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Research article

Association between base excess and 28-day mortality in sepsis patients: A secondary analysis based on the MIMIC- IV database

Jia Yuan [a], Xu Liu [a], Ying Liu [a], Wei Li [a], Xianjun Chen [a], Qiming Chen [a], Chuan Xiao [a], Ying Wan [b], Shuwen Li [a], Qing Li [a], Lu Li [a], Juan He [a], Lu Chen [b], Feng Shen [a,*]

[a] Department of Intensive Care Unit, The Affiliated Hospital of Guizhou Medical University, Guiyang, 550001, Guizhou Province, China
[b] Department of Good Clinical Practice, The Affiliated Hospital of Guizhou Medical University, Guiyang, 550001, Guizhou Province, China

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ABSTRACT

Objective: The relationship between base excess (BE) and 28-day death in sepsis patients remains to be elucidated. The aim of our clinical study is to explore the association of BE with 28-day mortality in patients with sepsis by using a large sample, multicenter Medical Information Mart for Intensive Care IV (MIMIC-IV) database.

Methods: We extracted the data of 35,010 patients with sepsis from the MIMIC-IV database, in which we used BE as an exposure variable and the 28-day mortality as an outcome variable, respectively, so as to explore the impact of BE on the 28-day mortality of patients with sepsis after adjusting for covariates.

Results: BE and the 28-day mortality of patients with sepsis appeared to have a U-shaped relationship. The calculated inflection points were −2.5 mEq/L and 1.9 mEq/L, respectively. Our data demonstrated that BE was negatively associated with 28-day mortality in the range of −41.0 mEq/L to −2.5 mEq/L (odds ratio: 0.95; 95% confidence intervals (95%CI): 0.93 to 0.96), $p < 0.0001$. When BE was in the range of 1.9 mEq/L to 55.5 mEq/L, however, a positive association existed between BE and 28-day mortality of patients with sepsis (odds ratio: 1.03; 95% CI: 1.00 to 1.05; $p < 0.05$).

Conclusion: The BE levels have a U-shaped relationship with the 28-day mortality in patients with sepsis, in which the mortality of patients will gradually decrease with a BE value from −41.0 mEq/L to −2.5 mEq/L, while the mortality will increase with a BE value from 1.9 mEq/L to 55.5 mEq/L.

1. Introduction

Sepsis is now defined as a series of life-threatening organ dysfunction symptoms resulting from a dysregulated host response to infection [1]. Sepsis is one of the leading causes of inpatient mortality worldwide [2,3], and its prevalence has been steadily increasing in recent years [4–6]. According to epidemiological data, the global number of sepsis patients still exceeds 30 million per year, with an overall mortality rate of 17% [7]. A recent study based on adult hospitalization data from seven high-income countries found that the

Abbreviations: BE, base excess; MIMIC-IV, Medical Information Mart for Intensive Care IV; ICU, intensive care unit; ICD, International Classification of Diseases; SOFAscore, Sequential Organ Failure Assessment score; GAM, generalized additive model.

* Corresponding author.
E-mail address: doctorshenfeng@gmc.edu.cn (F. Shen).

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annual incidence of sepsis was 19.4 million, and sepsis was responsible for about 5.3 million patient deaths [3].

