and Ca (P=0.003). The osmolality in AKI group was lower than that in the non-AKI group (P=0.0008). Even though there was no significant difference in pH and AG between these two groups, the levels of $PaCO_2$ (P=0.001), HCO_3^- (P<0.001), BE (P<0.001), SIDe (P<0.001) and SIG (P<0.001) were significantly different. The CO_2CP in AKI group was lower than that in the non-AKI group (P=0.028).

Table I. Baseline characteristics of all included patients before and after propensity score matching.

Variable	Before matching			Propensity score matching (1:2)		
	Non-AKI (n=64,354)	AKI (n=6,735)	P-value	Non-AKI (n=13,470)	AKI (n=6,735)	P-value
Age, yr	57.0±14.3	59.3±14.6	<0.001[a]	59.1±14.5	59.3±14.6	0.275[a]
Male sex, n (%)	38,131(59.3)	4,274(63.5)	<0.001	8467 (62.9)	4274 (63.5)	0.404
Renal function at admission						
SCr, μmol/l	70.0 (59.0-82.0)	76.0 (63.0-91.0)	<0.001	76.0 (63.0-89.0)	76.0 (63.0-91.0)	0.086
BUN, mmol/l	4.8 (3.9-5.8)	5.2 (4.1-6.6)	<0.001	5.3 (4.2-6.6)	5.2 (4.1-6.6)	0.096
Underlying diseases, n (%)						
Cardiovascular	16,543 (25.7)	741 (11.0)	<0.001	3,886 (28.8)	741 (11.0)	<0.001
General surgery	9,323 (14.5)	1,073 (15.9)	0.001	1,771 (13.1)	1,073 (15.9)	<0.001
Digestive	7,895 (12.3)	326 (4.8)	<0.001	1,565 (11.6)	326 (4.8)	<0.001
Cancer	7,297 (11.3)	1,371 (20.4)	<0.001	1,410 (10.5)	1,371 (20.4)	<0.001
Orthopedic surgery	3,533 (5.5)	147 (2.2)	<0.001	700 (5.2)	147 (2.2)	<0.001
Cardiothoracic surgery	2,549 (4.0)	1,752 (26.0)	<0.001	589 (4.4)	1,752 (26.0)	<0.001
Endocrine	2,297 (3.6)	58 (0.9)	<0.001	457 (3.4)	58 (0.9)	<0.001
Hematological	2,199 (3.4)	352 (5.2)	<0.001	407 (3.0)	352 (5.2)	<0.001
Renal	1,941 (3.0)	114 (1.7)	<0.001	476 (3.5)	114 (1.7)	<0.001
Neurological	1,835 (2.9)	207 (3.1)	0.299	382 (2.8)	207 (3.1)	0.344
Gynecological	1,779 (2.8)	104 (1.5)	<0.001	312 (2.3)	104 (1.5)	<0.001
Others	7,163 (11.1)	490 (7.3)	<0.001	1,515 (11.2)	490 (7.3)	<0.001
Clinical data at admission						
CO$_2$CP, mmol/l	24.0 (23.0-26.0)	24.0 (22.0-26.0)	<0.001	24.0 (23.0-26.0)	24.0 (22.0-26.0)	<0.001
MBP, mmHg	93.3 (86.7-98.0)	92.7 (83.3-97.7)	<0.001	93.3 (86.7-98.3)	92.7 (83.3-97.7)	<0.001
WBC, 10^9/l	5.9 (4.7-7.24)	6.1 (4.8-7.9)	<0.001	5.9 (4.8-7.3)	6.1 (4.8-7.9)	<0.001
Hemoglobin, g/l	131.0 (119.0-143.0)	126.0 (111.0-139.0)	<0.001	131.0 (118.0-143.0)	126.0 (111.0-139.0)	<0.001
AST, U/l	20.0 (16.0-28.0)	23.0 (17.0-36.0)	<0.001	20.0 (16.0-28.0)	23.0 (17.0-36.0)	<0.001
ALT, U/l	19.0 (13.0-30.0)	20.0 (13.0-36.0)	<0.001	19.0 (13.0-30.0)	20.0 (13.0-36.0)	<0.001
TBIL, μmol/l	9.5 (7.0-13.3)	10.5 (7.4-15.8)	<0.001	9.5 (7.0-13.2)	10.5 (7.4-15.8)	<0.001
Albumin, g/l	40.0 (37.0-43.0)	38.0 (35.0-41.0)	<0.001	40.0 (37.0-43.0)	38.0 (35.0-41.0)	<0.001
SUA, mmol/l	297.0 (240.0-357.0)	305.0 (239.0-377.0)	<0.001	311.0 (251.0-376.0)	305.0 (239.0-377.0)	<0.001
Glucose, mmol/l	5.2 (4.7-6.2)	5.3 (4.7-6.4)	0.126	5.3 (4.8-6.3)	5.3 (4.7-6.4)	0.315
Na, mmol/l	141.0 (139.0-143.0)	141.0 (138.0-143.0)	<0.001	141.0 (139.0-143.0)	141.0 (138.0-143.0)	<0.001
K, mmol/l	4.0 (3.8-4.3)	4.0 (3.8-4.3)	0.780	4.0 (3.9-4.3)	4.0 (3.8-4.3)	0.001
Cl, mmol/l	103.0 (101.0-105.0)	103.0 (100.0-105.0)	<0.001	103.0 (101.0-105.0)	103.0 (100.0-105.0)	<0.001
Mg, mmol/l	0.91 (0.86-0.97)	0.90 (0.84-0.96)	<0.001	0.91 (0.86-0.97)	0.90 (0.84-0.96)	<0.001

Table I. Continued.

Variable	Before matching			Propensity score matching (1:2)		
	Non-AKI (n=64,354)	AKI (n=6,735)	P-value	Non-AKI (n=13,470)	AKI (n=6,735)	P-value
Ca, mmol/l	2.31 (2.23-2.39)	2.28 (2.16-2.37)	<0.001	2.31 (2.23-2.40)	2.28 (2.16-2.37)	<0.001
P, mmol/l	1.12 (0.99-1.25)	1.12 (0.95-1.26)	<0.001	1.11 (0.98-1.24)	1.12 (0.95-1.26)	0.255
Osmolality, mOsm/l	293.3 (289.6-296.8)	292.9 (288.5-297.1)	<0.001	293.9 (290.1-297.6)	292.9 (288.5-297.1)	<0.001
Death, n (%)	256 (0.4)	268 (4.0)	<0.001	68 (0.5)	268 (4.0)	<0.001
Hospital stay, days	5.0 (2.5-8.5)	12.5 (8.0-19.0)	<0.001	5.0 (3.0-8.5)	12.5 (8.0-19.0)	<0.001
Hospital cost, RMB	14,803.5 (8,020.7-35,359.8)	52,479.7 (22,202.9-108,512.1)	<0.001	14,961.9 (7,993.8-37,631.1)	52,479.7 (22,202.9-108,512.1)	<0.001

[a]Unpaired Student's t-test. AKI, acute kidney injury; SCr, serum creatinine; BUN, blood urea nitrogen; CO$_2$CP, carbon dioxide combining power; MBP, mean blood pressure; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; SUA, serum uric acid; RMB, Ren Min Bi.

