Association Between Base Excess and Mortality Among Patients in ICU with Acute Kidney Injury

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Abstract

Objective This study aimed to explore the association between base excess (BE) and risk of 30-day mortality among patients with acute kidney injury (AKI) in ICU.

Methods This retrospective study including ICU patients with AKI from Medical Information Mart for Intensive Care (MIMIC)-IV database. We used multivariate Cox proportional-hazards model to calculate the hazard ratio (HR) for risk of 30-day mortality among patients with AKI. Furthermore, we utilized Cox proportional-hazard model with restrict cubic splines (RCS) to explore the potential no-linear association.

Results Of all the 14238 ICU patients with AKI, BE showed U-shaped relationship with risk of 30-day mortality for patients with AKI, and higher or lower BE value could increase the risk. Compared with normal base excess (-3~3 mmol/L), patients with difference groups (BE ≤ -9mmol/L, -9 mmol/L <BE≤-3 mmol/L, 3 mmol/L <BE≤9 mmol/L and BE□9 mmol/L) had different HR for mortality: 1.57(1.40,1.76), 1.26(1.14,1.39), 0.97(0.83,1.12), 1.53(1.17,2.02) respectively. And the RCS analyses also showed U-shaped curve between BE and 30-day mortality risk.

Conclusion Our results suggest both higher and lower BE in patients with AKI would increase the risk of 30-day mortality. BE measured at administration could be a critical prognostic indicator for ICU patients with AIK and provide guidance for clinicians.

Key Messages

- BE could be a good indicator for survival outcomes for AKI patients in ICU setting;
- The association between BE and 30-day mortality for AKI patients in ICU showed a U-shaped relationship.

Introduction

Acute kidney injury (AKI) could be considered as a severe complication in intensive care unit (ICU), as its association with higher morbidity, higher mortality and poorer outcomes. The incidence of AKI ranges from 2% in the community setting to 20% in hospitalized patients, and even up to 60% in ICU[1].

Patients with AKI show increased risk of mortality, chronic kidney disease (CKD) progression and cardiovascular complications[2]. Besides, diuretics, vasopressors, and renal replacement therapy (RRT) can be administered to these patients. The factors mentioned above can lead to disorders in the acid-base balance.

Base excess (BE) refers to the amount of acid or alkali needed to adjust the value to the normal range[3], which is considered as a pure indicator of metabolic acid-based balance[4]. Base excess has been widely used as a predictor for diagnosis of neonatal sepsis in preterm newborns[5], complications in cytoreductive surgery[6], or the outcome of neonatal acute respiratory distress syndrome[7]. The indicator also shows

significant representativeness in heart failure[3,4]. However, the association of BE and mortality of patients with AKI is unclear.

Smith[8] demonstrated that the base excess could be a prognostic indicator for patients admitted to intensive care. Those patients with BE on admissions less than − 4 mmol/L had higher mortality than those with BE greater or equal to -4 mmol/L (57.7% vs 17.6%, P < 0.0001). But in his study, other confounders, such as age, SOFA on admission, inotropes, and mechanical ventilation showed significant difference between two groups and were not adjusted.

Consequently, the aim of this study is to explore the effect of baseline BE on mortality in patients with AKI.

Materials And Methods

Source of data

The data of this study was from a large critical care database named Medical Information Mart for Intensive Care (MIMIC)-IV[9,10], which is a publicly and freely available database. MIMIC-IV database, an update to MIMIC-III, contained data for patients who were admitted to the Beth Israel Deaconess Medical Center (BIDMC) during 2008–2019. After successful completing the National Institutes of Health (NIH) Web-based training course and the Protecting Human Research Participants examination, we are permitted to extract data from MIMIC-IV. An author who had finished the Collaborative Institutional Training Initiative examination (Certification number 39090498 for author YY Qin) can access the database.

Participants

This study included adult patients(≥ 18 years) with AKI defined by The Kidney Disease Improving Global Outcomes (KDIGO) criteria. The KDIGO criteria were description as follows[11]: (1) SCR increased by 0.3mg/dL(or ≥ 26.5 μmol/L) within 48h; or (2) rised to ≥ 1.5-fold from baseline within the prior 7 days; and/or (3) a decrease in urine output (UO) < 0.5ml/kg/h for 6-12h. Patients without BE value when admitted to ICU and those who were discharged or died within 48 h after ICU admission were excluded. If a patient had multiple admission records or ICU stay records, we just take the first admission records and the first ICU stay record of him.

Variables

The variable which we are interested in is baseline BE. Thus, we extracted the first measurement of BE value at ICU admission as baseline BE value. It is the main exposure factor in our study.

Other variables were extracted from MIMIC-IV database for the first day of ICU admission as confounding factors which include: age at the time of hospital admission, gender, admission type, ethnicity, lactate, PH, PO_2, PCO_2, AKI stages were defined by both SCr and the volume of UO during the first 48 h after IUC admission according to KDIGO criteria, comorbidities, simplified Acute Physiology Score II (SAPAII), sequential organ failure assessment (SOFA) score, SCr level, urine output (UO), use of vasopressors, renal

replacement therapy(RRT), and mechanical ventilation. All these variables were extracted from MIMIC-IV by postgreSQL.

Endpoints

The primary endpoint was 30-day ICU mortality which was defined by the status of patient survival at the time of hospital discharge. Besides, ICU mortality, the in-hospital mortality, length of stay (LOS) in ICU, LOS in hospital was regarded as secondary endpoints.

Missing data

In the present study, all variables had less than 20% missing values. Multiple imputation[12] was used to impute missing values in variables including lactate, urine output, creatinine.