Despite significant efforts to discover novel medications and recognize the root cause of sepsis, the mortality of sepsis has unfortunately not decreased [4,8]. One of the bottlenecks is a lack of reliable models to anticipate the prognosis of sepsis and thus provide a platform for prognostic enrichment, resulting in clinical trials of new medicines lacking sufficient power. However, clarifying the true relationship between the predictors in the model and the outcome is a precondition for creating a reliable performance prediction model. Base excess (BE) is the exposure variable of interest in this study, which is defined as the quantity of acid or base necessary to return the pH value to the normal range. It is one of the indicators that responds to acid-base imbalance and is therefore often monitored in the agenda of intensive care unit (ICU) [9]. As we know, pH is influenced by respiratory and metabolic factors, making it not always fully reflect the true acid-base state. In contrast, BE value that will not be impacted by respiratory factor is a pure indicator reflecting metabolic acid-base balance [10], and it is associated with the severity of sepsis and therefore could be used as a marker of risk stratification in patients with sepsis. Lactate is a factor reflecting tissue perfusion, but it alone cannot fully explain the real situation of metabolic acidosis resulting from systemic hypoperfusion [11]. Studies have shown that BE reduction is superior to hyperlactatemia in predicting ICU mortality in patients undergoing heart surgery [12]. Reduced BE values, as compared to pH and lactate, could offer a more accurate estimate of metabolic acidosis related to systemic hypoperfusion in patients with severe sepsis [13,14]. Many studies have shown that BE is strongly associated with mortality in critically ill patients, such as those with chronic heart failure [9], trauma [15], acute kidney injury [16], and acute myocardial infarction [17]. However, there is a lack of evidence regarding the association between BE and a poor prognosis in sepsis. Given that sepsis is often combined with metabolic acid-base disorders, we speculate that BE may be associated with a poor prognosis in sepsis.

Therefore, in this study, we used MIMIC-IV, a sizable US multicenter sepsis database, to examine the relationship between BE and the 28-day risk of death from sepsis. The large sample size is beneficial to offer more stable and reliable results to better understand the relationship between BE and the 28-day risk of death in sepsis.

2. Methods

2.1. Description of data sources

The data used in this study were obtained from the MIMIC-IV database [18]. A retrospective cohort study was used to design the database, which collected clinical data from patients seen at Beth Israel Deaconess Medical Center (BIDMC) from 2008 to 2019. The database is available for free download upon completion of an approved course on their official website. After completing the recognized course, author Lu Chen gained access to the database and is responsible for data extraction (Record ID: 50668217). Our study was performed in accordance with the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) [19].

2.2. Queue information

The MIMIC-IV database contained 377,207 adult patient records in total, from which we extracted 35,010 patient records of patients with sepsis. The extraction depended on the International Classification of Diseases, Ninth revision (ICD-9) and International Classification of Diseases, Tenth revision (ICD-10) codes recorded in the database (ICD-9 codes 99,591–99592 or ICD-10 codes R652, R6520 and R6521). The MIMIC-IV database, an update of MIMIC-III, contained data on patients admitted to the BIDMC from 2008 to 2019. The baseline BE, as measured on the first day of ICU admission, was the exposure variable of interest in this investigation. It was recorded as a continuous variable. The outcome variable was 28-day mortality, which was recorded as a dichotomous variable ($Y = 1$, non-survival; $Y = 0$, survival). Patients with missing exposure variable information were not included in this study.

The main covariates we selected were: demographic characteristics (gender, age, ethnicity), vital signs (heart rate, respiratory rate, body temperature), lactate, Charlson comorbidity index, Sequential Organ Failure Assessment score (SOFA score), mechanical ventilation, glucocorticoids (dexamethasone, methylprednisolone, hydrocortisone), vasoactive drugs (dopamine, dobutamine), antibiotics (carbapenems, cephalosporins, penicillin, and vancomycin), immunoglobulins. All covariates are from the first day of ICU admission. The rationale for the selection of these covariates was based mainly on our clinical experience and the literature [20–23].

2.3. Ethics and informed consent statement

The database used in this study was the MIMIC-IV database, available on the Internet. And the database was permitted by the institutional review boards of Beth Israel Deaconess Medical Center in Boston, Massachusetts (2001-P-001699/14), and the Massachusetts Institute of Technology (0403000206). The informed consent was abrogated because the data is public and the patient's personal information is uncertain.

2.4. Missing data description

Since the percentage of missing variables in this study ranged from 0% to 4.1%, multiple interpolation was not employed to fill in the gaps.

