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Clinical Correlates of Moderate-to-Severe Bronchopulmonary Dysplasia in Preterm Infants following Surgical Necrotizing Enterocolitis

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Abstract

Objective—The aim of the study is to determine clinical correlates of moderate to severe bronchopulmonary dysplasia (BPD) in preterm infants following surgical necrotizing enterocolitis (NEC).

Study Design—This is a retrospective, single-center cohort study comparing patients with moderate to severe BPD to patients with non/mild BPD among surgical NEC infants. BPD was defined by NIH 2001 consensus definition.

Results—Of 92 consecutive neonates with surgical NEC, 77% (71/92) had moderate/severe BPD and 22% (21/92) had non/mild BPD. The patent ductus arteriosus (PDA) was significantly higher in those developing moderate/severe BPD (67.6% [48/71]) than non/mild BPD (28.6% [6/21]; $p = 0.001$). Postoperatively, infants with moderate/severe BPD had more severe acute kidney injury (AKI; 67.6 [48/71] vs. 28.6% [6/21]; $p = 0.001$), were intubated longer (40.5 [interquartile (IQR): 12, 59] vs. 6 days [IQR: 2, 13]; $p < 0.001$), received more parenteral nutrition (109 [IQR: 77, 147] vs. 55 days [IQR: 19, 70]; $p < 0.001$), developed higher surgical morbidity (46.5 [33/71] vs. 14.3% [3/21]; $p = 0.008$), had more intestinal failure (62.5 vs. 13.3%; $p < 0.001$), required a longer hospital stay (161 [IQR: 112, 186] vs. 64 days [IQR: 20, 91]; $p < 0.001$), and were more likely to need home oxygen. In a multivariable analysis, lower birth weight (OR = 0.3, [95% confidence

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Authors' Contributions

P.M.G. designed the study. P.M.G., M.P., M.Z., J.W., J.P., S.N., N.V., and W.B.H. collected and analyzed the data. PMG wrote the manuscript. All the authors contributed to and approved the manuscript.

Consent

Given the observational, retrospective study design, and requisite data security safeguards, the Institutional Review Board did not require patient consent.

Conflict of Interest

None declared.

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interval (CI): 0.1–0.5]; $p = 0.001$), PDA (OR = 10.3, [95% CI: 1.6–65.4]; $p = 0.014$), and longer parenteral nutritional days (OR = 8.8; [95% CI: 2.0–43.0]; $p = 0.005$) were significantly and independently associated with higher odds of moderate/severe versus non-/mild BPD.

Conclusion—Development of moderate/severe BPD occurred in the majority of preterm infants with surgical NEC in this consecutive series. Preterm infants with moderate/severe BPD were more likely to have a PDA before NEC. Development of moderate/severe BPD was associated with significantly greater burden and duration of postoperative morbidity following surgical NEC. Identifying surgical NEC infants at increased risk of moderate/severe BPD and developing lung protection strategies may improve surgical NEC outcomes.

Keywords

necrotizing enterocolitis; preterm Infants; BPD

Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal conditions requiring emergency surgery in the neonatal intensive care unit, affecting 5 to 10% of premature infants with a birth weight (BW) ≤1,500 grams.[1,2] NEC remains a leading cause of morbidity and death among preterm infants and requires increased hospital care and resource utilization.[3–9] NEC is associated with a severe systemic inflammatory response and septic shock-like presentation that can contribute to multiorgan dysfunction due to intravascular volume depletion, capillary leak syndrome, and hypotension.[10] Hemodynamic changes, surgical stresses, anesthetic agents, hypotension, and an inflammatory surge affect multiple organs.[11,12] In addition, NEC has been associated with severe kidney injury and white matter injury in neonates.

Preterm infants diagnosed with medical and surgical NEC are also more likely to be diagnosed with BPD.[13] The high diagnosis rate of BPD in preterm term infants with NEC may be due to a greater need for mechanical ventilation as a result of BPD's attendant volutrauma, barotrauma, and hyperoxia effects on preterm lungs. Evolving evidence suggests that interactions between the intestine and lungs are mediated by various pathways involving the microbiome, immune system, and metabolites, as shown in animal models.[14] The intestinal dysbiosis, seen in preterm infants with NEC, modulates the gut immune tolerance[15] and affects the premature lungs. The clinical impact of NEC on the underdeveloped premature lung is not well studied. Currently, there is a lack of data on the pre-and postoperative course, along with the surgical course, in infants who suffer from both BPD and NEC, and how specific characteristics increase the risk for BPD.