Statistical analysis

Descriptive statistics were used to present the differences between characteristics across five groups of baseline BE value (BE ≤ -9mmol/L, -9 mmol/L < BE≤-3 mmol/L, -3 mmol/L < BE ≤ 3 mmol/L, 3 mmol/L < BE ≤ 9, mmol/L and BE 9 mmol/L). Continuous variables were presented as mean ± standard deviation or median(IQR), and the differences between groups were identified with Analysis of variance(ANOVA) or Kruskal-Wallis test. Categorical variables were presented as percentages, and comparisons between groups were made using the chi-square test or Fisher's exact test.

Cox proportional-hazards model was used to estimate the association between predefined groups according to baseline BE values and outcomes among critically ill patients with AKI. The model was adjusted by multiple covariates which have P value < 0.05 in univariate analysis.

In consideration of the hypothesis that the relationship between BE and risk of 30-day hospital mortality was nonlinear, we further performed Cox models with restricted cubic splines (RCS)[13–15], with five knots (the 10th, 25th, 50th, 75th, and 90th percentiles) for BE adjusting for all covariates above to flexibly model the association of baseline BE values with mortality. We also used a likelihood ratio test to examine the non-linearity comparing the model with only linear term and with linear and cubic spline terms.

All statistical analysis were performed using R software(version4.0.0). All reported P values were two-sided, and P < 0.05 was regarded as statistically significant.

Results

A total of 18855 patients fulfilled the definition of AKI. And 14238 patients whose ICU time more than 2 days had the BE value within 24 h after ICU admissions. The study flow diagram was shown in Fig. 1.

Baseline characteristics for the five BE groups are depicted in Table 1. Compared with normal group (-3mmol/L < BE ≤ 3 mmol/L), those with lower BE values tended to be female, younger, and the values of lactate, creatinine, SOFA score, SAPSII were higher, while the pH value, PO_2, PCO_2, and urine output were lower. And the proportions of using vasopressor and RRT were also higher. Patients with higher BE values

tended to be female, older, and have lower value on lactate, PO_2. These patients had higher value on Ph, PCO_2, SOFA, SAPSII, and tended to use less vasopressor, ventilation, and more likely have co-morbidities such as congestive heart failure, chronic pulmonary disease, etc.

Table 1
Baseline characteristics between BE groups

	BE≤-9	-9 < BE≤-3	-3 < BE ≤ 3	3 < BE ≤ 9	BE > 9	P value
	N = 1369	N = 3041	N = 8037	N = 1543	N = 248	
Gender: Male	747 (54.6%)	1762 (57.9%)	4834 (60.1%)	812 (52.6%)	106 (42.7%)	<0.001
Age	62.4 (17.1)	64.8 (17.3)	67.5 (15.1)	68.8 (14.9)	69.6 (14.5)	<0.001
AKI stage:						<0.001
1	170 (12.4%)	502 (16.5%)	1772 (22.0%)	283 (18.3%)	45 (18.1%)	
2	427 (31.2%)	1324 (43.5%)	4267 (53.1%)	799 (51.8%)	127 (51.2%)	
3	772 (56.4%)	1215 (40.0%)	1998 (24.9%)	461 (29.9%)	76 (30.6%)	
Ethnicity						<0.001
BLACK	152 (11.1%)	255 (8.39%)	560 (6.97%)	143 (9.27%)	22 (8.87%)	
OTHER	443 (32.4%)	911 (30.0%)	2027 (25.2%)	351 (22.7%)	63 (25.4%)	
WHITE	774 (56.5%)	1875 (61.7%)	5450 (67.8%)	1049 (68.0%)	163 (65.7%)	
Admission type						<0.001
Elective	137 (10.0%)	384 (12.6%)	1380 (17.2%)	241 (15.6%)	26 (10.5%)	
Emergency	919 (67.1%)	1805 (59.4%)	3515 (43.7%)	693 (44.9%)	141 (56.9%)	
Emergency surgery	37 (2.70%)	186 (6.12%)	1312 (16.3%)	155 (10.0%)	7 (2.82%)	
urgent	276 (20.2%)	666 (21.9%)	1830 (22.8%)	454 (29.4%)	74 (29.8%)	
Lactate	5.19 (3.95)	2.69 (2.34)	1.72 (0.96)	1.46 (0.77)	1.29 (1.20)	0.000
Ph	7.17 (0.12)	7.31 (0.07)	7.39 (0.07)	7.43 (0.08)	7.42 (0.11)	0.000
po2	163 (113)	166 (115)	219 (142)	200 (141)	132 (114)	<0.001
pco2	40.2 (16.0)	41.0 (11.5)	41.9 (10.6)	48.1 (15.9)	67.6 (23.3)	<0.001