2.5. Statistical analysis

Continuous variables are represented by the mean ± standard deviation (Gaussian distribution) or the median (minimum, maximum) (skewed distribution). Categorical variables are expressed in the form of rates. Given that this study was a cohort study, we divided the exposure variables into 4 subgroups (quartile) and looked at the distribution of patient baseline information across subgroups. The One-way ANOVA (Gaussian distribution), Kruskal-Wallis H (skewed distribution) test and chi-square test (categorical variables) were used to determine any statistical differences between the means and proportions of the groups. Univariate and multivariate binary logistic regression models were used to evaluate the association between BE and 28-day mortality. Given that BE is normally distributed (Supplementary Fig. 1), we enter the regression equation directly with BE. We present both the unadjusted model (Model 1), the minimally-adjusted model (adjusted for demographic characteristics only, Model 2), and the fully-adjusted model (adjusted for all covariates presented in Table 1, Model 3) and present odds ratio values (OR) with 95% confidence intervals (95%CI). Additionally, for sensitivity analysis, we transferred BE from a continuous to a categorical variable (Decile) and calculated *p* for trend. The purpose was to see whether the results were robust when BE was used as a continuous variable versus a categorical variable.

Given the limitations of binary logistic regression models to handle non-linear associations, a generalized additive model (GAM) was used to identify the putative non-linear relationship between BE and 28-day mortality. In contrast to the binary logistic regression model, the GAM uses a non-linear smoothing term to fit a non-linear relationship between BE and 28-day mortality (Logit (28-day mortality) = aX1 + S(BE)). The implementation is based on the mgcv package's gam(*) function. Despite the fact that GAM may efficiently fit non-linear relationships, its clinical interpretability is frequently poor. To better interpret the non-linear relationships, we first computed the BE inflection point using a recursive algorithm, then constructed two piecewise linear models on either side of the inflection point and gave OR values and 95% confidence intervals (the glm(*) function in the stats package).

All the analyses were performed with the statistical packages R (http://www.R-project.org, The R Foundation) and Empower Stats (http://www. empowerstats.com, Solutions, Inc., Boston, MA), and *p* values less than 0.05 (two-sided) were considered statistically significant.

3. Results

The MIMIC-IV database contained 377,207 patients, of whom 35,010 sepsis patients remained after excluding 342,197 non-sepsis patients. Among these 35,010 patients with sepsis, 9896 patients with missing BE information were further excluded, leaving 25,114 patients for the final data analysis (see flow chart Fig. 1).

The baseline characteristics of the patients are listed in Table 1. Based on quadratic subgroups, we divided BE into four groups

Table 1
Baseline characteristics of participants.