Independent risk factors for incidence of AKI. For patients with ABG, multivariate logistic regression analysis, and three Cox proportional hazards models were used to determine the independent risk factors of incidence of AKI. For the final multiple logistic analysis, 13 variables were kept in the model for AKI, including male sex, hyponatremia, pH>7.45, HCO$_3^-$<22 mmol/l, HCO$_3^-$>27 mmol/l, BE<-3 mmol/l, BE>3 mmol/l and so on. To cut off the interaction of acid-base indexes, we conducted three Cox proportional hazards models. In model 1, all potential variables were included for final analysis, and ten variables were identified including pH<7.35 (HR 1.810, 95% CI: 1.298-2.524, P<0.001), HCO$_3^-$<22 mmol/l (HR 2.051, 95% CI: 1.498-2.809, P<0.001), hypomagnesemia, hypermagnesemia and so forth. In model 2, the variable of HCO$_3^-$ was not included. Further, two variables were kept: metabolic acidosis (HR 1.160, 95% CI: 1.001-1.344, P=0.049) and PaCO$_2$<35 mmHg (HR 1.253, 95% CI: 1.053-1.492, P=0.011). In model 3, the variable of PaCO$_2$ was not included; the final analysis was similar to model 1. The detailed results were listed in Table III.

In all included patients, multivariate logistic regression analysis and Cox proportional hazards model were used to determine the independent risk factors of incidence of AKI during the following hospitalization. For the final multiple logistic analysis, 22 variables were kept in the model for AKI, including age, male sex, CO$_2$CP <23 mmol/l (OR 1.220, 95% CI: 1.150-1.295, P<0.001), mean blood pressure <70 mmHg, hyponatremia, hypernatremia, and so on. After propensity matching, 14 variables were selected in Cox proportional hazards model for the development of AKI, including CO$_2$CP <23 mmol/l (HR 1.099, 95% CI: 1.041-1.161, P=0.001), mean blood pressure <70 mmHg, hypernatremia, and so on. The detailed results were listed in Table IV.

Independent risk factors for hospital mortality. For patients with ABG, multivariate logistic regression analysis, and three Cox proportional hazards models were used to determine the independent risk factors for hospital mortality. For the final multiple logistic analysis, four variables were kept in the model for hospital mortality, including age, pH>7.45, AST, and albumin. Three Cox proportional hazards models were also conducted as above; six variables were kept in more than one model, including age, pH<7.35, PaCO$_2$ <35 mmHg, hypo-osmolality, AST, and decreased albumin. The detailed results were listed in Table V.

In all included patients, multivariate logistic regression analysis and Cox proportional hazards model were used to identify the independent risk factors for hospital mortality. For the final multiple logistic analysis, 14 variables were kept in the model for hospital mortality, including age, male sex, CO$_2$CP <23 mmol/l (OR 1.344, 95% CI: 1.107-1.632, P=0.003), hyponatremia, hypochloremia, and so on. After propensity matching, 11 variables were selected in Cox proportional hazards model for hospital mortality. CO$_2$CP<23 mmol/l was also an independent risk factor for hospital mortality (HR 1.294, 95% CI: 1.026-1.632, P=0.030). The detailed results were listed in Table VI.

ROC curves of CO$_2$CP. In all included patients, the area under the ROC of CO$_2$CP was 0.557 (95% CI: 0.550-0.565, P<0.001)

Table II. Baseline characteristics of included patients with arterial blood gas analysis before and after propensity score matching.