	BE≤-9	-9 < BE≤-3	-3 < BE ≤ 3	3 < BE ≤ 9	BE > 9	P value
Urine output	1409 (1588)	1595 (1235)	1734 (1098)	1716 (1227)	2009 (1540)	<0.001
SOFA	10.8 (4.20)	8.36 (4.01)	6.39 (3.39)	6.40 (3.38)	6.48 (3.40)	0.000
SAPSII	51.8 (15.6)	45.2 (15.0)	39.3 (13.0)	39.6 (12.3)	40.1 (12.9)	<0.001
Creatinine	2.55 (2.46)	1.88 (1.93)	1.24 (1.14)	1.32 (1.41)	1.19 (1.06)	<0.001
RRT	219 (16.0%)	197 (6.48%)	274 (3.41%)	88 (5.70%)	7 (2.82%)	<0.001
vasopressor	286 (20.9%)	249 (8.19%)	344 (4.28%)	60 (3.89%)	7 (2.82%)	<0.001
ventilation	348 (25.4%)	1074 (35.3%)	3651 (45.4%)	696 (45.1%)	102 (41.1%)	<0.001
Co-morbidities						
Myocardial infarct	306 (22.4%)	640 (21.0%)	1582 (19.7%)	284 (18.4%)	34 (13.7%)	0.003
Congestive heart failure	395 (28.9%)	941 (30.9%)	2478 (30.8%)	711 (46.1%)	144 (58.1%)	<0.001
Cerebrovascular disease	161 (11.8%)	431 (14.2%)	1532 (19.1%)	224 (14.5%)	24 (9.68%)	<0.001
Chronic pulmonary disease	327 (23.9%)	743 (24.4%)	2146 (26.7%)	627 (40.6%)	153 (61.7%)	<0.001
Peptic ulcer disease	61 (4.46%)	104 (3.42%)	159 (1.98%)	29 (1.88%)	7 (2.82%)	<0.001
Mild liver disease	363 (26.5%)	543 (17.9%)	878 (10.9%)	161 (10.4%)	18 (7.26%)	<0.001
diabetes	453 (33.1%)	957 (31.5%)	2430 (30.2%)	530 (34.3%)	88 (35.5%)	0.005
Renal disease	345 (25.2%)	767 (25.2%)	1558 (19.4%)	370 (24.0%)	46 (18.5%)	<0.001
Malignant cancer	161 (11.8%)	443 (14.6%)	953 (11.9%)	176 (11.4%)	28 (11.3%)	0.002
Severe liver disease	177 (12.9%)	262 (8.62%)	413 (5.14%)	80 (5.18%)	5 (2.02%)	<0.001
Metastatic solid tumor	70 (5.11%)	197 (6.48%)	393 (4.89%)	97 (6.29%)	13 (5.24%)	0.009

	BE≤-9	-9 < BE≤-3	-3 < BE ≤ 3	3 < BE ≤ 9	BE > 9	P value
AIDS	11 (0.80%)	21 (0.69%)	31 (0.39%)	2 (0.13%)	2 (0.81%)	0.010
The rates of missing values for lactate, urine output, and creatinine are 11.72%,1.55%,0.01% respectively.						

Table 2 showed the association of BE with all-cause mortality in patients with AKI. In the unadjusted model (Model 1), compared with the normal group, the hazard ratio (95%CI) of the first, second, fourth, and fifth baseline BE group were 1.57(1.40,1.76),1.26(1.14,1.39),0.97(0.83,1.12),1.53(1.17,2.02) respectively. And in the multivariable adjusted model (Model 3), the baseline BE showed an U-shaped association with 30-day ICU all-cause mortality. We can observed in the model 3, the third group(-3 mmol/L < BE ≤ 3 mmol/L) had the lowest HR, and the fifth group had the highest HR(1.54,95%CI:1.16,2.05). The HRs(95%CI) of the first, second, fourth, and fifth group were 1.29(1.13,1.47), 1.12(1.01,1.24), 1.00 (0.86,1.17), respectively.

Table 2
HR of 30-day hospital mortality according to BE in patients with AKI

BE value	N	events	Hazard ratio(95%CI)					
			Model 1	P	Model 2	P	Model 3	P
BE≤-9	1369	389	1.57(1.40,1.76)	< 0.01	1.71(1.53,1.92)	< 0.01	1.29(1.13,1.47)	< 0.01
-9 < BE≤-3	3041	584	1.26(1.14,1.39)	< 0.01	1.31(1.19,1.45)	< 0.01	1.12(1.01,1.24)	0.04
-3 < BE ≤ 3	8037	965	Reference					
3 < BE ≤ 9	1543	197	0.97(0.83,1.12)	0.64	0.94(0.81,1.09)	0.43	1.00(0.86,1.17)	0.99
BE > 9	248	54	1.53(1.17,2.02)	< 0.01	1.46(1.11,1.92)	< 0.01	1.54(1.16,2.05)	< 0.01
Model 1: unadjusted model. Model 2: adjusted for age and gender. Model 3: adjusted by gender, age, ethnicity, AKI stage, PCO_2, Co-morbidities, urine output, SOFA, SAPSII, RRT, vasopressor, ventilation, Creatinine								

Table 3

Multiple Cox regression* result for secondary outcomes according to BE groups in patients with AKI

BE(mmol/L)	ICU mortality			In-hospital mortality		
	N(event)	HR (95%CI)*	P	n(event)	HR (95%CI)*	P
BE≤-9	1369(376)	1.33(1.15,1.52)	< 0.01	1369(426)	1.27(1.12,1.44)	< 0.01
-9 < BE≤-3	3041(546)	1.16(1.04,1.30)	< 0.01	3041(658)	1.10(1.00,1.22)	0.06
-3 < BE ≤ 3	8037(858)	reference		8037(1093)	reference	
3 < BE ≤ 9	1543(174)	0.98(0.83,1.16)	0.85	1543(216)	1.02(0.88,1.18)	0.83
BE > 9	248(43)	1.43(1.04,1.97)	0.03	248(55)	1.60(1.21,2.12)	< 0.01

* Adjusted by gender, age, ethnicity, AKI stage, PCO_2, Co-morbidities, urine output, SOFA, SAPSII, RRT, vasopressor, ventilation, creatinine

Table 4

Multiple linear regression* results examining the effect of BE in patients with AKI

BE value	N	LOS of ICU			LOS of hospital		
		Median (IQR)**	β	P value	Median (IQR)**	β	P value
BE≤-9	1369	6.12(3.54,11.0)	0.65	< 0.01	11.8(6.47,20.40)	0.75	< 0.01
-9 < BE≤-3	3041	5.03(3.14,9.31)	0.48	< 0.01	10.9(6.61,17.90)	1.23	0.06
-3 < BE ≤ 3	8037	4.07(2.80,7.21)	reference		8.36(5.65,14.60)	reference	
3 < BE ≤ 9	1543	4.64(2.95,8.16)	0.41	0.03	9.07(6.14,15.00)	0.01	0.78
BE > 9	278	4.21(2.96,8.82)	-0.15	0.74	9.35(5.80,14.70)	-0.03	0.98

