Original Article

Exploring the predictive value of pH in stratified mortality risk of NEC patients undergoing surgery: a retrospective study based on the PIC database

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Background: Neonatal necrotizing enterocolitis (NEC) represents a severe gastrointestinal condition characterized by a high mortality rate, with a paucity of reliable prognostic biomarkers. The presence of an acidic pH, indicative of systemic acidosis and intestinal ischemia, has potential as a predictor of adverse outcomes. However, the relationship between pH levels and inflammatory markers, as well as its applicability across surgical and non-surgical patient subgroups, remains inadequately understood. Utilizing data from pediatric intensive care units, this study investigates the prognostic significance of pH in stratifying mortality risk in NEC and examines its association with variations in neutrophil and leukocyte counts.

Methods: Clinical and laboratory data of NEC patients were collected from pediatric critical care datasets. The population was stratified based on whether surgical treatment was performed. Each stratum was further divided into two groups: the mortality group and the discharge group. Intergroup comparisons and multivariate analyses were conducted to evaluate the predictive value of acidic pH levels for outcomes in NEC patients.

Results: A total of 124 NEC neonates were included, with a median age at admission of 9 days and a median weight of 2.34 kg. In both the non-surgical and surgical subgroups, neonates in the mortality group exhibited acidic pH levels. Multivariate regression analysis in the surgical group identified acidic pH as a risk factor for adverse outcomes. Among all NEC neonates, stratification based on pH levels revealed the highest mortality rate in the acidic pH group. A generalized linear regression model using pH as the dependent variable demonstrated that, in addition to conventional factors such as lactate and potassium (K+), increases in neutrophils and white blood cells (WBCs) also contributed to pH variations.

Conclusions: Acidic pH is closely associated with adverse outcomes in NEC neonates. Inflammation-related increases in WBC and neutrophils may reflect changes in pH levels in these patients.

Keywords: Neonatal disease; necrotizing enterocolitis (NEC); pH; prognosis

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Introduction

Necrotizing enterocolitis (NEC) has a high mortality rate, reportedly reaching 17–20% (1,2). NEC is a common and devastating inflammatory gastrointestinal disease, representing a leading cause of death in neonatal intensive care units (NICUs), accounting for approximately 10% of all NICU mortality cases (3,4).

The pathogenesis of NEC is complex and multifactorial, involving gut dysbiosis, immune responses, ischemia-reperfusion injury, intestinal immaturity, and genetic predispositions (5). Researchers have extensively investigated various clinical factors related to these mechanisms (6). However, the role of acid-base imbalance in the prognosis of NEC has received insufficient attention. Dysbiosis of the gut microbiome can lead to the overgrowth of harmful bacteria, which produce metabolic byproducts such as lactic acid, creating an acidic environment (7,8). Patients with NEC also experience exaggerated immune and inflammatory responses, with inflammatory mediators potentially inducing increased production of acidic metabolic byproducts (9). Furthermore, ischemia-reperfusion injury not only disrupts intestinal function but also contributes to systemic acid-base imbalances (10).

The Pediatric Intensive Care (PIC) database (http://pic.nbscn.org), established by the National Center for Children's Health Clinical Research, is a unique, single-center, bilingual, and large-scale dataset designed for pediatric critical care research (11). It encompasses clinical data for 12,881 critically ill children treated in the intensive care unit (ICU) from 2010 to 2018, including laboratory measurements, patient observation records during critical care, vital signs monitoring data from operating rooms, and structured symptom data extracted from patient hospitalization records.

This study retrospectively analyzed the clinical and laboratory data of patients with NEC from the PIC database. By stratifying these patients based on the type of surgical intervention received, the study explores the relationship between acid-base levels, particularly pH values, and the outcomes of neonates diagnosed with NEC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-2025-3/rc).

Highlight box

Key findings

- Acidic pH levels (a marker of systemic acidosis) are independently associated with mortality in both surgical and non-surgical neonates with necrotizing enterocolitis (NEC).
- In surgical NEC patients, acidic pH emerged as a significant risk factor for adverse outcomes (adjusted odds ratio reported).
- Stratification by pH revealed the highest mortality rate in neonates with acidic pH compared to normal or alkaline subgroups.
- Beyond traditional acidosis drivers [e.g., lactate, potassium (K+)], elevated white blood cells (WBCs) and neutrophils were novel contributors to pH derangements.

What is known and what is new?

- Known: NEC is a leading cause of neonatal mortality, and systemic acidosis (reflected by low pH) correlates with disease severity.
- New: This study establishes pH as a prognostic marker across surgical/non-surgical subgroups and links inflammatory surges (WBC/neutrophils) to pH dynamics, proposing a previously underrecognized interplay between inflammation and acid-base imbalance in NEC.

What is the implication, and what should change now?