Variable	Before matching			Propensity score matching (1:2)		
	Non-AKI (n=3,926)	AKI (n=947)	P-value	Non-AKI (n=1,894)	AKI (n=947)	P-value
Age, yr	58.9±12.6	59.3±13.3	0.461[a]	59.5±12.7	59.3±13.3	0.583[a]
Male sex, n (%)	2,366 (60.3)	637 (67.3)	<0.001	1242 (65.6)	637 (67.3)	0.370
Renal function at admission						
SCr, μmol/l	62.0 (55.0-72.0)	64.0 (56.0-74.0)	0.060	63.0 (56.0-72.0)	64.0 (56.0-74.0)	0.162
BUN, mmol/l	4.6 (3.8-5.5)	4.8 (3.8-5.9)	0.001	4.9 (3.9-5.9)	4.8 (3.8-5.9)	0.501
Clinical data at admission						
CO_2CP, mmol/l	24.1±2.5	23.9±2.6	0.002[a]	24.1±2.5	23.9±2.6	0.028[a]
MBP, mmHg	93.3 (86.0-96.7)	93.0 (84.3-96.7)	0.457	92.7 (85.3-96.7)	93.0 (84.3-96.7)	0.795
WBC, 10^9/l	5.9 (4.7-7.4)	6.0 (4.8-7.5)	0.093	5.9 (4.7-7.3)	6.0 (4.8-7.5)	0.128
Hemoglobin, g/l	130.0 (118.0-141.0)	129.0 (115.0-141.0)	0.071	130.0 (118.0-142.0)	129.0 (115.0-141.0)	0.045
AST, U/l	19.0 (15.0-27.0)	21.0 (16.0-33.3)	<0.001	19.0 (15.0-27.0)	21.0 (16.0-33.3)	<0.001
ALT, U/l	18.0 (12.0-29.0)	20.0 (13.0-34.0)	<0.001	18.0 (12.0-29.0)	20.0 (13.0-34.0)	<0.001
TBIL, μmol/l	9.5 (7.1-13.2)	10.7 (7.6-15.4)	<0.001	9.5 (7.1-13.3)	10.7 (7.6-15.4)	<0.001
Albumin, g/l	39.0 (37.0-42.0)	39.0 (35.0-41.0)	<0.001	39.0 (36.0-42.0)	39.0 (35.0-41.0)	<0.001
SUA, mmol/l	278.0 (226.8-332.0)	276.0 (212.0-341.0)	0.398	280.0 (229.0-334.0)	276.0 (212.0-341.0)	0.188
Glucose, mmol/l	5.8±2.1	5.9±2.2	0.422[a]	5.9±2.3	5.9±2.2	0.970[a]
Na, mmol/l	141.0 (140.0-143.0)	141.0 (139.0-143.0)	0.003	141.0 (140.0-143.0)	141.0 (139.0-143.0)	0.029
K, mmol/l	4.0 (3.8-4.3)	4.0 (3.7-4.3)	0.255	4.0 (3.8-4.3)	4.0 (3.7-4.3)	0.126
Cl, mmol/l	103.0 (101.0-105.0)	103.0 (100.0-105.0)	0.002	103.0 (101.0-105.0)	103.0 (100.0-105.0)	0.008
Mg, mmol/l	0.92 (0.86-0.97)	0.90 (0.84-0.96)	<0.001	0.92 (0.86-0.97)	0.90 (0.84-0.96)	<0.001
Ca, mmol/l	2.29 (2.20-2.37)	2.27 (2.15-2.36)	<0.001	2.28 (2.19-2.36)	2.27 (2.15-2.36)	0.003
P, mmol/l	1.12 (0.99-1.25)	1.10 (0.94-1.25)	0.003	1.11 (0.99-1.24)	1.10 (0.94-1.25)	0.128
Osmolality, mOsm/l	293.3 (289.6-296.7)	292.9 (288.5-296.8)	0.026	293.3 (289.0-296.9)	292.9 (288.5-296.8)	0.008
PH	7.42 (7.40-7.44)	7.42 (7.39-7.44)	0.870	7.42 (7.40-7.44)	7.42 (7.39-7.44)	0.783
$PaCO_2$, mmHg	40.0 (36.0-43.0)	39.0 (35.4-42.2)	<0.001	40.0 (26.0-43.0)	39.0 (35.4-42.2)	0.001
HCO_3^-, mmol/l	25.4 (23.4-27.2)	24.4 (21.7-26.6)	<0.001	23.3 (25.4-27.2)	24.4 (21.7-26.6)	<0.001
BE, mmol/l	1.2 (-0.7-2.9)	0.6 (-1.9-2.7)	<0.001	1.2 (-0.8-2.9)	0.6 (-1.9-2.7)	<0.001
AG, mmol/l	14.0 (13.0-16.0)	14.0 (13.0-16.0)	0.172	14.2±2.6	14.4±2.9	0.091[a]
SIDa, mmol/l	48.4 (46.7-50.0)	48.2 (46.3-50.0)	0.046	48.4 (46.6-49.9)	48.2 (46.3-50.0)	0.222
SIDe, mmol/l	44.2 (41.5-46.4)	42.8 (39.0-45.3)	<0.001	44.0 (41.4-46.2)	42.8 (39.0-45.3)	<0.001
SIG, mmol/l	4.3 (2.1-6.7)	5.6 (3.0-8.7)	<0.001	4.4 (2.2-6.8)	5.6 (3.0-8.7)	<0.001
Death, n (%)	28 (0.7)	48 (5.1)	<0.001	17 (0.9)	48 (5.1)	<0.001
Hospital stay, days	10.0 (7.0-13.5)	15.5 (11.5-23.0)	<0.001	10.0 (7.0-23.0)	15.5 (11.5-23.0)	<0.001

Table II. Continued.

	Before matching			Propensity score matching (1:2)		
Variable	Non-AKI (n=3,926)	AKI (n=947)	P-value	Non-AKI (n=1,894)	AKI (n=947)	P-value
Hospital cost, RMB	39,559.3 (19,529.7-58,308.5)	73,051.7 (45,782.8-58,308.5)	<0.001	39,481.1 (19,587.8-58,471.2)	73,051.7 (45,782.8-121,322.4)	<0.001

[a]Unpaired Student's t-test. AKI, acute kidney injury; SCr, serum creatinine; BUN, blood urea nitrogen; CO_2CP, carbon dioxide combining power; MBP, mean blood pressure; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; SUA, serum uric acid; BE, base excess; AG, anion gap; SIDa, apparent strong ion difference; SIDe, effective strong ion difference; SIG, strong ion gap; RMB, Ren Min Bi.

for predicting of not developing AKI and 0.590 (95% CI: 0.563-0.618, P<0.001) for predicting of no hospital death. And the optimal cut-off values of CO_2CP were 23.5 (sensitivity 65.3%, specificity 43.5%) and 22.5 mmol/l (sensitivity 77.8%, specificity 38.0%), respectively (Fig. 2A and B). In patients with ABG, the area under the ROC of CO_2CP was 0.746 (95% CI: 0.730-0.763, P<0.001) for diagnosis of no metabolic acidosis and the optimal cut-off values of CO_2CP were 23.5 (sensitivity 70.9%, specificity 68.6%), indicating reasonable biomarker performance (Fig. 2C). We also conduct ROC curves of CO_2CP for excluding the diagnosis of any acid-base disturbances (Fig. 2D), simple, dual and triple acid-base disturbances. There were reasonable biomarker performances to exclude diagnosis of dual (AUC 0.769, 95%: CI 0.750-0.787, P<0.001, Fig. 2E) and triple (AUC 0.719, 95%: CI 0.673-0.765, P<0.001, Fig. 2F) acid-base disturbances with 22.5 mmol/l as the optimal cut-off value.

Subgroup analysis of CO_2CP as a contributor of AKI and hospital mortality. The total incidence of AKI in decreased CO_2CP group was significantly higher than normal CO_2CP group (12.4% and 8.6, respectively, OR 1.45, 95% CI: 1.37-1.54, P<0.001). Subgroup analysis showed that the ORs increased along with older age with significant differences at every age stage (18-34 years, P=0.004; other stages, P<0.001). The effect sizes of decreased CO_2CP on AKI varied according to different diseases, and there were significant differences in digestive (OR 3.10, P<0.001), cardiovascular diseases (OR 1.77, P<0.001), orthopedic surgery (OR 1.71, P=0.002), neurological diseases (OR 1.68, P=0.001), general surgery (OR 1.66, P<0.001), hematological diseases (OR 1.35, P=0.012), cancer (OR 1.16, P=0.026) and others (OR 2.03, P<0.001) (Fig. 3).

The total hospital mortality in decreased CO_2CP group was 1.3%, significantly higher than normal CO_2CP group (0.6%) (OR 1.98, 95% CI: 1.66-2.37, P<0.001). The increasing trend of ORs along with older age was not present, and there were significant differences only at the age stages of 50-64 years (OR 2.91, P<0.001), 65-79 years (OR 2.36, P<0.001), and >80 years (OR 1.61, P=0.007). The effect sizes of decreased CO_2CP on hospital mortality were significantly different in digestive (OR 4.41, P<0.001), cardiovascular diseases (OR 2.80, P<0.001), general surgery (OR 2.47, P=0.008), cancer (2.27 1.61, P=0.001), neurological diseases (OR 1.83, P=0.033), and others (OR 1.83, P=0.003) (Fig. 4).