* Adjusted by gender, age, ethnicity, AKI stage, PCO2, Co-morbidities, urine output, SOFA, SAPSII, RRT, vasopressor, ventilation, Creatinine ** By Kruskal-Wallis H test, P value less than 0.05

Table 5
HR of 30-day ICU mortality according to BE among Subgroups

Subgroups	Hazard ratio(95%CI)				
	BE≤-9mmol/L	-9 < BE≤-3 mmol/L	-3 < BE ≤ 3 mmol/L	3 < BE ≤ 9 mmol/L	BE > 9 mmol/L
Male					
N(event)	747(215)	1762(342)	4834(573)	812(99)	106(21)
adjusted HR(95%CI)	1.27(1.07,1.52)	1.12(0.97,1.29)	Reference	1.01(0.81,1.26)	1.36(0.87,2.12)
P value	< 0.01	0.12		0.93	0.17
Female					
N(event)	622(190)	1279(272)	3203(457)	731(107)	142(33)
adjusted HR(95%CI)	1.30(1.07,1.58)	1.11(0.95,1.30)	Reference	0.98(0.79,1.22)	1.66(1.14,2.42)
P value	< 0.01	0.20		0.88	< 0.01
AKI stage is 1,2					
N(event)	597(107)	1826(227)	6039(516)	1082(102)	172(24)
adjusted HR(95%CI)	1.39(1.10,1.74)	1.20(1.02,1.41)	Reference	1.08(0.87,1.35)	1.45(0.94,2.24)
P value	< 0.01	0.03		0.47	0.09
AKI stage is 3					
N(event)	772(298)	1215(387)	1998(514)	461(104)	76(30)
adjusted HR(95%CI)	1.23(1.05,1.44)	1.07(0.93,1.23)	Reference	0.94(0.76,1.16)	1.67(1.14,2.43)
P value	0.01	0.32		0.55	< 0.01
SOFA ≥ 10					
N(event)	747(215)	1762(342)	4834(573)	812(99)	106(21)
adjusted HR(95%CI)	1.16(0.99,1.37)	1.12(0.97,1.31)	Reference	0.74(0.55,0.99)	1.18(0.72,1.94)
P value	0.07	0.12		0.04	0.51
7 ≤ SOFA < 10					
N(event)	280(78)	839(138)	2084(301)	392(64)	66(18)
adjusted	1.78(1.37,2.32)	1.11(0.91,1.37)	Reference	1.10(0.84,1.46)	2.10(1.27,3.48)

HR(95%CI)					
P value	< 0.01	0.33		0.47	< 0.01
4 ≤ SOFA < 7					
N(event)	191(25)	788(102)	2992(264)	570(69)	90(11)
adjusted HR(95%CI)	2.16(1.40,3.31)	1.33(1.05,1.69)	Reference	1.26(0.96,1.67)	1.41(0.73,2.70)
P value	< 0.01	0.02		0.10	0.30
SOFA2 < 4					
N(event)	53(3)	303(20)	1592(106)	307(20)	45(8)
adjusted HR(95%CI)	1.93(0.59,6.30)	1.29(0.78,2.11)	Reference	1.06(0.64,1.77)	3.66(1.55,8.62)
P value					
SAPS II ≥ 40					
N(event)	1066(367)	1895(511)	3584(695)	719(125)	115(37)
adjusted HR(95%CI)	1.33(1.16,1.53)	1.18(1.05,1.33)	Reference	0.89(0.73,1.08)	1.51(1.07,2.12)
P value	< 0.01	< 0.01		0.23	0.02
SAPS II < 40					
N(event)	303(38)	1146(103)	4453(335	824(81)	133(17)
adjusted HR(95%CI)	1.48(1.03,2.11)	1.07(0.85,1.34)	Reference	1.27(0.99,1.64)	1.89(1.12,3.20)
P value	0.03	0.58		0.06	0.02

Furthermore, we used restricted cubic spline to flexibly model and visualized the relationship of baseline BE value with 30-day ICU all-cause mortality. In the restricted quadratic spline regression model, base excess was taken as a continuous variable. In the Fig. 2A, the univariate analysis showed that the risk of 30-day ICU all-cause mortality was decreasing until 1 mmol/L and became more steeply when baseline BE value exceeded − 5 mmol/L. We observed the lowest HR when baseline BE value was 3 mmol/L and the risk started to increase afterwards (P for non-linearity < 0.01). We can also draw a conclusion that when baseline BE value in the range of 0 mmol/L to 5 mmol/L was a protective factor(HR < 1). And when the BE value was out of this range, it was a risk factor(HR > 1). The result in multivariate analysis (Fig. 2B) was similar. The risk of mortality was decreasing and reached the lowest HR when BE was 3 mmol/L, and then started to increase afterwards (P for non-linearity < 0.01).

The result of secondary endpoints was shown in table 3 and table 4. The risk of ICU mortality, and risk of in-hospital mortality also showed the U-shaped relationships. The median of LOS in ICU and LOS in hospital were significant different between groups. Patients in normal group (-3 mmol/L < BE ≤ 3 mmol/L) showed

shortest LOS in ICU and LOS in hospital(4.07 days,8.36 days respectively). Both lower and higher BE would increase the LOS in ICU or in hospital. Multiple linear regression results showed that (Table 4), compared with the normal group, the first, second, fourth group would increase the LOS of ICU by 0.65 day, 0.48day, 0.41day respectively. As for the LOS of hospital, the first group would increase 0.75 day. And other groups had no significant difference.