- Acidic pH should be integrated into early risk stratification tools for NEC mortality, particularly in surgical decision-making contexts. Clinicians should monitor inflammatory markers (WBC, neutrophils) alongside conventional acidosis indicators to refine prognostic models. Future research should validate pH-guided protocols and explore mechanisms connecting neutrophilic inflammation to pH alterations in NEC.

Methods

Inclusion and exclusion

This retrospective cohort study analyzed data from the PIC database (2010–2018), a single-center registry maintained by the National Center for Children's Health Clinical Research. Diagnoses were recorded according to the International Classification of Diseases, 10th Revision (ICD-10). NEC was identified using the code P77.x00 in both admission and discharge records. Initially, 225 patients were included in this retrospective cohort study. After eliminating duplicate hospitalizations, 193 unique patients remained. The inclusion criteria required an age of less than 31 days at admission, resulting in the exclusion of 66 cases. Furthermore, 3 cases were excluded due to insufficient data resulting from hospitalization lasting less than 24 hours. A total of 124 patients were ultimately included in the analysis.

NEC diagnosis

Neonatal gastrointestinal diseases, including NEC,

congenital megacolon, and congenital intestinal malrotation, often present with overlapping symptoms such as abdominal distension, bloody stools, vomiting, and diarrhea. For each neonate, we meticulously reviewed the primary symptoms as well as both admission and discharge diagnoses to confirm NEC as the primary diagnosis and to exclude other gastrointestinal diseases.

Outcome measures

Neonatal outcomes were classified into two categories: the discharge group and the mortality group. Records of who were neonates readmitted for a second hospitalization were excluded from this analysis. Only outcomes from the initial hospitalization were considered, with successful discharges categorized accordingly and NEC identified as the primary diagnosis in cases resulting in death. Mortality data were extracted as an endpoint from the 'patients' section of the PIC dataset.

Clinical data extraction

Access to the PIC database was granted upon successful completion of the Collaborative Institutional Training Initiative (CITI) program. Clinical data were extracted using unique hospitalization IDs from the PIC database. All included patients were directly admitted to this center (i.e., non-transferred cases), and only their first hospitalization was analyzed to ensure uniformity in the definition of 'time of admission'. The parameters collected within the first 24 hours of admission included age at admission, admission weight, gender, treatment modality (surgical or non-surgical), and laboratory markers such as blood glucose, pH, albumin, total protein, C-reactive protein (CRP), creatinine, lactate, total bilirubin, fecal occult blood test (FOBT), hemoglobin, WBC, potassium (K^+), sodium (Na^+), and chloride (Cl^-). This 24-hour window was selected to capture early physiological parameters potentially predictive of NEC, even if the definitive diagnosis was later confirmed during hospitalization.

The completeness rate for all predictor variables exceeded 80%. Missing values were imputed using the Generative Adversarial Imputation Network (GAIN), a machine learning model based on generative adversarial networks (GANs). Within this framework, a generator synthesizes plausible imputations by learning the underlying data distribution, while a discriminator assesses both the authenticity of the imputed values and the patterns of missing data. This dual process enhances robustness in clinical scenarios where the occurrence of missing data may correlate with unobserved severity. As demonstrated by Weinan Dong (12), GAIN outperforms traditional methods such as multiple imputation by chained equations (MICE) and missForest in terms of accuracy, effectiveness, and efficiency, even with missing rates of up to 50%. This innovative machine learning approach was utilized to address missing values in this study. The GAIN model was executed with the following hyperparameters: batch_size =128, hint_rate =0.9, alpha =100, and iterations =10,000.

Ethics approval and informed consent

The use of data from the PIC database was approved in accordance with its governance protocols. All data were de-identified following HIPAA standards, with protected health information permanently removed. Researchers accessing the database are bound by data security agreements to prevent re-identification. Given the fully anonymized and retrospective nature of this study, ethical approval and informed consent requirements were waived. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

Statistical analysis

Statistical analyses were conducted using R version 4.4.1. Due to the limited sample size, continuous variables were expressed as median (Q25, Q75), and intergroup comparisons were conducted using either the Wilcoxon rank-sum test. Categorical variables were reported as frequencies and percentages, with intergroup comparisons performed using the chi-square test or Fisher's exact test. Patients were stratified into surgical and non-surgical groups based on their treatment modality. Within each group, comparisons were made between the discharge and mortality subgroups. Laboratory variables that exhibited statistically significant differences were included in a multivariate regression analysis to construct predictive models. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Subsequently, patients were further stratified based on pH levels to compare mortality rates across pH groups. Utilizing pH as the dependent variable, stepwise generalized linear regression was performed to identify factors influencing pH changes. A P value of less than 0.05 was deemed statistically significant.