Discussion

The present study focuses on the variables in the electrolyte and acid-base balance among non-respiratory patients associated with the occurrence of AKI and hospital mortality using a propensity score matching method. Primary analysis in patients with ABG demonstrated that several variables which could result in decreased CO_2CP, such as acidosis (pH<7.35), metabolic acidosis, decreased HCO_3^- and hypocapnia were associated with the development of AKI, while acidosis and hypocapnia were independent predictors of hospital mortality. Further analysis found decreased CO_2CP was an independent risk factor for AKI and hospital mortality. AUC-ROC indicated that CO_2CP was a reasonable biomarker to exclude metabolic acidosis, dual and triple acid-base disturbances with 22.5 or

Table III. Independent risk factors for acute kidney injury including patients with arterial blood gas analysis.

Variable	Multiple logistic analysis OR (95%CI)	P-value	Cox proportional hazards model 1 HR (95%CI)	P-value	Cox proportional hazards model 2 HR (95%CI)	P-value	Cox proportional hazards model 3 HR (95%CI)	P-value
Male sex	1.427 (1.214-1.677)	<0.001						
Hyponatremia	0.510 (0.271-0.961)	0.037						
Hypernatremia	0.653 (0.332-1.282)	0.215						
Hypomagnesemia	0.601 (0.467-0.774)	<0.001	3.399 (1.578-7.322)	0.002	2.191 (1.299-3.695)	0.003	2.123 (1.257-3.586)	0.005
Hypermagnesemia	2.040 (1.065-3.909)	0.032	1.965 (1.509-2.559)	<0.001	1.631 (1.303-2.042)	<0.001	1.593 (1.272-1.996)	<0.001
Hypophosphatemia	0.728 (0.576-0.921)	0.008						
Hyperphosphatemia	0.911 (0.679-1.221)	0.532						
Hypouricemia	0.596 (0.445-0.798)	0.001	1.270 (1.023-1.578)	0.031	1.165 (0.986-1.376)	0.073	1.150 (0.973-1.359)	0.101
Hyperuricemia	0.730 (0.521-1.024)	0.068	1.768 (1.272-2.457)	0.001	1.397 (1.098-1.776)	0.006	1.399 (1.101-1.779)	0.006
Metabolic acidosis					1.160 (1.001-1.344)	0.049		
pH<7.35	1.022 (0.816-1.280)	0.849	1.810 (1.298-2.524)	<0.001	1.386 (1.107-1.735)	0.004	1.357 (1.072-1.718)	0.011
pH>7.45	1.853 (1.306-2.631)	0.001	1.029 (0.805-1.314)	0.820	1.010 (0.832-1.225)	0.922	1.034 (0.856-1.249)	0.727
HCO_3^- <22 mmol/l	1.553 (1.179-2.045)	0.002	2.051 (1.498-2.809)	<0.001			1.497 (1.194-1.876)	<0.001
HCO_3^- >27 mmol/l	3.072 (2.142-4.407)	<0.001	0.640 (0.476-0.860)	0.003			0.745 (0.587-0.944)	0.015
$PaCO_2$ <35 mmHg					1.253 (1.053-1.492)	0.011		
$PaCO_2$> 45 mmHg					1.097 (0.884-1.361)	0.399		
BE <-3 mmol/l	0.631 (0.478-0.833)	0.001	0.754 (0.518-1.098)	0.141			0.866 (0.661-1.135)	0.296
BE >3 mmol/l	0.513 (0.339-0.777)	0.002	1.639 (1.213-2.213)	0.001			1.369 (1.084-1.728)	0.008
AST, per 40 U/l increase	1.140 (1.075-1.209)	<0.001	1.148 (1.073-1.227)	<0.001	1.060 (1.018-1.104)	0.005	1.068 (1.026-1.113)	0.001
Albumin, per 5 g/l decrease	1.211 (1.110-1.322)	<0.001	1.184 (1.077-1.302)	0.001	1.106 (1.029-1.118)	0.006	1.103 (1.028-1.184)	0.006

BE, base excess; AST, aspartate aminotransferase; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

Table IV. Independent risk factors for acute kidney injury including all patients.

Variable	Multiple logistic analysis		Cox proportional hazards model	
	OR (95%CI)	P-value	HR (95%CI)	P-value
Age, per 10-year increase	1.077 (1.057-1.097)	<0.001		
Male sex	1.141 (1.079-1.207)	<0.001		
$CO_2CP<23$ mmol/l	1.220 (1.150-1.295)	<0.001	1.099 (1.041-1.161)	0.001
MBP<70 mmHg	2.232 (1.771-2.812)	<0.001	1.360 (1.130-1.636)	0.001
Hyponatremia	1.159 (1.052-1.276)	0.003	1.085 (0.999-1.180)	0.054
Hypernatremia	1.590 (1.224-2.065)	0.001	1.522 (1.244-1.861)	<0.001
Hypokalemia	1.109 (1.006-1.223)	0.037		
Hyperkalemia	1.843 (1.197-2.839)	0.006		
Hypochloremia	1.375 (1.241-1.524)	<0.001	1.197 (1.096-1.308)	<0.001
Hyperchloremia	0.905 (0.689-1.189)	0.473	0.862 (0.692-1.074)	0.185
Hypocalcemia	1.658 (1.523-1.804)	<0.001	1.319 (1.224-1.421)	<0.001
Hypercalcemia	1.007 (0.803-1.264)	0.949	0.992 (0.803-1.227)	0.944
Hypomagnesemia	2.373 (1.862-3.024)	<0.001	1.319 (1.090-1.597)	0.005
Hypermagnesemia	1.340 (1.193-1.505)	<0.001	1.085 (0.977-1.204)	0.126
Hypophosphatemia	1.181 (1.085-1.285)	<0.001	1.113 (1.032-1.200)	0.005
Hyperphosphatemia	1.604 (1.472-1.749)	<0.001	1.347 (1.246-1.456)	<0.001
Hypouricemia	0.863 (0.797-0.934)	<0.001	1.021 (0.952-1.095)	0.568
Hyperuricemia	1.765 (1.632-1.911)	<0.001	1.160 (1.081-1.245)	<0.001
Hypoosmolality	0.935 (0.807-1.083)	0.368		
Hyperosmolality	3.255 (2.334-4.540)	<0.001		
Hemoglobin, per 10 g/l decrease	1.073 (1.052-1.095)	<0.001	1.021 (1.004-1.039)	0.018
WBC<4x10⁹/l	0.996 (0.922-1.076)	0.924	1.094 (1.019-1.174)	0.014
WBC>12x10⁹/l	1.727 (1.546-1.930)	<0.001	1.242 (1.130-1.366)	<0.001
AST, per 40 U/l increase	1.088 (1.071-1.105)	<0.001	1.033 (1.022-1.044)	<0.001
TBIL, per 20 μmol/l increase	1.023 (1.006-1.040)	0.007		
Albumin, per 5 g/l decrease	1.220 (1.179-1.264)	<0.001	1.120 (1.087-1.154)	<0.001

CO_2CP, carbon dioxide combining power; MBP, mean blood pressure; WBC, white blood cell; AST, aspartate aminotransferase; TBIL, total bilirubin; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

23.5 mmol/l as optimal cut-off values. Furthermore, the effect sizes of decreased CO_2CP on AKI and hospital mortality varied according to age and different underlying diseases.