Subgroup analysis

Subgroup analysis were based on the following strata: gender (female vs male), AKI stage (stage3 vs stage1, 2), SOFA score(SOFA ≥ 10, 7 ≤ SOFA < 10, 4 ≤ SOFA < 7, SOFA < 4), SAPS II score. We divided patients into four subgroups according to quartile of SOFA score. Besides, we also divided patients into two groups according the median of SAPS II (median = 40). In almost subgroups, when BE was in the range of -3 mmol/L to 9 mmol/L, the patients had the lowest risk for mortality, and the patients of fifth BE group (BE > 9mmol/L) had the highest risk (Table 5). The similar trends of non-linear association between BE and all-cause mortality were presented in Fig. 3. After using multiple Cox model with RCS, BE showed U-shape relationship with all-cause mortality in most subgroups (except SOFA ≥ 10 subgroup). The results of subgroup analysis for secondary endpoints were shown in table S1-S4 (supplement material).

Discussion

Base excess was considered to be among the most widely used markers in IUC, both to diagnose metabolic acidosis by steps and to guide resuscitation or clinical intervention[16].In this study, we explored the U-shape relationship between BE and all-cause mortality in ICU patients with AKI. Patients with AKI in ICU had the lowest hazard for mortality when BE is in the rage of -3mmol/L to 9 mmol/L. Both higher or lower BE would increase the hazard.

BE is convenient and intuitive to reflect acid-based status in ICU setting. There were plenty of studies focusing on base excess as one of the most essential indicators in ICU setting. For patients with trauma, the use of base excess appeared to be better than vital signs or shock index for mortality prediction or rapid physiological assessment[17]. A systematic review involving 34 studies about trauma patients consistently showed BE was associated with increasing mortality, significant injuries, and major complications[18].

The use of base excess has also been studied extensively in burn. A prospective study including 42 major burn patients suggested that base deficit (BD, which is equal to -BE), as well as serum albumin level, hemoglobin concentration, were independent predictors for mortality among burn patients[19]. Binary logistic regression analysis declared that the odd ratio of base deficit is 2.23(95%CI: 1.66–16.75). Furthermore, BE was also used in newborns and children, such as prediction to early diagnosis of neonatal sepsis.

The vital role of BE in prognosis and prediction had been demonstrated in many diseases. In order to sought to determine the prognostic value of BE on admission in patients with acute heart failure (AHF), Hiroki Nakano[4] concluded that high BE was an independent determinant of all-cause death for AHF patients. Similarly, the unadjusted spline curve revealed a U-shaped relationship between BE and risk of all-cause

death. In multivariable RCS model, there was a positive linear relation. Another study also showed the U-shaped relationship between BE and survival outcome in patients with congestive heart failure[3].

As for AKI, the relationship between BE and all-cause mortality was more complex. The kidney played a vital role in maintaining electrolyte homeostasis and acid-base balance. Acid-base disorder was not only a consequence, but a contributor to the progression of kidney dysfunction.

As the U-shaped curve showed, lower BE (≤ -3 mmol/L) which indicated metabolic acidosis would increase the risk of all-cause mortality for AKI patients. The result was consistent with other study[20] which suggested that metabolic acidosis was an independent risk factor for the development of AKI and hospital mortality. The mechanisms may be explained that acidosis can reduce renal blood flow and increase inflammatory mediator release[21]. Another study [22] demonstrated that hyperchloremic acidosis was associated with postoperative AKI after abdominal surgery. AKI patients with severe metabolic alkalosis (BE > 9mmol/L), just showed in the U-shaped curve, had higher risk of all-cause death. Significant metabolic alkalosis was rare in AKI, and was related to diuretic use, red blood cells or fresh frozen plasma administration, RRE, and so on. [23]

The results of subgroups according to SOFA or SAPS II showed that the risk of mortality was monotonic decreasing when SOFA > 10, and the risk of mortality was also showed U shaped when 4 < SOFA < 7, 7 < SOFA < 10,SAPS II ≥ 40 and SAPS < 40. When SOFA less than 4, there showed no significant U-shaped relationship (Fig. 3). Some researches recommended that organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points[24,25]. And several studies also showed that patients with SAPS II greater than 80 had higher survival rate[26,27]. However, if we divided patients into subgroups by SOFA (≥ 2 or < 2), SAPS II(> 80 or ≤ 80), there would be less sample size in one group and get the inaccuracy results. Therefore, we divided subgroups by median or quartile.

The limitations of this study should be clarified. First, BE remains a convenient and sensitive indicator for metabolic acid-base status, but it is not consistent with other markers such as lactate, bicarbonate or anion gap[28]. Thus, clinicians should be careful and take these markers into consideration comprehensively. Besides, AKI can influence the acid-base imbalance, in turn; acid-base status can also be the result of therapies of deteriorating renal function, such as fluid resuscitation, use of diuretic, RRT. Thus, for prerenal kidney disease, BE was appropriate to measure the acid-base status. In contrast, for renal of postrenal kidney disease, BE had minimal utility. For example, when patients on RRT in ICU setting, BE only reflected the concentration of bicarbonate buffer and the duration of treatment. Furthermore, we just considered the first measurement of BE at administration, regardless of the influence of dynamic variation in BE. In the follow-up study, we would build Joint Model for longitudinal and time-to-event data[29,30] to control measurement error, and explore the effect of BE variation in risk of all-cause death for AKI patients.