Results

Clinical data of all NEC patients

This retrospective cohort study included a total of 124 neonatal patients diagnosed with NEC, of whom 17 (8.7%) succumbed during hospitalization. The median age at admission to the ICU was 9 days [interquartile range (IQR): 3 to 19.5 days], and the median admission weight was 2.34 kg (IQR: 1.90 to 2.80 kg). The cohort consisted of 43 females and 81 males. Among these patients, 56 underwent surgical intervention, while 68 were managed non-surgically.

Comparison of clinical indicators in the surgical NEC group

Significant differences were observed in serum creatinine, pH, and lactate levels between the discharge and death groups. The pH level in the death group was 7.25 (7.19, 7.26), which was significantly lower than the 7.40 (7.34, 7.44) observed in the discharge group (P=0.001). Serum creatinine levels in the death group were 96.50 (91.00, 115.00) μmol/L, significantly higher than the 48.00 (36.00, 62.00) μmol/L recorded in the discharge group (P=0.002). Furthermore, lactate concentrations were markedly elevated in the death group, measuring 12.55 (6.20, 20.00) mmol/L, in contrast to 2.30 (1.48, 3.17) mmol/L in the discharge group. No statistically significant differences were observed in demographic parameters (age: P=0.52; weight: P=0.40) or cellular components of complete blood count (lymphocytes P=0.67, monocytes P=0.40, neutrophils P>0.99, platelets P=0.71). Similarly, glucose metabolism (P=0.82) and electrolyte profiles (Na^+ P=0.73, K^+ P=0.77, Cl^- P=0.11) showed comparable results between groups (see *Table 1*).

Comparison of clinical indicators in the non-surgical NEC group

In the non-surgical group, neonates were categorized into discharge and mortality groups. The pH values exhibited significant differences, with the mortality group showing lower pH levels 7.24 (7.12, 7.30) compared to the discharge group 7.37 (7.33, 7.42) (P<0.001). The red blood cell (RBC) counts in the mortality group 2.76 (2.43, 3.76) $\times 10^{12}$/L were significantly lower than those in the discharge group 3.86 (3.33, 4.47) $\times 10^{12}$/L (P=0.02). Albumin levels were also reduced in the mortality group 22.70 (19.87, 31.00) g/L compared to the discharge group 29.70 (25.70, 32.40) g/L (P=0.04). Furthermore, platelet counts were significantly lower in the mortality group 122.00 (42.00, 200.00) $\times 10^9$/L compared to the discharge group 225.00 (152.50, 289.00) $\times 10^9$/L (P=0.006). Other variables, including age (P=0.78), weight (P=0.19), RDW (P=0.058), lymphocytes (P=0.09), PCT (P=0.71), fibrinogen (P=0.56) and monocytes (P=0.09), did not show significant differences (see *Table 2*).

Construction and evaluation of multivariate regression models

Significant variables from the non-surgical group, including RBC, albumin levels, platelet count, total protein, and pH were incorporated into a multivariate logistic regression model to predict mortality outcomes (0= discharge, 1= death). Although Na+ levels differed between groups, these deviations were minor and thus excluded from the model. To accurately reflect the relationship between pH and mortality, pH values were dichotomized into acidic pH (pH<7.35, coded as 1) and non-acidic (coded as 0). Acidic pH was subsequently included in the regression model to evaluate its impact alongside other biomarkers. Acidic pH demonstrated the strongest association with mortality (coefficient =1.184), suggesting that an acidic pH environment significantly increases the risk of death (*Table 3*). Other variables exhibited weak associations, including RBC (coefficient =–0.571), albumin (0.064), platelet count (–0.008), and total protein (–0.075). Although some variables did not reach statistical significance, the findings underscore clinically relevant markers associated with mortality. The model's predictive performance was visualized using a nomogram and evaluated with calibration and ROC curves, yielding an area under the curve (AUC) of 0.841 (95% CI: 0.694–0.987), with a good calibrated curve fit (*Figures 1-3*). Decision curve analysis (DCA) curves demonstrated that the predicted risk had a moderate clinical predictive value in the range of 1% to 83% (*Figure 4*).

Mortality risk in different pH groups

Patients were categorized into acidic, normal, and alkaline pH groups to further investigate the relationship between pH levels and mortality. The Mortality rate was highest in the acidic group at 28.31%, which was significantly greater than the 3.92% observed in the normal pH group (P<0.001). Notably, no deaths were recorded in the alkaline pH group. These findings indicate a distinct association between pH levels and mortality risk in neonates with NEC (refer to *Table 4* and *Figure 5*).