Whether acid-base disturbances are contributors to acute kidney injury or rather are simple epiphenomena has rarely been discussed in previous studies. The role of serum bicarbonate level as a risk factor for renal outcomes (end-stage renal disease or 50% reduction in evaluated glomerular filtration rate) has been evaluated in patients with CKD. After adjustment for covariates, the risk of developing a renal endpoint is 3% lower per 1 mM increase in serum bicarbonate level (HR 0.97, 95% CI: 0.94-0.99) (14). However, it is not known whether metabolic acidosis affects the development of AKI in a clinical setting. Our research found that acidosis, especially metabolic acidosis, hypocapnia, and decreased CO_2CP were contributors to the incidence of AKI. Besides, the previous study (1) showed that patients with acidosis are 4 to 5 times as likely to die as patients who do not, and the mortality among patients with metabolic acidosis is highest for patients with lactic acidosis (high AG) and SIG acidosis. We found that

acidosis, hypocapnia, and decreased CO_2CP were predictors of hospital mortality, and significantly higher SIG was observed in AKI group than the non-AKI group, indicating that SIG should also be carefully monitored, especially in critically ill patients. Although the roles of metabolic acidosis in the development of AKI and death were confirmed, the benefits and administration timing of sodium bicarbonate for prevention and treatment of AKI are still not clear now (15).

In this study, we restricted our analysis to patients without respiratory diseases and patients with increased CO_2CP at admission were also excluded, for several reasons. As discussed above, CO_2CP does not reflect the actual state of the acid-base balance when respiratory acid-base balances exist. Two major acid-base disturbances, respiratory acidosis, and metabolic alkalosis, both of which can result in increased CO_2CP, are not uncommon in respiratory patients. If respiratory diseases, such as chronic obstructive pulmonary diseases, are excluded, the impact of respiratory acid-base balances to CO_2CP can be minimized. On the other hand, reduced CO_2CP suggests metabolic acidosis (1) or respiratory alkalosis (16),

Table V. Independent risk factors for hospital mortality including patients with arterial blood gas analysis.

Variable	Multiple logistic analysis		Cox proportional hazards model 1		Cox proportional hazards model 2		Cox proportional hazards model 3	
	OR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, per 10-year increase	1.500 (1.233-1.826)	<0.001	1.360 (1.103-1.677)	0.004	1.333 (1.092-1.627)	0.005	1.346 (1.103-1.642)	0.003
pH<7.35	0.674 (0.370-1.229)	0.198	5.064 (2.438-10.518)	<0.001	3.915 (1.966-7.795)	<0.001	4.533 (2.328-8.828)	<0.001
pH>7.45	2.827 (1.316-6.074)	0.008	1.793 (0.928-3.464)	0.082	1.879 (1.005-3.511)	0.048	2.295 (1.258-4.188)	0.007
PaCO$_2$<35 mmHg	0.551 (0.246-1.235)	0.148	2.636 (1.406-4.943)	0.003	2.491 (1.360-4.562)	0.003		
PaCO$_2$>45 mmHg	1.307 (0.556-3.073)	0.539	2.103 (0.892-4.956)	0.089	1.951 (0.866-4.398)	0.107		
Hypoosmolality	1.192 (1.032-1.158)	0.072	2.233 (1.109-4.496)	0.024	1.870 (0.988-3.539)	0.054	2.052 (1.091-3.859)	0.026
Hyperosmolality	0.480 (0.075-3.067)	0.438	4.032 (0.669-24.296)	0.128	3.610 (0.818-15.941)	0.090	3.921 (0.876-17.549)	0.074
AST, per 40 U/l increase	1.462 (1.245-1.715)	<0.001	1.220 (1.095-1.359)	<0.001	1.173 (1.065-1.293)	0.001	1.217 (1.106-1.339)	<0.001
Albumin, per 5 g/l decrease	1.688 (1.348-2.116)	<0.001	1.647 (1.296-2.094)	<0.001	1.507 (1.217-1.865)	<0.001	1.425 (1.120-1.814)	0.004

AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

both of which are indicators of poor outcomes. Although ABG analysis has become an essential test to diagnose acid-base disturbances, only a small percentage of patients received this test for its invasive procedure and complications. In this respect, CO$_2$CP is easier for patients to obtain from venous blood than ABG analysis from arterial blood. Furthermore, if integrated with clinical and electrolytes for full consideration, more exact information about acid-base disturbances can be obtained from CO$_2$CP.

Most often, decreased CO$_2$CP signifies the presence of metabolic acidosis, but it also could reflect a decline in the bicarbonate concentration as compensation for respiratory alkalosis. Respiratory alkalosis is a disturbance in acid and base balance due to alveolar hyperventilation. Respiratory alkalosis is the most common acid-base disturbance observed in patients who are critically ill. When respiratory alkalosis is present, the cause may be a minor non-life-threatening disorder. However, more serious disease processes may exist, especially in critically ill patients. In our study, hypocapnia at admission in non-respiratory patients was associated with poor outcomes, including the development of AKI and hospital mortality. Furthermore, in non-respiratory patients, AUC-ROC stated that CO$_2$CP was a reasonable biomarker to exclude metabolic acidosis, dual and triple acid-base disturbances with 22.5 or 23.5 mmol/l as optimal cut-off values.

The relationship of electrolyte disturbances and poor outcomes is complex. They may often be a para-phenomenon, as an indicator of the severity of the underlying diseases. However, according to our multiple logistic regression and propensity-matched analysis, some disorders were independent contributors to hospital mortality, such as hyponatremia, hypochloremia, hyperkalemia, hypermagnesemia, and hyperosmolality. We also found that several types of electrolyte disturbances were associated with AKI (hyponatremia, hypernatremia, hypochloremia, hypocalcemia, hypomagnesemia, hypophosphatemia and hyperphosphatemia).