Base Excess (mEq/L), quartile	Q1 (-41.00–4.00)	Q2 (-3.50–1.50)	Q3 (-1.00-1.00)	Q4 (1.50–55.50)	*P* value
	n = 6279	n = 4832	n = 7669	n = 6334	
Demographics					
Age, mean ± sd, years	64.86 ± 16.47	65.22 ± 15.89	66.45 ± 15.50	67.77 ± 14.93	<0.001
Gender (Female), n (%)	3484 (55.49)	2961 (61.28)	4780 (62.33)	3574 (56.43)	<0.001
Ethnicity (White), n (%)	3878 (61.76)	3204 (66.31)	5235 (68.26)	4387 (69.26)	<0.001
Vital signs					
Heart rate, mean ± sd, beats/min	110.48 ± 26.31	104.01 ± 23.21	102.77 ± 23.38	102.96 ± 23.42	<0.001
Respiratory rate, mean ± sd, beats/min	27.96 ± 9.89	26.07 ± 9.84	26.17 ± 9.84	26.93 ± 9.75	<0.001
Body temperature, mean ± sd, °C	36.47 ± 1.56	36.74 ± 1.35	36.85 ± 1.27	36.86 ± 1.21	<0.001
Lactate, mean ± sd, mmol/L	3.89 ± 3.16	2.32 ± 1.46	1.93 ± 1.01	1.71 ± 0.92	<0.001
Scoring system					
Charlson comorbidity index, mean ± sd, score	6.25 ± 3.10	5.78 ± 2.92	5.77 ± 2.83	6.17 ± 2.81	<0.001
SOFA score, mean ± sd, score	9.81 ± 4.29	7.20 ± 3.59	6.04 ± 3.20	6.06 ± 3.12	<0.001
Mechanical Ventilation, n (%)	4222 (67.24)	3136 (64.90)	4098 (53.44)	3289 (51.93)	<0.001
Glucocorticoids					
Dexamethasone administration, n (%)	528 (8.41)	438 (9.06)	828 (10.80)	729 (11.51)	<0.001
Methylprednisolone administration, n (%)	1161 (18.49)	727 (15.05)	1170 (15.26)	1515 (23.92)	<0.001
Hydrocortisone administration, n (%)	181 (2.88)	68 (1.41)	111 (1.45)	130 (2.05)	<0.001
Vasoactive drugs					
Dopamine administration, n (%)	715 (11.39)	300 (6.21)	405 (5.28)	431 (6.80)	<0.001
Dobutamine administration, n (%)	478 (7.61)	194 (4.01)	232 (3.03)	233 (3.68)	<0.001
Antibiotics					
Carbapenems administration, n (%)	1719 (27.38)	883 (18.27)	1289 (16.81)	1334 (21.06)	<0.001
Cephalosporin administration, n (%)	447 (7.12)	368 (7.62)	629 (8.20)	575 (9.08)	<0.001
Penicillin administration, n (%)	3738 (59.53)	2228 (46.11)	3388 (44.18)	3239 (51.14)	<0.001
Vancomycin administration, n (%)	5585 (88.95)	3865 (79.99)	5914 (77.12)	5274 (83.26)	<0.001
Immunoglobulin administration, n (%)	167 (2.66)	94 (1.95)	155 (2.02)	163 (2.57)	0.011
28-day mortality, n (%)	2116 (33.70)	693 (14.34)	928 (12.10)	934 (14.75)	<0.001

Continuous data (mean ± sd), Categorical data n (%)
SOFA score, Sequential Organ Failure Assessment score

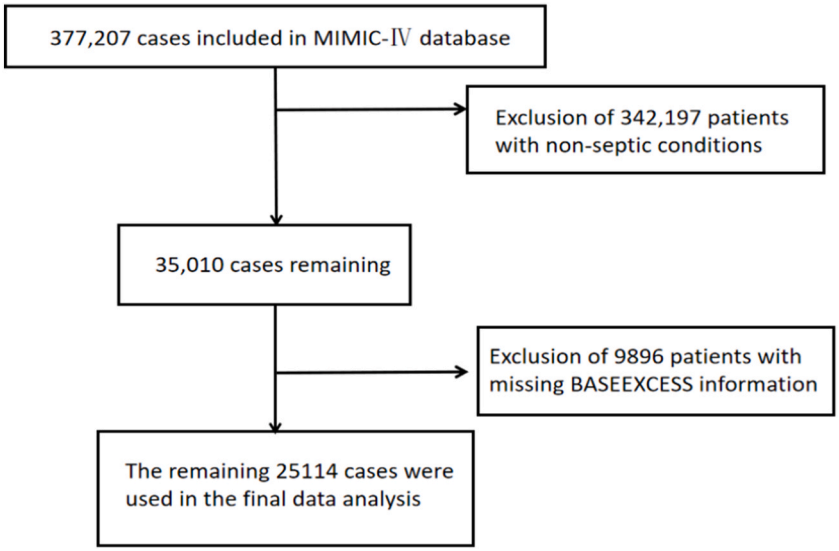

Fig. 1. Flow chart of subject selection.