Table 1 Comparison of clinical indicators in the surgical NEC group

Variable	Discharge (n=52)	Death (n=4)	U/χ^2	P
Gender			<0.01	>0.99
Female	21 (40.38)	2 (50.00)		
Male	31 (59.62)	2 (50.00)		
Prematurity			<0.01	>0.99
No	41 (78.85)	3 (75.00)		
Yes	11 (21.15)	1 (25.00)		
Stool culture			<0.01	>0.99
No	44 (84.62)	3 (75.00)		
Yes	8 (15.38)	1 (25.00)		
Age (days)	7.50 (1.75, 19.25)	4.50 (0.75, 11.00)	124.5	0.52
Weight (kg)	2.39 (1.88, 2.91)	2.65 (2.45, 2.7)	19	0.40
Lymphocyte ($\times10^9$/L)	3.27 (1.78, 4.94)	3.58 (2.54, 4.97)	90	0.67
Monocyte ($\times10^9$/L)	0.90 (0.66, 1.93)	0.75 (0.36, 1.23)	131	0.40
Neutrophils ($\times10^9$/L)	5.06 (2.89, 8.08)	9.54 (1.65, 17.45)	104	>0.99
RDW	15.80 (14.90, 17.32)	15.20 (14.55, 16.88)	127	0.47
RBC ($\times10^{12}$/L)	3.85 (3.15, 4.58)	3.50 (2.35, 4.46)	127	0.47
WBC ($\times10^9$/L)	10.32 (7.23, 16.03)	15.49 (6.43, 23.90)	95	0.79
Hb (g/L)	117.00 (98.50, 142.25)	128.50 (83.00, 172.50)	98.5	0.87
PCT (ng/mL)	0.19 (0.03, 1.52)	0.70 (0.08, 1.49)	100	0.91
CRP (mg/L)	13.50 (5.00, 36.75)	17.50 (9.50, 30.25)	99	0.89
Albumin (g/L)	29.50 (25.93, 32.08)	21.00 (19.15, 25.88)	156	0.10
Lactate (mmol/L)	2.30 (1.48, 3.17)	12.55 (6.20, 20.00)	11.5	0.003
Fibrinogen (g/L)	1.67 (1.33, 2.03)	2.32 (1.31, 3.23)	84.5	0.55
Platelet ($\times10^9$/L)	259.00 (156.25, 321.75)	282.50 (213.75, 347.75)	92	0.71
Oxygen saturation (%)	98.20 (92.40, 98.85)	81.55 (76.42, 88.65)	161	0.07
PO_2 (mmHg)	102.00 (63.00, 147.50)	43.55 (36.77, 57.67)	166	0.051
Total protein (g/L)	43.35 (38.50, 48.17)	30.20 (25.72, 38.20)	161	0.07
Creatinine (μmol/L)	48.00 (36.00, 62.00)	96.50 (91.00, 115.00)	6	0.002
Blood glucose (mmol/L)	2.37 (1.91, 2.86)	2.01 (1.82, 2.94)	112	0.82
Na^+ (mmol/L)	137.00 (135.00, 140.00)	137.50 (135.75, 139.75)	92.5	0.73
K^+ (mmol/L)	4.10 (3.70, 4.50)	4.15 (3.60, 4.83)	94.5	0.77
Cl^- (mmol/L)	111.00 (108.00, 115.00)	107.00 (104.25, 109.25)	154.5	0.11
pH	7.40 (7.34, 7.44)	7.25 (7.19, 7.26)	205	0.001

Data are presented as median (interquartile range) or n (%). U: Mann-Whitney *U* statistic (non-parametric test for between-group comparisons). Albumin: serum albumin concentration; CRP, C-reactive protein; Cl^-, chloride; Hb, hemoglobin; K^+, potassium; Na^+, sodium; NEC, necrotizing enterocolitis; PO_2, partial pressure of oxygen; PCT, procalcitonin; RDW, red cell distribution width; RBC, red blood cell count; WBC, white blood cell.