Conclusions

BE could be an independent factor for risk of all-cause death in AKI patients in ICU setting. Abnormal BE could be risk factor for these patients. We also found a U-shaped association between baseline BE and all-

cause mortality in AKI patients. No matter lower (BE ≤ -3 mmol/L) or higher (BE ≥ 9 mmol/L), BE can increase risk of 30-day ICU mortality for AKI patients. Thus, BE measured at administration could be a good indicator to reflect the severity of illness and provide guidance for clinicians.

Abbreviations

AKI
acute kidney injury; BE:base excess; RCS:restrict cubic splines; ICU:intensive care unit; CKD:chronic kidney disease; RRT:renal replacement therapy; KDIGO:the Kidney Disease Improving Global Outcomes; SAPSII:simplified Acute Physiology Score II; SOFA:sequential organ failure assessment; UO:urine output; LOS:length of stay; ANOVA:Analysis of variance;

Declarations

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Not applicable.

Authors' contributions

YC, YyQ and CW designed the study and wrote the manuscript. YjT, BxT, WG and XC performed the statistical analysis. RQ, DdL, YfZ, SyW and RhZ collected the study data. All authors participated in writing and revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

An author who had finished the Collaborative Institutional Training Initiative examination (Certification number 39090498 for author YY Qin) can access the MIMIC-IV database.

Consent for publication

All authors have given their consent for publication.

Competing interests

All the authors have not disclosed any potential competing interests.

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References

1. Gameiro J, Carreiro C, Fonseca JA, et al. Acute kidney disease and long-term outcomes in critically ill acute kidney injury patients with sepsis: a cohort analysis. *Clin Kidney J.* May 2021;14(5):1379-1387.

2. Horne KL, Packington R, Monaghan J, Reilly T, Selby NM. Three-year outcomes after acute kidney injury: results of a prospective parallel group cohort study. *BMJ Open.* Mar 29 2017;7(3):e015316.

3. Guo W, Peng C, Liu Q, et al. Association between base excess and mortality in patients with congestive heart failure. *ESC Heart Fail.* Feb 2021;8(1):250-258.

4. Nakano H, Nagai T, Honda Y, et al. Prognostic value of base excess as indicator of acid-base balance in acute heart failure. *Eur Heart J Acute Cardiovasc Care.* Aug 2020;9(5):399-405.

5. Arayici S, Simsek GK, Canpolat FE, Oncel MY, Uras N, Oguz SS. Can Base Excess be Used for Prediction to Early Diagnosis of Neonatal Sepsis in Preterm Newborns? *Mediterr J Hematol Infect Dis.* 2019;11(1):e2019014.

6. Eng OS, Dumitra S, O'Leary M, et al. Base Excess as a Predictor of Complications in Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy. *Ann Surg Oncol.* Sep 2017;24(9):2707-2711.

7. Wu H, Hong X, Qu Y, et al. The value of oxygen index and base excess in predicting the outcome of neonatal acute respiratory distress syndrome. *J Pediatr (Rio J).* Aug 19 2020.

8. Smith I, Kumar P, Molloy S, et al. Base excess and lactate as prognostic indicators for patients admitted to intensive care. *Intensive Care Med.* Jan 2001;27(1):74-83.

9. Novak V, Hu K, Desrochers L, et al. Cerebral flow velocities during daily activities depend on blood pressure in patients with chronic ischemic infarctions. *Stroke.* Jan 2010;41(1):61-66.

10. Goldberger A, L. Amaral, L. Glass J, et al. PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals. *Circulation [Online].* 2000;101(23):e215–e220.

11. Ricci Z, Romagnoli S. Acute Kidney Injury: Diagnosis and Classification in Adults and Children. *Contrib Nephrol.* 2018;193:1-12.

12. Zhang Z. Missing data imputation: focusing on single imputation. *Ann Transl Med.* Jan 2016;4(1):9.

13. Qin Y, Wei X, Han H, et al. Association between age and readmission after percutaneous coronary intervention for acute myocardial infarction. *Heart.* Oct 2020;106(20):1595-1603.

14. Lee DH, Keum N, Hu FB, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. *BMJ.* Jul 3 2018;362:k2575.

15. Bhaskaran K, dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. *The Lancet Diabetes & Endocrinology.* 2018;6(12):944-953.

16. Berend K. Diagnostic Use of Base Excess in Acid-Base Disorders. *N Engl J Med.* Apr 12 2018;378(15):1419-1428.

17. Dunham MP, Sartorius B, Laing GL, Bruce JL, Clarke DL. A comparison of base deficit and vital signs in the early assessment of patients with penetrating trauma in a high burden setting. *Injury.* Sep 2017;48(9):1972-1977.

18. Ibrahim I, Chor WP, Chue KM, et al. Is arterial base deficit still a useful prognostic marker in trauma? A systematic review. *Am J Emerg Med.* Mar 2016;34(3):626-635.

19. Megahed M.A. E-HRH, * Gad S.S., Mansour M.M., Elkandary K.A. Base Deficit, Serum Albumin Level And Blood Haemoglobin Concentration Can Be Used As Predictor Factors For Mortality In Major Burn Patients. *Ann Burns Fire Disasters.* 2020;33:209-245.

20. Hu J, Wang Y, Geng X, et al. Metabolic acidosis as a risk factor for the development of acute kidney injury and hospital mortality. *Exp Ther Med.* May 2017;13(5):2362-2374.

21. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg.* Jul 2012;256(1):18-24.

22. Toyonaga Y KM. Hyperchloremic acidosis is associated with acute kidney injury after abdominal surgery. *Nephrology (Carlton).* 2017;22:720-727.

23. Claure-Del Granado R, Bouchard J. Acid-base and electrolyte abnormalities during renal support for acute kidney injury: recognition and management. *Blood Purif.* 2012;34(2):186-193.

24. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama.* 2016;315(8).

25. Alan E. Jones M, Stephen Trzeciak, MD, MPH, Jeffrey A. Kline, MD. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Critical Care Medicine.* 2009;37(9):1649-1654.

26. Myung Jin Choi M, * Sang Ook Ha, MD,* Hyoung Soo Kim, MD, PhD, Sunghoon Park, MD, PhD, Sang Jin Han, MD, and Sun Hee Lee, APN. The Simplified Acute Physiology Score II as a Predictor of Mortality in Patients Who Underwent Extracorporeal Membrane Oxygenation for Septic Shock. *Annals of Thoracic Surgery.* 2016.

27. Kim KI, Lee HS, Kim HS, et al. The pre-ECMO simplified acute physiology score II as a predictor for mortality in patients with initiation ECMO support at the emergency department for acute circulatory and/or respiratory failure: a retrospective study. *Scand J Trauma Resusc Emerg Med.* Aug 17 2015;23:59.

28. Juern J, Khatri V, Weigelt J. Base excess: a review. *J Trauma Acute Care Surg.* Jul 2012;73(1):27-32.

29. Rizopoulos D. Joint Models for Longitudinal and Time-to-Event Data. 2012.

30. Robert M.Elashoff GL, Ning Li. Joint Modeling of Longitudinal and Time□to□Event Data. 2017.

Figures

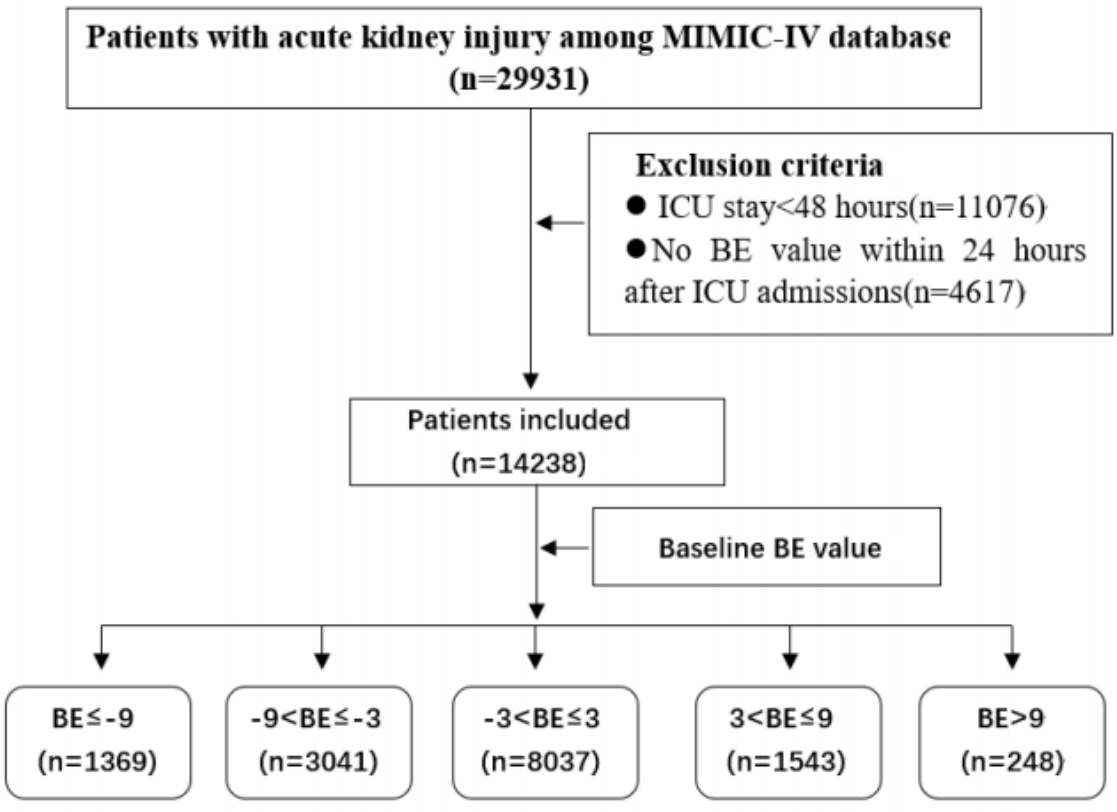

Figure 1

Flowchart of patient selection

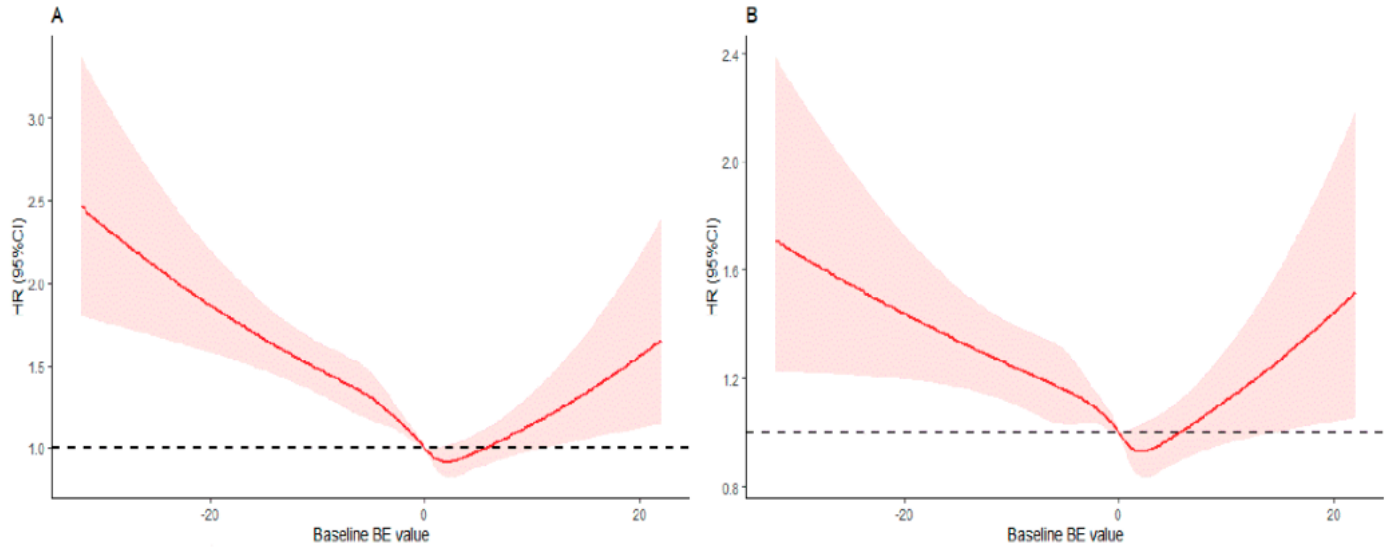

Figure 2

hazard ratio of all-cause mortality as a function of baseline BE value. (A) Baseline BE was modelled as a continuous variable and fitted in an unadjusted model using restricted quadratic spline regression. (B) Baseline BE was modelled as a continuous variable and adjusted by gender, age, ethnicity, AKI stage, PCO2, Co-morbidities, urine output, SOFA, SAPSII, RRT, vasopressor, ventilation, Creatinine.

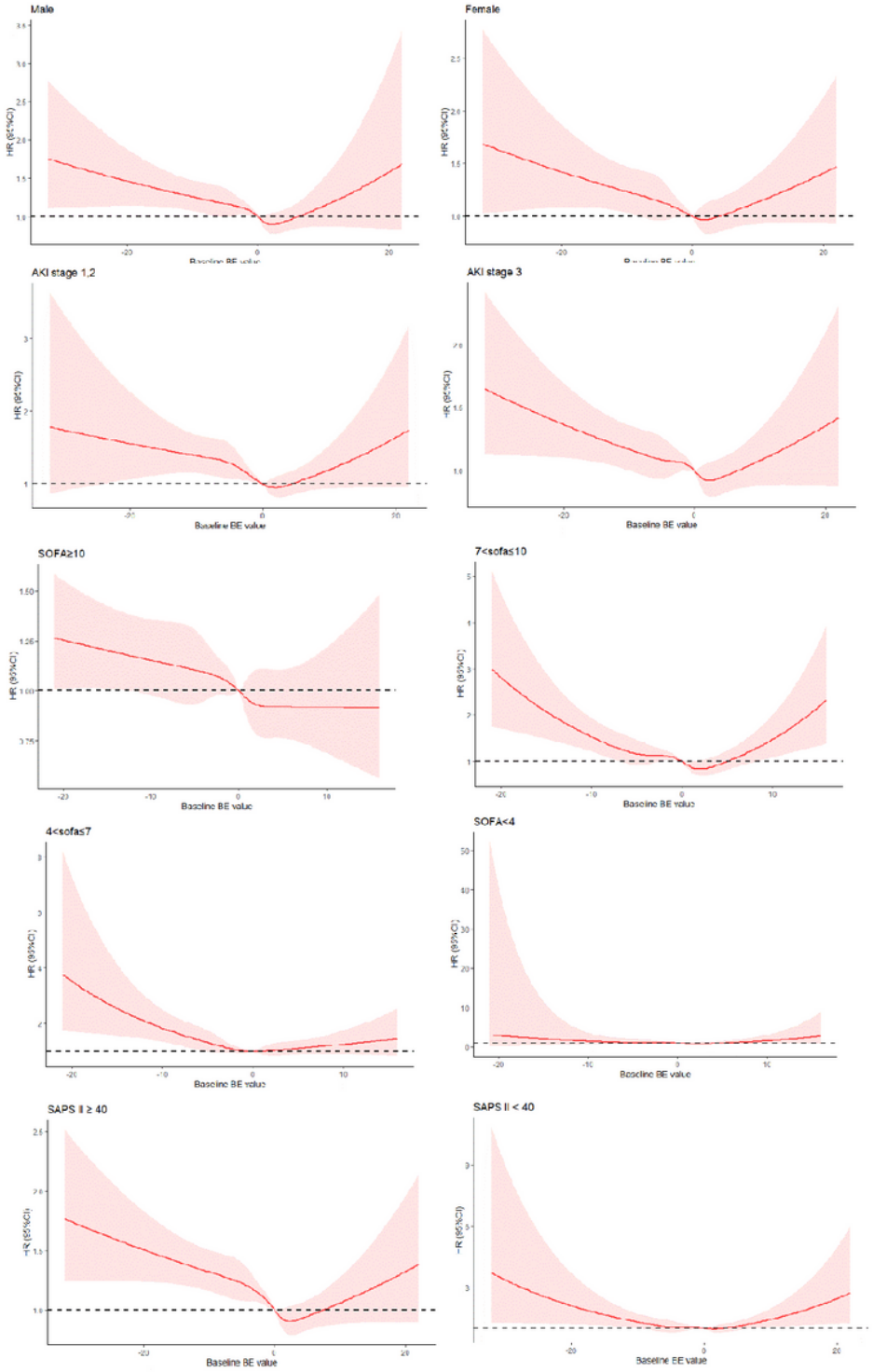

Figure 3

Risk of all-cause mortality according to BE among four subgroups (gender, AKI stage, SOFA, SAPS II)

Supplementary Files

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