(Q1–Q4). We observed trends in the distribution of each variable among the different subgroups after grouping. The patients' average lifespan was 60.4 ± 10.1 years. The incidence of 28-day death was 18.60% (4671/25,114). Analytical results showed that patients in groups Q1, Q2, and Q3 were younger, had fewer white, lower temperature levels, and were received a lower percentage of dexamethasone, methylprednisolone, and cephalosporin compared to patients in group Q4. Patients in groups Q2 and Q3 had a lower Charlson comorbidity index, a lower respiratory rate, a lower proportions of dopamine, hydrocortisone, carbapenems, penicillin, immunoglobulin administration, and a lower 28-day mortality compared to patients in group Q4. In contrast, we observed higher lactate levels and a higher proportion of mechanical ventilation in patients of groups Q1, Q2, and Q3 than in patients of group Q4.

3.1. Results of univariate and multivariate analysis of base excess

We explored the relationship between BE and 28-day mortality by using various covariate adjustment strategies, and the results are displayed in Table 2. In the unadjusted model, each 1 mEq/L increase in BE reduced the risk of 28-day death by 10% (OR: 0.90, 95% CI: 0.90 to 0.91). We obtained the same results after adjusting for demographic characteristics as in the unadjusted model (OR: 0.90, 95% CI: 0.89 to 0.90). However, after adjusting for all covariates presented in Table 1, we found no significant association between BE and 28-day mortality in sepsis patients, with a *p* value larger than 0.05. (OR: 1.00, 95% CI: 0.99 to 1.01). We converted BE into a categorical variable (Decile) based on the sensitivity analysis's goal and then calculated *p* values for the trend test. The results indicated consistency between the outcomes when BE was used as a continuous variable and the outcomes when BE was used as a categorical variable (Table 2).

Table 2
The results of univariate and multivariate analysis using non-adjusted and adjusted binary logistic regression models.

Exposure	Model 1		Model 2		Model 3	
	OR, 95%CI	*p* value	OR, 95%CI	*p* value	OR, 95%CI	*p* value
Base Excess	0.90 (0.90, 0.91)	<0.0001	0.90 (0.89, 0.90)	<0.0001	1.00 (0.99, 1.01)	0.7627
Base Excess (Deciles)						
percentile 10%	1		1		1	
percentile 10–20%	0.41 (0.37, 0.47)	<0.001	0.41 (0.36, 0.46)	<0.001	0.81 (0.70, 0.94)	<0.0061
percentile 20–30%	0.27 (0.24, 0.31)	<0.001	0.26 (0.23, 0.30)	<0.001	0.73 (0.62, 0.87)	<0.0004
percentile 30–40%	0.18 (0.16, 0.21)	<0.001	0.17 (0.15, 0.20)	<0.001	0.62 (0.51, 0.75)	<0.0001
percentile 40–50%	0.17 (0.15, 0.20)	<0.001	0.17 (0.14, 0.19)	<0.001	0.69 (0.57, 0.83)	<0.0001
percentile 50–60%	0.15 (0.13, 0.17)	<0.001	0.14 (0.12, 0.16)	<0.001	0.66 (0.55, 0.80)	<0.0001
percentile 60–70%	0.16 (0.14, 0.18)	<0.001	0.15 (0.13, 0.17)	<0.001	0.78 (0.66, 0.93)	<0.0048
percentile 70–80%	0.14 (0.12, 0.17)	<0.001	0.14 (0.12, 0.16)	<0.001	0.70 (0.57, 0.86)	<0.0005
percentile 80–90%	0.16 (0.14, 0.18)	<0.001	0.15 (0.13, 0.17)	<0.001	0.76 (0.63, 0.91)	<0.0033
percentile 90–100%	0.24 (0.21, 0.27)	<0.001	0.22 (0.19, 0.25)	<0.001	1.07 (0.90, 1.27)	0.4391
p for trend	0.89 (0.88, 0.90)	<0.001	0.89 (0.88, 0.89)	<0.001	1.00 (0.99, 1.01)	0.8514