Table 2 Comparison of clinical indicators in the non-surgical NEC group

Variable	Discharge (n=55)	Death (n=13)	U/χ^2	P
Gender			0.05	0.83
Female	17 (30.91)	3 (23.08)		
Male	38 (69.09)	10 (76.92)		
Prematurity			0.55	0.46
No	42 (76.36)	8 (61.54)		
Yes	13 (23.64)	5 (38.46)		
Stool culture			<0.01	>0.99
No	50 (90.91)	12 (92.31)		
Yes	5 (9.09)	1 (7.69)		
Age (days)	11.00 (5.00, 18.50)	15.00 (0.00, 20.00)	375.5	0.78
Weight (kg)	2.31 (1.92, 3.00)	2.10 (1.75, 2.60)	407	0.19
RDW	16.30 (15.25, 17.95)	17.00 (16.70, 18.40)	235.5	0.058
RBC ($\times10^{12}$/L)	3.86 (3.33, 4.47)	2.76 (2.43, 3.76)	503	0.02
WBC ($\times10^{9}$/L)	11.15 (8.34, 14.28)	8.59 (3.41, 12.09)	456	0.13
Lymphocyte ($\times10^{9}$/L)	3.69 (1.71, 4.70)	1.92 (1.00, 3.77)	466	0.09
Monocyte ($\times10^{9}$/L)	1.11 (0.74, 1.65)	0.43 (0.20, 1.20)	466.5	0.09
Neutrophils ($\times10^{9}$/L)	4.66 (3.64, 7.33)	5.34 (1.96, 13.43)	341	0.80
CRP (mg/L)	10.00 (4.00, 54.00)	34.00 (4.00, 95.00)	300.5	0.34
PCT (ng/mL)	0.13 (0.03, 1.11)	0.20 (0.03, 0.39)	382	0.71
Albumin (g/L)	29.70 (25.70, 32.40)	22.70 (19.87, 31.00)	490	0.04
Lactate (mmol/L)	1.80 (1.25, 2.70)	2.00 (1.50, 7.70)	285	0.26
Fibrinogen (g/L)	1.79 (1.46, 2.27)	1.65 (1.21, 2.21)	395	0.56
Platelet ($\times10^{9}$/L)	225.00 (152.50, 289.00)	122.00 (42.00, 200.00)	533	0.006
Oxygen saturation (%)	97.80 (93.95, 99.00)	95.00 (80.50, 98.40)	436.5	0.22
PO_2 (mmHg)	84.50 (62.95, 122.50)	69.60 (46.80, 84.80)	453	0.14
Total protein (g/L)	41.10 (37.85, 47.30)	36.10 (26.50, 39.80)	535	0.006
Hb (g/L)	123.00 (105.50, 138.00)	131.00 (90.00, 157.00)	348	0.89
Creatinine (μmmol/L)	53.00 (42.50, 70.00)	63.50 (54.00, 68.00)	309.5	0.46
Blood glucose (mmol/L)	2.10 (1.48, 2.45)	2.12 (1.11, 3.56)	356	0.99
Na^+ (mmol/L)	136.00 (133.00, 139.00)	132.00 (128.00, 136.00)	509.5	0.02
K^+ (mmol/L)	4.00 (3.60, 4.45)	4.40 (3.90, 4.90)	265	0.15
Cl^- (mmol/L)	108.00 (105.00, 111.00)	105.00 (101.00, 111.00)	462.5	0.10
pH	7.37 (7.33, 7.42)	7.24 (7.12, 7.30)	581.5	<0.001

Data are presented as median (interquartile range) or n (%). U: Mann-Whitney *U* statistic (non-parametric test for between-group comparisons). Albumin, serum albumin concentration; CRP, C-reactive protein; Cl^-, chloride; K^+, potassium; Hb, hemoglobin; Na^+, sodium; NEC, necrotizing enterocolitis; PCT, procalcitonin; PO_2, partial pressure of oxygen; RDW, red cell distribution width; RBC, red blood cell count; WBC, white blood cell.

Table 3 Logistic regression analysis of factors influencing mortality

Variable	B	SE	Wald	P	OR	95% CI
RBC ($\times10^{12}$/L)	−0.571	0.381	2.243	0.13	0.565	0.268–1.193
Albumin (g/L)	0.064	0.093	0.469	0.49	1.066	0.888–1.279
Platelet ($\times10^{9}$/L)	−0.008	0.004	3.305	0.07	0.992	0.983–1.001
Total protein (g/L)	−0.075	0.069	1.188	0.28	0.928	0.811–1.061
Acidic pH	1.184	0.934	1.605	0.21	3.267	0.523–20.388
Const	2.399	2.322	1.068	0.30	11.016	–

B, regression coefficient; OR, odds ratio; RBC, red blood cell count; SE, standard error; Wald, Wald statistic; 95% CI, 95% confidence interval.