However, some limitations must be considered. Firstly, although we attempted to control for confounders by using multiple logistic regression analysis and Cox proportional hazards model after propensity score matching, this retrospective observational design does not establish causal relationships of acid-base disturbances with the development of AKI and hospital mortality. Secondly, only non-respiratory patients were considered in this study, which may lead to potential bias and we could not give a reasonable explanation for different effect sizes of decreased CO$_2$CP on various underlying diseases in our study. Thirdly, although we tried to collect the data about the intervention of acid-base disturbances, for example, the administration of sodium bicarbonate and fluid management, it was too hard to obtain these data for a retrospective study. Further well-designed and prospective research is needed.

Metabolic acidosis is an independent risk factor for the development of AKI and hospital mortality. In non-respiratory patients without ABG, decreased CO$_2$CP is also an independent contributor to AKI and mortality, and can be used as an indicator of metabolic acidosis. Further ABG test is needed, and close attention should be paid to high-risk patients with decreased CO$_2$CP.

Table VI. Independent risk factors for hospital mortality including all patients.

Variable	Multiple logistic analysis		Cox proportional hazards model	
	OR (95% CI)	P-value	HR (95% CI)	P-value
Age, per 10-year increase	1.611 (1.504-1.727)	<0.001		
Male sex	1.364 (1.124-1.655)	0.002		
CO_2CP<23 mmol/l	1.344 (1.107-1.632)	0.003	1.294 (1.026-1.632)	0.030
Hyponatremia	1.563 (1.190-2.053)	0.001	1.592 (1.147-2.210)	0.005
Hypernatremia	1.916 (0.935-3.927)	0.076	1.647 (0.749-3.619)	0.214
Hypokalemia			1.453 (1.081-1.953)	0.013
Hyperkalemia			1.487 (0.685-3.227)	0.315
Hypochloremia	1.968 (1.484-2.610)	<0.001	1.877 (1.349-2.610)	<0.001
Hyperchloremia	0.728 (0.378-1.401)	0.342	0.676 (0.323-1.414)	0.299
Hypomagnesemia	0.295 (0.090-0.966)	0.044	0.350 (0.111-1.098)	0.072
Hypermagnesemia	1.565 (1.104-2.220)	0.012	1.594 (1.112-2.286)	0.011
Hypouricemia	1.283 (1.025-1.606)	0.030	1.278 (0.980-1.666)	0.070
Hyperuricemia	1.742 (1.324-2.291)	<0.001	1.520 (1.127-2.051)	0.006
Hypoosmolality	0.936 (0.684-1.281)	0.679	1.086 (0.761-1.548)	0.650
Hyperosmolality	5.029 (2.549-9.923)	<0.001	3.588 (1.767-7.285)	<0.001
Hemoglobin, per 10 g/l decrease	1.204 (1.145-1.265)	<0.001	1.128 (1.067-1.192)	<0.001
WBC<4x10^9/l	1.064 (0.817-1.387)	0.645	0.889 (0.635-1.272)	0.546
WBC>12x10^9/l	2.917 (2.274-3.741)	<0.001	2.096 (1.580-2.782)	<0.001
AST, per 40 U/l increase	1.126 (1.094-1.160)	<0.001	1.068 (1.039-1.098)	<0.001
TBIL, per 20 μmol/l increase	1.032 (1.001-1.065)	0.043		
Albumin, per 5 g/l decrease	1.492 (1.355-1.643)	<0.001	1.294 (1.026-1.632)	<0.001

CO_2CP, carbon dioxide combining power; WBC, white blood cell; AST, aspartate aminotransferase; TBIL, total bilirubin; OR, odds ratio; HR, hazard ratio; CI, confidence interval.
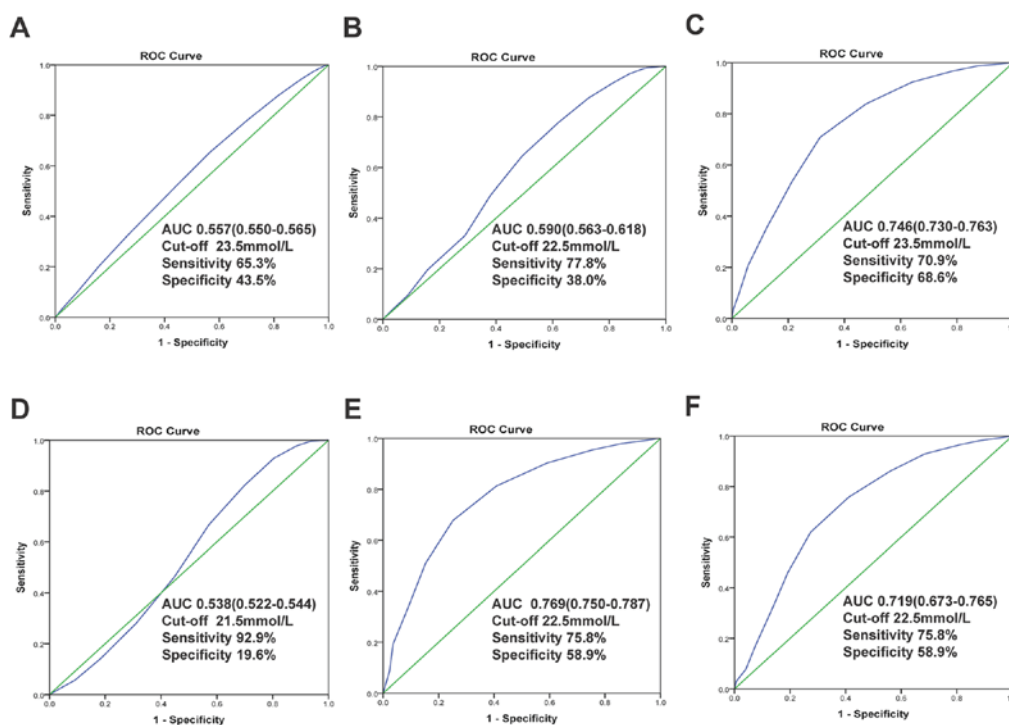
Figure 2. Receiver operator characteristic curves of carbon dioxide combining power. For predicting of not developing of (A) acute kidney injury and (B) no hospital death; For excluding the diagnosis of (C) metabolic acidosis, (D) any acid-base disturbances, (E) dual and (F) triple acid-base disturbances. The AUC, cut-off values of CO_2CP, sensitivity and specificity for diagnosis were provided. ROC, receiver operator characteristic; AUC, areas under the curve.