Model 1: unadjusted model.
Model 2: adjusted for gender, age and ethnicity.
Model 3: adjusted for all covariates presented in Table 1

3.2. Non-linear association between base excess and 28-day mortality

The researchers used a generalized additive model and smoothed curve fitting to observe the nonlinear relationship between BE and 28-day mortality. Our results suggested that the association between BE and 28-day mortality is U-shaped after adjusting for covariates (same adjustment strategy as the fully-adjusted model) (Fig. 2). We calculated the inflection points for BE, obtaining the lower (−2.5 mEq/L) and upper (1.9 mEq/L) inflection points respectively by using a two-piecewise linear model and the recursive algorithm. When BE is in the range of −41.00 mEq/L to −2.5 mEq/L, each 1 mEq/L increase was related to a 5% reduction in the risk of 28-day death from sepsis (OR: 0.95, 95% CI: 0.93 to 0.96, $p < 0.0001$). When BE was in the range of −2.5 mEq/L to 1.9 mEq/L, each 1 unit increase in BE was associated with a 4% increase in the risk of death at 28 days, but the association was not significant (OR: 1.04, 95% CI: 0.99 to 1.08, $p = 0.0957$). When BE climbed to the range of 1.9 mEq/L to 55.5 mEq/L, however, each 1 mEq/L increase was associated with a 3% increase in the risk of death at 28 days (OR: 1.03, 95% CI: 1.00 to 1.05, $p < 0.05$) (Table 3).

4. Discussion

BE is one of the most commonly used markers in the management of ICU patients, it can be used to diagnose, guide, and intervene in disorders of acid-base balance [2]. Therefore, elucidating the relationship between BE and 28-day mortality in sepsis will provide additional clinical evidence to study the management of sepsis. In this study, by analyzing data from a large sample of sepsis patients (n = 25,114) in the multicenter MIMIC-IV database, we found a U-shaped association between BE and the probability of sepsis death at 28 days. According to the results, patients with sepsis in the ICU had a lower risk of 28-day death when BE was in the −2.5 mEq/L to1.9 mEq/L range, with either a too-low or too-high value of BE is associated with an increased risk of sepsis mortality.

According to a multicenter retrospective analysis of 1073 children with sepsis, a lower BE was associated with a higher risk of death from sepsis [24]. Another study, which included 561 adult Korean sepsis patients, discovered that BE was associated with a 28-day death risk [11]. These findings are similar to ours and can be explained mechanically. Increase of negative value of BE frequently imply metabolic acidosis, which is associated with tissue hypoxia, hypoperfusion, and lactate accumulation [11,25], all of which are involved in the pathophysiology of sepsis [26]. Previous studies have found that a prolonged base deficit has been linked to poor outcomes in critically ill patients [21,27,28]. However, in the large multicenter sample of data we analyzed, we discovered that high BE was also related to a significant risk of death. A positive value increase in BE are often indicative of metabolic alkalosis [29]. To the best of our knowledge, studies investigating the effects of metabolic alkalosis are very limited. We suspect it is due to the following factors: (1) Metabolic alkalosis is the most common acid-base balance disturbance in intensive care patients, and it is commonly regarded as a relatively benign condition that is only life-threatening in extreme situations [29,30]. (2) Previous studies had small sample sizes and lead to patients with high BE were not included. However, Simon Kreü et al., as well as Raphael KL et al., have all confirmed that severe alkalosis is associated with increased mortality [30,31]. Given the study's large sample size of over 20,000 people and the wide range of BE values (−41 mEq/L to 55.5 mEq/L), the U-shaped correlation between BE and 28-day mortality identified in our study is more interpretable and more compatible with clinical reality.