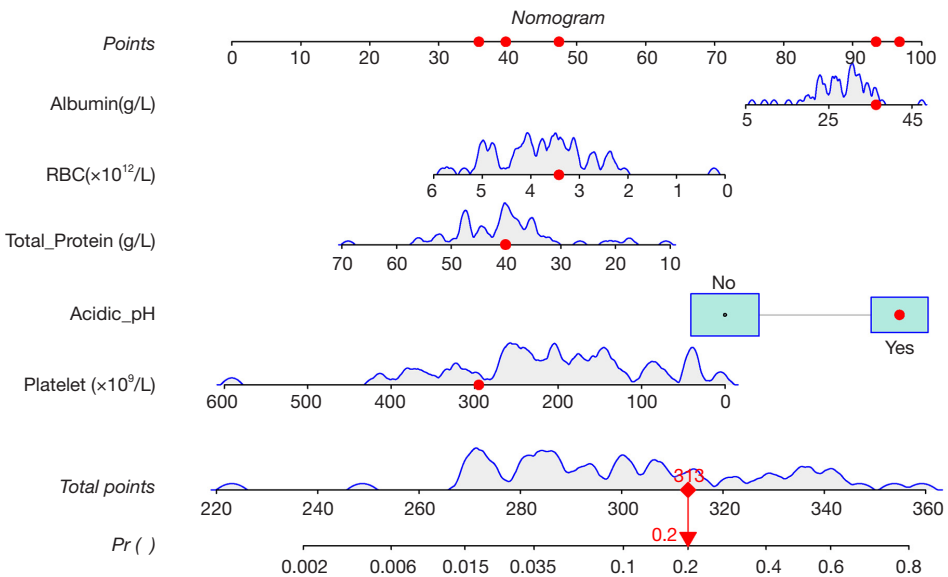

Figure 1 Nomogram of risk factors for adverse outcomes in non-surgical NEC patients. The gray density plot illustrates the distribution of NEC patients included in the study across different predictive factors and total scores. The top axis represents the scoring scale. Each variable contributes a specific score based on its value, which is summed to calculate the total score. The total score corresponds to a predicted risk probability. For example, as shown in the figure, when albumin is 36.4 g/L, RBC is 3.42×10^{12}/L, total protein is 40.1 g/L, and acidic pH is "yes", the total score is 313 points, indicating a non-negligible risk level, with a predicted probability of adverse outcomes reaching 20%. NEC, necrotizing enterocolitis; RBC, red blood cell count.

Exploring clinical factors influencing pH

A generalized linear regression model was developed to identify clinical factors affecting pH levels among patients with NEC. The model demonstrated a reasonable fit, with the following statistics: AIC =−247.30, BIC =−553.48, Deviance =0.85, and Pearson Chi-square =0.85. The regression equation is expressed as follows: pH = 6.9895 − 0.0041 × Neutrophils + 0.0052 × WBC − 0.0075 × Lactate + 0.0021 × Oxygen Saturation + 0.0005 × PO_2 + 0.0049 × Total Protein − 0.0274 × K^+ + 0.0018 × Age (*Table 5*). Key findings indicate that Neutrophils are negatively correlated with pH (P=0.005), suggesting that higher counts contribute to a reduction in pH. Conversely, WBC exhibited a positive correlation with pH (P<0.001), indicating that increased counts are associated with higher pH levels. Lactate also showed a negative correlation with pH (P<0.002),

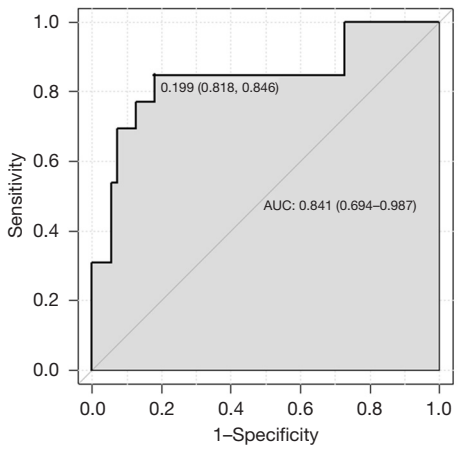

Figure 2 Receiver operating characteristic curve of the predictive model. AUC, area under the curve.

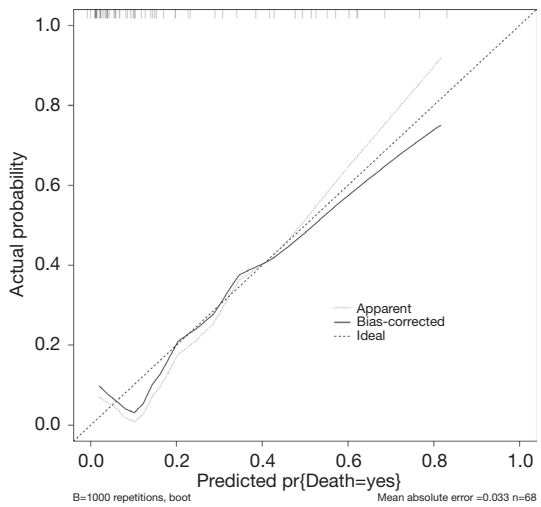

Figure 3 Calibration curve of the predictive model. The calibration curve demonstrates the agreement between the nomogram-predicted probability of death (x-axis) and the observed probability (y-axis). The black solid line (Apparent) represents the original calibration curve, the black dashed line (Bias-corrected) indicates the Bootstrap bias-corrected calibration curve (B=1,000 repetitions), and the black diagonal line (Ideal) denotes the perfect prediction reference. The mean absolute error of the model was 0.033 (n=68), indicating good agreement between predicted and actual probabilities.

reaffirming the relationship between metabolic acidosis and pH decline. Additionally, oxygen saturation (P=0.006) and PO_2 (P=0.02) were positively correlated with pH. Total protein (P<0.001) demonstrated a positive correlation, whereas K^+ (P=0.02) exhibited a negative correlation. Age was positively correlated with pH (P<0.03). These results suggest that inflammation, metabolic acidosis, and electrolyte imbalances are critical factors influencing pH levels in neonates with NEC.