In current literature, there is no study combining clinical, postoperative course, and pathology findings to identify the subgroup of infants with surgical NEC at higher risk of moderate/severe BPD. Therefore, we assessed moderate/severe BPD at 36 weeks corrected gestational age (CGA) using the 2001 NIH consensus BPD definition.[16] This study aims to determine the clinical and intestinal pathological factors associated with moderate/severe BPD at 36 weeks CGA in preterm infants before and following surgical NEC.

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Materials and Methods

Population and Study Design

The study was conducted in the level 4 neonatal intensive care unit at the University of Mississippi Medical Center (UMMC), with approximately 1,000 annual admissions and referrals from throughout the state. The UMMC Institutional Review Board had approved this chart review study (2017–0127). All preterm infants admitted between January 2013 and December 31, 2018, with an NEC diagnosis (Bell's stage III) were included in the study.[17] The Vermont Oxford Network (VON) database's 2019 report shows that UMMC has an NEC rate of 12.8% (vs. 5.1% for all VON included hospitals) in infants with a BW less than 1,500 grams. Infants diagnosed with medical NEC, spontaneous intestinal perforation, congenital heart disease, intestinal atresia, and missing clinical data were excluded from the analysis.

Demographic and Clinical Information

We collected demographic data, including gestational age (GA), BW, sex, appropriate for gestational age (AGA) status, race, outborn status, mode of delivery, and Apgar's score ≤6 at 5 minutes. We also collected maternal variables, including chorioamnionitis, pregnancy-induced hypertension, and antenatal steroid usage. In addition, we collected information on duration, FiO_2 requirement, and mode of ventilation (invasive/noninvasive) before and following NEC. Additional recorded clinical details included patent ductus arteriosus (PDA) and indomethacin/ibuprofen treatment before NEC onset, frequency of PDA surgical ligation, and inotrope (dopamine) use 24 hours after NEC onset. Sepsis-related variables included blood culture-proven sepsis at the time of NEC onset and duration of antibiotics. Blood culture-proven sepsis was defined as positive blood culture samples collected at NEC onset. We also recorded the frequency of cholestasis (serum bilirubin >2 mg/dL) after NEC onset. We also recorded growth data on weight, length, and weight for length at 36 weeks corrected GA. Sex-specific Fenton growth charts were used for anthropometric measurement. We also collected data on infants discharged on home oxygen.

Necrotizing Enterocolitis Information

NEC was defined using Bell's criteria.[17] The diagnosis of NEC was made by clinical signs/symptoms and based upon radiological NEC findings, including pneumatosis, portal venous gas, and pneumoperitoneum on the abdominal X-ray. The frequency of surgical NEC (Bell's stage III) was collected.[17] We recorded information on the age (in days) at the time of diagnosis of NEC. Neonates who died 48 hours after NEC onset, or if massive bowel necrosis was found during laparotomy or autopsy, were classified as having fulminant NEC.[18] Patients with NEC were managed surgically if they had clinical deterioration due to intestinal perforation, hypotension, persistent electrolyte imbalances (e.g., hyperkalemia and metabolic acidosis), increasing ventilator support, as well as anemia and thrombocytopenia despite repeated red blood cell and platelet transfusions. The practice of surgical management of NEC did not change substantially throughout the study period. At UMMC, preterm infants with pneumoperitoneum who weigh less than 1 kg at the time of NEC diagnosis and are hemodynamically unstable are treated first with a Penrose drain at the bedside but may later receive laparotomy.

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Histopathological Evaluation

Hematoxylin and eosin-stained surgical resected intestinal tissue sections were evaluated for necrosis, inflammation, hemorrhage and reparative changes. A score of 0 was assigned when the exam appeared normal, 1 for 1 to 25% necrosis/inflammation, 2 when 25 to 50% of the area was involved, 3 when 50 to 75% area was affected, and 4 when >75% changes were seen.