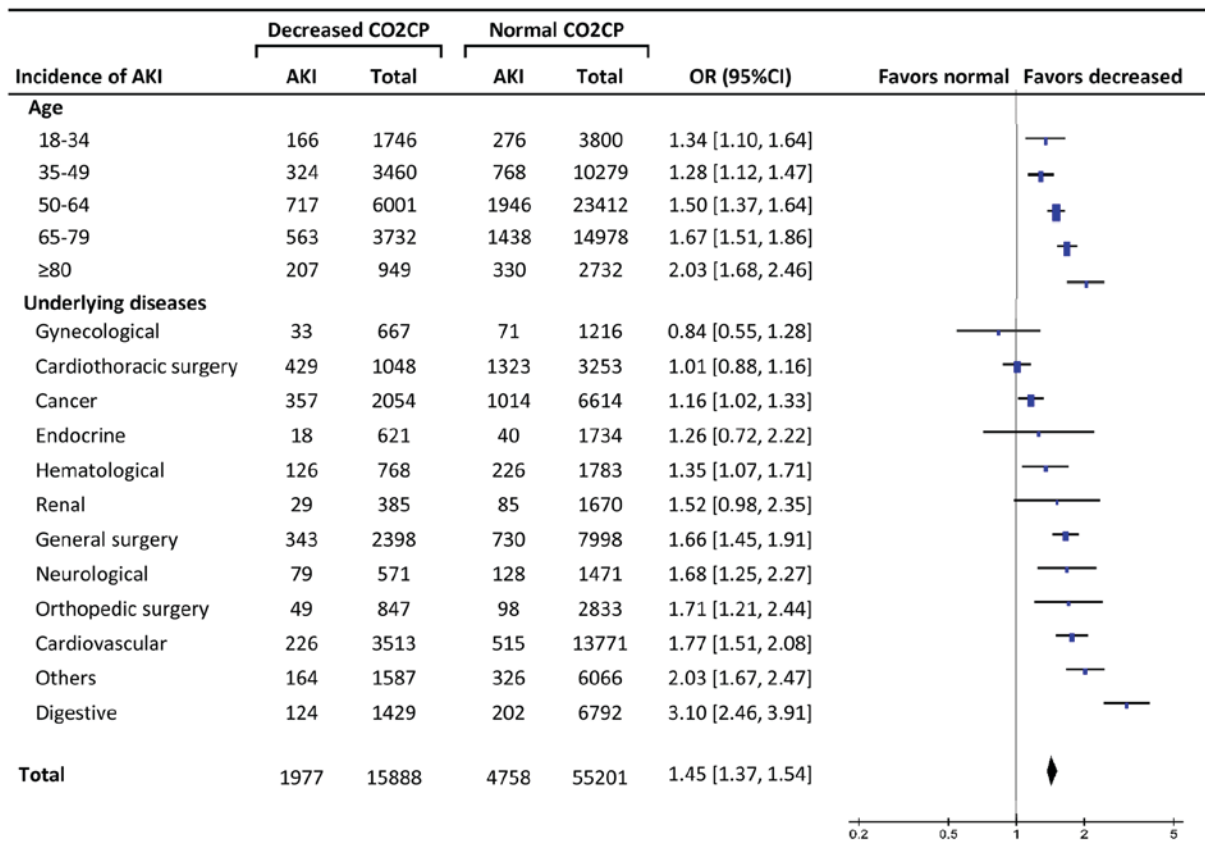| Incidence of AKI	Decreased CO2CP		Normal CO2CP		OR (95%CI)	Favors normal Favors decreased
	AKI	Total	AKI	Total		
Age						
18-34	166	1746	276	3800	1.34 [1.10, 1.64]	
35-49	324	3460	768	10279	1.28 [1.12, 1.47]	
50-64	717	6001	1946	23412	1.50 [1.37, 1.64]	
65-79	563	3732	1438	14978	1.67 [1.51, 1.86]	
≥80	207	949	330	2732	2.03 [1.68, 2.46]	
Underlying diseases						
Gynecological	33	667	71	1216	0.84 [0.55, 1.28]	
Cardiothoracic surgery	429	1048	1323	3253	1.01 [0.88, 1.16]	
Cancer	357	2054	1014	6614	1.16 [1.02, 1.33]	
Endocrine	18	621	40	1734	1.26 [0.72, 2.22]	
Hematological	126	768	226	1783	1.35 [1.07, 1.71]	
Renal	29	385	85	1670	1.52 [0.98, 2.35]	
General surgery	343	2398	730	7998	1.66 [1.45, 1.91]	
Neurological	79	571	128	1471	1.68 [1.25, 2.27]	
Orthopedic surgery	49	847	98	2833	1.71 [1.21, 2.44]	
Cardiovascular	226	3513	515	13771	1.77 [1.51, 2.08]	
Others	164	1587	326	6066	2.03 [1.67, 2.47]	
Digestive	124	1429	202	6792	3.10 [2.46, 3.91]	
Total	1977	15888	4758	55201	1.45 [1.37, 1.54]	

0.2 0.5 1 2 5

Figure 3. Subgroup analysis of decreased carbon dioxide combining power (<23 mmol/l) as a contributor to acute kidney injury. The effect of different age subgroups and underlying diseases were analyzed. AKI, acute kidney injury; CO_2CP, carbon dioxide combining power; OR, odds ratio; CI, confidence interval.