Discussion

High mortality and complexity of NEC

NEC remains a severe condition characterized by a high mortality rate and diverse clinical presentations. Early identification of NEC is hindered by the absence of specific laboratory markers. The complex pathogenesis of NEC involves gut immune dysfunction, microbiota dysbiosis, oxidative stress, breastfeeding practices, transfusion, and inflammatory mediators (13). These mechanisms frequently result in acid-base disturbances, which play a critical role in the progression and fatal outcomes of NEC. Therefore, exploring the relationship between acid-base imbalances and NEC prognosis is essential for advancing our understanding in this area.

Role of acid-base imbalances in prognosis

Critically ill patients with NEC in intensive care often present with severe and multifaceted conditions, leading to high mortality rates. This study utilized the PIC database, a globally recognized clinical dataset for pediatric patients, to analyze outcomes and laboratory parameters of NEC patients (11).

The stratification of NEC patients into surgical and non-surgical groups aimed to isolate the impact of surgical intervention from disease severity on outcomes. The findings indicate that both surgical and non-surgical NEC patients who succumbed exhibited significantly acidic pH levels. Based on our data and previous studies, a pH threshold of <7.25, particularly when combined with elevated lactate, may serve as a pragmatic warning sign for clinicians to prioritize surgical evaluation. These results align with previous studies, such as those by Tefera *et al.*, which reported that lower pH and elevated CRP levels increase the likelihood of requiring surgical intervention (14). Furthermore, other research has shown that patients with persistent metabolic acidosis are less likely to recover (15), while a 1 mmol/L increase in lactate is associated with a 40–45% rise in mortality risk (16). Collectively, these studies suggest that severe acidosis correlates with poorer outcomes

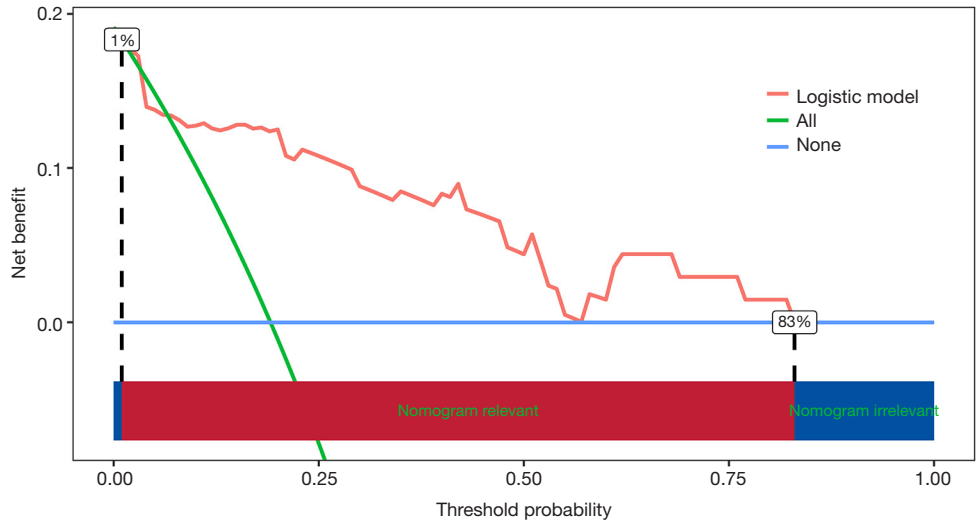

Figure 4 Decision curve analysis of the predictive model.

Table 4 Conversion of pH continuous variables to categorical variables

pH level	Definition	Assigned value	Discharge	Death	χ^2	P
Acidic pH	pH <7.35	1	38 (71.69%)	15 (28.31%)	16.85	<0.001
Normal pH	7.35≤ pH ≤7.45	2	49 (96.08%)	2 (3.92%)		
Alkaline pH	pH >7.45	3	20 (100%)	0		

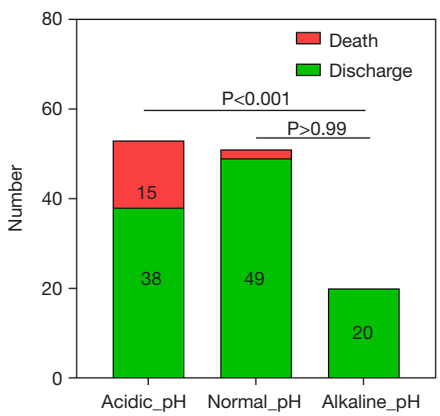

Figure 5 Comparison of adverse outcomes by acid-base status. The figure compares adverse outcomes among groups stratified by acid-base status (acidic, normal, and alkaline pH levels). The acidic pH group included 53 patients, with 15 deaths. The non-acidic pH group included 71 patients, with 2 deaths. A significant difference was observed between these two groups. Within the non-acidic pH group: Normal pH subgroup had 51 patients, with 2 deaths. Alkaline pH subgroup had 20 patients, with no deaths. No statistically significant difference was observed between the normal and alkaline pH subgroups.

in NEC patients.

