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**SUPPLEMENTAL DATA**

# Risk factors for surgery in neonatal necrotizing enterocolitis without pneumoperitoneum: Bell stage IIb or higher

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**Supplemental material 1. Exploratory sensitivity analysis using LASSO regression.**

## Supplementary methods

Least absolute shrinkage and selection operator (LASSO) regression with ten-fold cross-validation and the lambda.1se criterion was performed for variable selection, to assess whether the significant variables identified by the primary analysis were retained and whether the directions of association were consistent.

## Supplementary results

Eleven candidate variables were entered into the LASSO regression. Ten-fold cross-validation was performed, and the optimal penalty parameter was determined according to the lambda.1se criterion ($\lambda = 0.0663$; $\log \lambda = -2.713$), as shown in Figure S1A and Figure S1B. Based on the lambda.1se criterion, eight variables were ultimately retained in the LASSO regression, as shown in Table S1. These eight variables included all five significant variables identified in the primary analysis, with consistent directions of effect between the two regressions.

**Table S1. Exploratory sensitivity analysis using LASSO regression**

| Variable | Significant in the primary analysis | LASSO coefficient at λ.1se | Retained by LASSO |
|---|---|---|---|
| Blood products (Yes) | No | 0 | No |
| WBC count | No | -0.003 | Yes |
| CRP | No | 0.001 | Yes |
| Blood gas pH (per 0.1 unit) | Yes | -0.237 | Yes |
| Blood gas lactate | Yes | 0.081 | Yes |
| Blood gas SBE | No | 0 | No |
| Intestinal obstruction (Yes) | Yes | 1.026 | Yes |
| Ascites (Yes) | Yes | 0.311 | Yes |

| | | | |
|---|---|---|---|
| Heart rate | No | 0.007 | Yes |
| Bloody stools (Yes) | No | 0 | No |
| Vasoactive drugs (Yes) | Yes | 0.772 | Yes |

Abbreviations: CRP, C-reactive protein; LASSO, least absolute shrinkage and selection operator; SBE, standard base excess; WBC, white blood cell.

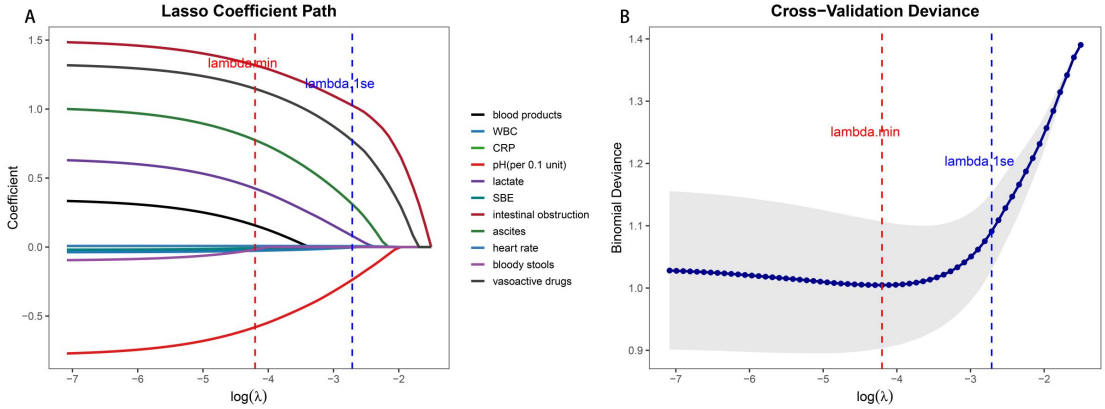



**Figure S1. LASSO logistic regression analysis. (A)** Coefficient paths for the candidate variables across values of the penalty parameter λ. **(B)** Ten-fold cross-validation curve showing binomial deviance across values of λ. The gray shaded band represents the ±1 standard-error range around the mean cross-validated binomial deviance at each λ. Red and blue dashed lines mark lambda.min and lambda.1se, respectively. The lambda.1se criterion was used to select the final penalty parameter (λ = 0.0663; log λ = −2.713). **Abbreviations**: CRP, C-reactive protein; LASSO, least absolute shrinkage and selection operator; SBE, standard base excess; WBC, white blood cell.

**Supplemental material 2. Sensitivity analysis using clinically selected variables.**

## Supplementary methods

A multivariable Firth logistic regression was performed using a prespecified set of variables. These variables were selected a priori based on clinical relevance and covered five domains: neonatal characteristics, inflammation, tissue perfusion, severity of intestinal lesions, and organ support requirements. The 12 prespecified variables were gestational age, birth weight, C-reactive protein (CRP), platelet count, blood pH, blood lactate, portal venous gas, ascites, intestinal obstruction, reduced bowel sounds, respiratory support, and vasoactive drugs. Collinearity was assessed using the variance inflation factor (VIF), and variables with a VIF > 5 were excluded. Univariable and multivariable Firth logistic regression were then fitted. Associations were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

## Supplementary results

The results are presented in Table S2. Multivariable Firth logistic regression analysis showed that intestinal obstruction on abdominal radiography, ascites on ultrasound, need for vasoactive drugs, elevated blood lactate levels, and CRP levels were independent risk factors for surgical intervention, whereas higher blood pH was an independent protective factor. These six variables included all five significant variables identified in the primary analysis.