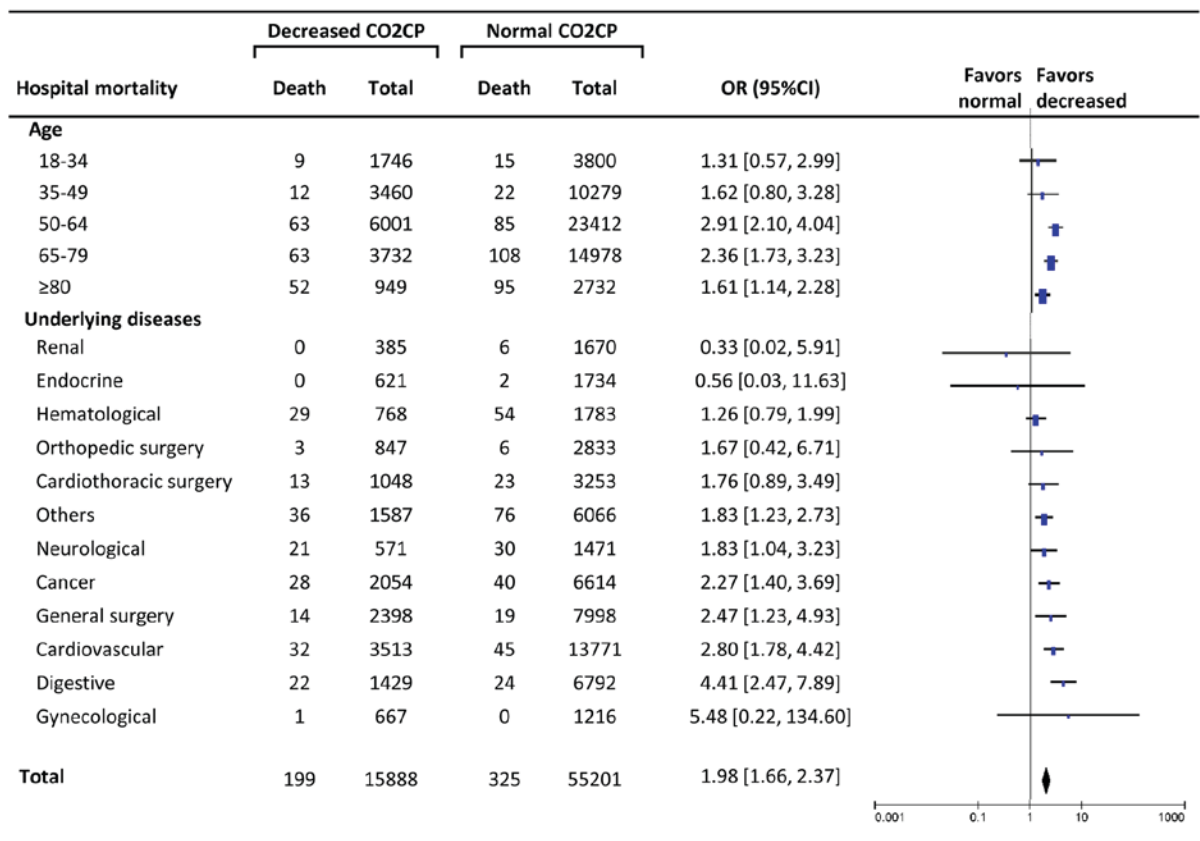| Hospital mortality	Decreased CO2CP		Normal CO2CP		OR (95%CI)	Favors normal Favors decreased
	Death	Total	Death	Total		
Age						
18-34	9	1746	15	3800	1.31 [0.57, 2.99]	
35-49	12	3460	22	10279	1.62 [0.80, 3.28]	
50-64	63	6001	85	23412	2.91 [2.10, 4.04]	
65-79	63	3732	108	14978	2.36 [1.73, 3.23]	
≥80	52	949	95	2732	1.61 [1.14, 2.28]	
Underlying diseases						
Renal	0	385	6	1670	0.33 [0.02, 5.91]	
Endocrine	0	621	2	1734	0.56 [0.03, 11.63]	
Hematological	29	768	54	1783	1.26 [0.79, 1.99]	
Orthopedic surgery	3	847	6	2833	1.67 [0.42, 6.71]	
Cardiothoracic surgery	13	1048	23	3253	1.76 [0.89, 3.49]	
Others	36	1587	76	6066	1.83 [1.23, 2.73]	
Neurological	21	571	30	1471	1.83 [1.04, 3.23]	
Cancer	28	2054	40	6614	2.27 [1.40, 3.69]	
General surgery	14	2398	19	7998	2.47 [1.23, 4.93]	
Cardiovascular	32	3513	45	13771	2.80 [1.78, 4.42]	
Digestive	22	1429	24	6792	4.41 [2.47, 7.89]	
Gynecological	1	667	0	1216	5.48 [0.22, 134.60]	
Total	199	15888	325	55201	1.98 [1.66, 2.37]	

0.001 0.1 1 10 1000

Figure 4. Subgroup analysis of decreased carbon dioxide combining power (<23 mmol/l) as a contributor to hospital mortality. The effect of different age subgroups and underlying diseases were analyzed. AKI, acute kidney injury; CO_2CP, carbon dioxide combining power; OR, odds ratio; CI, confidence interval.

Acknowledgements

References

1. Gunnerson KJ, Saul M, He S and Kellum JA: Lactate versus non-lactate metabolic acidosis: A retrospective outcome evaluation of critically ill patients. Crit Care 10: R22, 2006.
2. Silva Júnior GB, Daher Edf F, Mota RM and Menezes FA: Risk factors for death among critically ill patients with acute renal failure. Sao Paulo Med J 124: 257-263, 2006.
3. Bockenkamp B and Vyas H: Understanding and managing acute fluid and electrolyte disturbances. Current Paediatrics 13: 520-528, 2003.
4. Chen W and Abramowitz MK: Metabolic acidosis and the progression of chronic kidney disease. BMC Nephrol 15: 55, 2014.
5. Chowdhury AH, Cox EF, Francis ST and Lobo DN: A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 256: 18-24, 2012.
6. Peppicelli S, Bianchini F, Contena C, Tombaccini D and Calorini L: Acidic pH via NF-κB favours VEGF-C expression in human melanoma cells. Clin Exp Metastasis 30: 957-967, 2013.
7. Magalhães PA, de Brito TS, Freire RS, da Silva MT, dos Santos AA, Vale ML, de Menezes DB, Martins AM and Libório AB: Metabolic acidosis aggravates experimental acute kidney injury. Life Sci 146: 58-65, 2016.
8. Khwaja A: KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 120: c179-c184, 2012.
9. Engle JE: Clinical physiology of acid-base and electrolyte disorders. JAMA 263: 2375-2376, 1990.
10. Fencl V, Jabor A, Kazda A and Figge J: Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 162: 2246-2251, 2000.
11. Fulop M: Flow diagrams for the diagnosis of acid-base disorders. J Emerg Med 16: 97-109, 1998.
12. Swets JA: Measuring the accuracy of diagnostic systems. Science 240: 1285-1293, 1988.
13. Youden WJ: Index for rating diagnostic tests. Cancer 3: 32-35, 1950.
14. Dobre M, Yang W, Chen J, Drawz P, Hamm LL, Horwitz E, Hostetter T, Jaar B, Lora CM, Nessel L, et al: Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: A report from the chronic renal insufficiency cohort (CRIC) study. Am J Kidney Dis 62: 670-678, 2013.
15. Hewitt J, Uniacke M, Hansi NK, Venkat-Raman G and McCarthy K: Sodium bicarbonate supplements for treating acute kidney injury. Cochrane Database Syst Rev CD009204, 2012.
16. Shirakabe A, Hata N, Kobayashi N, Shinada T, Tomita K, Tsurumi M, Matsushita M, Okazaki H, Yamamoto Y, Yokoyama S, et al: Clinical significance of acid-base balance in an emergency setting in patients with acute heart failure. J Cardiol 60: 288-294, 2012.