Predictive model insights

This study developed a predictive model for non-surgical NEC patients, incorporating acidic pH alongside RBC, albumin, platelet count, and total protein. Although the model did not achieve statistical significance at α=0.05 due to a limited sample size, it demonstrated good discrimination and calibration. Acidic pH emerged as the strongest risk factor for mortality, emphasizing its clinical relevance (17,18).

Decreased RBC counts suggest anemia and impaired oxygen transport, which may exacerbate intestinal damage in preterm infants (19). Research indicates that reduced hemoglobin levels significantly increase the risk of NEC, underscoring the prognostic impact of anemia (20,21). Fluctuations in plasma proteins, including total protein and albumin, were associated with NEC outcomes (22). Interestingly, the opposing coefficients for total protein and albumin suggest that the albumin-to-total protein ratio warrants further exploration as a potential indicator.

Table 5 Generalized linear regression model for pH values in NEC patients

Variable	Coefficient	SE	95% CI	Wald Chi-square	P
Const	6.9895	0.0998	6.7940 to 7.1851	4907.2391	<0.001
Neutrophils (×10^9/L)	−0.0041	0.0015	−0.0070 to −0.0012	7.7374	0.005
WBC (×10^9/L)	0.0052	0.0014	0.0026 to 0.0079	14.9998	<0.001
Lactate (mmol/L)	−0.0075	0.0024	−0.0123 to −0.0028	9.5472	0.002
Oxygen saturation	0.0021	0.0008	0.0006 to 0.0036	7.5183	0.006
PO_2 (mmHg)	0.0005	0.0002	0.0001 to 0.0010	5.4669	0.02
Total protein (g/L)	0.0049	0.0009	0.0030 to 0.0067	26.9823	<0.001
K^+ (mmol/L)	−0.0274	0.0121	−0.0510 to −0.0038	5.1581	0.02
Age (day)	0.0018	0.0008	0.0002 to 0.0034	4.8966	0.03

Coefficient, regression coefficient; NEC, necrotizing enterocolitis; SE, standard error of the coefficient; 95% CI, 95% confidence interval.

Additionally, platelet reduction was linked to poor prognosis, reflecting possible coagulopathy. Prior studies have identified thrombocytopenia as an independent prognostic factor in NEC, indicating more severe disease progression in patients with low platelet counts (23).

Stratification by pH and mortality risk

Stratifying patients by pH levels revealed the highest mortality rates among those with acidic pH, underscoring the prognostic significance of acid-base disturbances. Research conducted in pediatric intensive care units (PICU) indicates that metabolic acidosis occurs in 60.2% of critically ill children, demonstrating a significant correlation between the severity of acidosis and mortality (24). These findings emphasize the necessity of evaluating and addressing acid-base imbalances in the management of NEC.

Factors influencing pH changes

A generalized linear regression model identified several factors influencing pH levels, including lactate, oxygen saturation, PO_2, total protein, K^+, age, neutrophils, and WBC counts. Age exhibited a positive correlation with pH, likely reflecting the development and maturation of the neonatal respiratory system (23,25). WBC counts were also positively associated with pH, indicating the role of the systemic inflammatory response in mitigating acidosis. Conversely, lactate displayed a negative correlation with pH, underscoring its involvement in metabolic acidosis and adverse outcomes. Furthermore, oxygen saturation and PO_2 positively influenced pH, highlighting the significance of oxygenation in maintaining acid-base balance (26). Neutrophils showed a negative association with pH, suggesting that inflammation may contribute to acid-base disturbances through oxidative stress and the release of inflammatory mediators (27,28).

Limitations

This study has several limitations: (I) retrospective design: the absence of perinatal factors in the analysis constrains the breadth of conclusions that can be drawn. Future research should stratify data according to perinatal variables, particularly gestational age. (II) Sample size: the limited sample size within the surgical and stratified subgroups restricted the statistical significance of the predictive models, although clinical relevance was maintained. (III) Single-center dataset: multi-center studies are essential to validate the findings and evaluate the prognostic value of pH across diverse clinical settings.

Conclusions

Acidic pH is strongly associated with adverse outcomes in patients with NEC. Inflammatory markers, such as neutrophils and WBC, may reflect the underlying changes that lead to acidic pH. This study enhances the understanding of the prognostic significance of pH in NEC and underscores the necessity for future research to visualize and elucidate the factors driving acid-base disturbances. The findings offer valuable insights for assessing mortality

risks in NEC and guiding clinical management strategies.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-2025-3/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-2025-3/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Given the fully anonymized and retrospective nature of this study, ethical approval and informed consent requirements were waived. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

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