**Table S2. Sensitivity analysis using Firth logistic regression with clinically selected variables**

| Variable | Univariable OR (95% CI) | *p* value | Adjusted OR (95% CI) | *p* value | VIF |
|---|---|---|---|---|---|
| Gestational age | 1.007 (0.935, 1.084) | 0.863 | 0.976 (0.777, 1.228) | 0.834 | 4.896 |
| Birth weight | 1.000 (1.000, 1.000) | 0.722 | 1.001 (0.999, 1.002) | 0.306 | 4.595 |
| Platelet count | 0.998 (0.996, 1.001) | 0.174 | 0.999 (0.995, 1.002) | 0.402 | 1.136 |
| CRP | 1.010 (1.004, 1.017) | < 0.001 | 1.011 (1.002, 1.020) | 0.011 | 1.378 |
| Blood gas pH (per 0.1 unit) | 0.467 (0.310, 0.679) | < 0.001 | 0.365 (0.197, 0.628) | < 0.001 | 1.360 |
| Blood gas lactate | 1.565 (1.177, 2.151) | 0.001 | 1.905 (1.207, 3.144) | 0.004 | 1.301 |
| Intestinal obstruction (Yes) | 7.253 (3.655, 15.123) | < 0.001 | 10.070 (3.648, 32.067) | < 0.001 | 1.672 |
| Portal venous gas (Yes) | 1.177 (0.648, 2.144) | 0.592 | 1.936 (0.787, 4.981) | 0.152 | 1.286 |
| Ascites (Yes) | 3.640 (1.914, 7.122) | < 0.001 | 3.311 (1.298, 8.963) | 0.012 | 1.354 |
| Reduced bowel sounds (Yes) | 1.683 (0.693, 4.327) | 0.253 | 0.351 (0.070, 1.710) | 0.195 | 1.587 |
| Respiratory support (Yes) | 1.322 (0.724, 2.425) | 0.363 | 0.376 (0.113, 1.182) | 0.095 | 2.102 |
| Vasoactive drugs (Yes) | 4.658 (2.478, 8.986) | < 0.001 | 4.852 (2.061, 12.212) | < 0.001 | 1.235 |

Abbreviations: CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; VIF, variance inflation factor.

**Supplemental material 3. Complete-case sensitivity analysis.**

## Supplementary methods

A complete-case analysis was performed to assess the potential impact of missing data. Patients with missing values for any of the variables included in the primary multivariable Firth logistic regression were excluded. The same univariable and multivariable Firth logistic regression as in the primary analysis was then refitted in the complete-case dataset.

## Supplementary results

The results are presented in Table S3. Multivariable Firth logistic regression analysis showed that intestinal obstruction on abdominal radiography, need for vasoactive drugs, elevated blood lactate levels, and CRP levels were independent risk factors for surgical intervention, whereas higher blood pH was an independent protective factor. Although the ascites variable did not reach statistical significance, its OR point estimate remained greater than 1 and was directionally consistent with the primary analysis.

**Table S3. Complete-case sensitivity analysis using Firth logistic regression**

| Variable | Univariable OR (95% CI) | *p* value | Adjusted OR (95% CI) | *p* value | VIF |
|---|---|---|---|---|---|
| Blood products (Yes) | 2.324 (1.131, 4.888) | 0.021 | 0.855 (0.286, 2.437) | 0.772 | 1.338 |
| WBC count | 0.865 (0.789, 0.939) | < 0.001 | 0.950 (0.848, 1.060) | 0.365 | 1.273 |
| CRP | 1.010 (1.004, 1.018) | 0.001 | 1.006 (0.998, 1.015) | 0.136 | 1.320 |
| Blood gas pH (per 0.1 unit) | 0.491 (0.318, 0.731) | < 0.001 | 0.509 (0.265, 0.926) | 0.026 | 1.451 |
| Blood gas lactate | 1.584 (1.150, 2.272) | 0.003 | 1.670 (1.000, 2.899) | 0.050 | 1.376 |
| Blood gas SBE | 0.880 (0.794, 0.969) | 0.009 | 0.993 (0.857, 1.150) | 0.927 | 1.480 |
| Intestinal obstruction (Yes) | 7.039 (3.365, 15.597) | < 0.001 | 3.398 (1.393, 8.602) | 0.007 | 1.346 |
| Ascites (Yes) | 3.924 (1.943, 8.237) | < 0.001 | 2.337 (0.912, 6.228) | 0.077 | 1.284 |
| Heart rate | 1.046 (1.023, 1.072) | < 0.001 | 1.013 (0.984, 1.044) | 0.394 | 1.569 |
| Bloody stools (Yes) | 0.512 (0.256, 1.008) | 0.053 | 1.043 (0.424, 2.639) | 0.927 | 1.119 |
| Vasoactive drugs (Yes) | 5.226 (2.618, 10.789) | < 0.001 | 3.360 (1.465, 7.950) | 0.004 | 1.141 |

Abbreviations: CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; SBE, standard base excess; VIF, variance inflation factor; WBC, white blood cell.