Our analysis has some advantages. First, BE is an important monitoring index for intensive care patients and is extensively used clinically. Second, in the current study, we adjusted a series of covariates, including lactate, that are closely related to sepsis. Third, a series of sensitivity analyses improves the robustness of the results and reduces the likelihood that our findings could be chancing findings. Meanwhile, we used more sophisticated algorithms, including the GAM as well as the two-piecewise linear model, which may better find a clinically realistic association between BE and the 28-day risk of death in patients with sepsis.

5. Limitations

Our research simultaneously existed several limitations. First, since the data come mainly from patients in the United States, more clinical analysis is needed to testify whether our results are applicable to the patients with sepsis in China. Second, our analysis would unavoidably be affected by some confounding factors because of the observational study itself. Fortunately, we have rigorously adjusted for confounding factors and thoroughly assessed the results with sensitivity analysis. Third, because of the nature of observational studies, we can only observe associations and cannot assess a causal relationship between BE and the risk of death from sepsis. Fourth, our study only assessed baseline BE and was unable to assess the impact of dynamic changes in BE values on survival outcomes, and finally, the exact interval between the acquisition time of BE and the diagnosis time of sepsis cannot be calculated because the information on the diagnosis time of sepsis is not included in the database. Therefore, further clinical trials with higher levels of evidence involving larger populations are required to verify our results.

6. Conclusion

BE was associated with a U-shaped relationship with the risk of 28-day death, with both too-low (−41.00 mEq/L to −2.5 mEq/L) or too-high BE levels (1.9 mEq/L to 55.5 mEq/L) associating with a higher risk of 28-day death for sepsis patients in the United States. The range of −2.5 mEq/L to 1.9 mEq/L was associated with a lower risk of death.

Author contribution statement

Jia Yuan: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

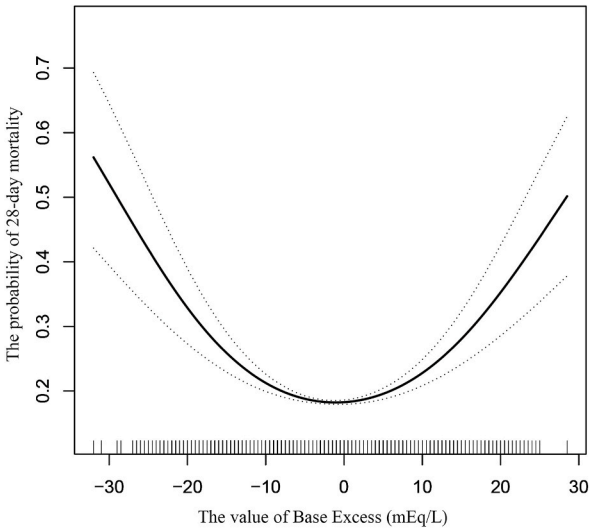

Fig. 2. The relationship between base excess and the probability of 28-day mortality in sepsis patients. The solid line represents the smoothed curve fit, while the dashed line represents the 95% confidence interval.

Table 3
Non-Linear relationships addressing.

Outcome:	OR, 95%CI	*P*-value
Fitting model using standard logistic regression model	1.00 (0.99, 1.01)	0.7627
Fitting model using two-piecewise linear model		
Inflection points of base excess	−2.5, 1.9	
< −2.5 mEq/L	0.95 (0.93, 0.96)	<0.0001
≥1.9 mEq/L	1.03 (1.00, 1.05)	0.0186
Log-likelihood ration test	<0.001	

The adjustment strategy is the same as the fully-adjusted model.

Xu Liu; Ying Liu; Wei Li; Xianjun Chen; Qiming Chen; Chuan Xiao; Ying Wan; Shuwen Li; Qing Li; Lu Li; Juan He: Performed the experiments.

Lu Chen: Contributed reagents, materials, analysis tools or data.

Feng Shen: Conceived and designed the experiments; Wrote the paper.

Data availability statement

Data associated with this study has been deposited at The data are available on the MIMIC-IV database website at https://mimic-iv.mit.edu/.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15990.

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