Postoperative Information

To assess the impact of postoperative clinical factors of infants with surgical NEC on BPD, data such aspostoperative ileus days (defined as infants being NPO after laparotomy), time to reach full feeds (≥120 mL/kg/d), total parenteral nutrition days, length of stay, and mortality were measured. The length of hospitalization was defined as the total hospital duration from the day of admission until discharge or death. Mortality was defined as death due to any cause before hospital discharge.

We also recorded information on intestinal failure (parenteral nutrition >90 days) and surgical morbidity which was classified as surgical site infections (including dehiscence and abscesses), strictures, fistulas, adhesions, and perforations.

Bronchopulmonary Dysplasia Data

We collected data on bronchopulmonary dysplasia status at 36 weeks of corrected GA and the type of steroid (-hydrocortisone/dexamethasone) used during the clinical course. Bronchopulmonary dysplasia was classified as mild, moderate, or severe based on the oxygen requirement at assessment.[16] To determine the assessment time, patients were separated based on the GA of less than 32 weeks and greater than or equal to 32 weeks. Patients born with a CGA of less than 32 weeks were assessed at 36 weeks postmenstrual age or at discharge, whichever came first, and patients born with a GA of greater than or equal to 32 weeks were evaluated at 56 days after birth or discharge, whichever came first. Mild BPD for each CGA group was classified as requiring >21% oxygen for at least 28 days and breathing room air at the assessment time. Moderate BPD needed less than 30% oxygen at the assessment time. Severe BPD was classified as requiring greater than or equal to 30% oxygen or positive pressure ventilation at the assessment time. Since 2016, UMMC has used volume ventilation and continuous positive airway pressure (CPAP) more frequently compared to previous years. This study compared infants with moderate to severe BPD criteria and infants with mild to none BPD.

Renal Function Data

The incidence of acute kidney injury (AKI) was determined using the Modified Neonatal Staging Criteria as previously described in the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI.[19–23] We examined serum creatinine (SCr) measurements and daily UOP the day before NEC diagnosis, at NEC onset, at 24/48/72/96 hours after onset, and 1 week after NEC diagnosis. The maximum AKI stage reported was the highest SCr or UOPAKI stage 7 days after NEC onset. Our hospital laboratories measured SCr using the isotope dilution mass spectrometry method. The UOP was estimated using weighed diapers recorded by bedside nurses in the electronic medical charts. We

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stratified neonates as without severe (no or stage 1) and with severe (stage 2 and 3) AKIs as had been done in previous neonatal and pediatric studies.[20,24]

Statistical Methods

We summarized the data as mean and standard deviation (±SD) for normally distributed continuous variables. Comparisons between those with non/mild BPD and moderate to severe BPD were performed using Student's *t*-test, Welch's *t*-test, and ANOVA with or without Welch–Satterthwaite estimation of degrees of freedom depending on the equality of the variances. For continuous data exhibiting skewed distribution, the median with interquartile range (IQR; first quartile; third quartile) is presented, and differences in the data were tested using the Mann–Whitney *U*-test or Kruskal–Wallis test. Categorical data were summarized as counts with relative frequencies as percentages, and differences in the groups were analyzed using the Chi-square test (χ^2 test) or Fisher's exact tests when appropriate.[25] The multivariable effect of clinical and histopathological variables on the presence of moderate to severe BPD in preterm infants with surgical NEC was further evaluated with multiple logistic regression. We chose multivariable model candidate variables based on a priori selection for clinical importance and required univariate *p*-values ≤0.15 for association tests with moderate to severe BPD. Evaluations for significant multicollinearity led to the length of stay, necrosis, and GA being eliminated from the multivariable modeling process. A *p*-value of <0.05 was considered statistically significant for all the analyses, and all tests were two-sided. All the statistical analyses were performed in SAS (version 9.4).

Results

Ninety-two infants were included in the analysis. Out of 92,77.1% (71/92) of infants had moderate to severe BPD, and 22.8% (21/92) of infants had non/mild BPD at 36 weeks CGA. The cohort had a median GA of 26.2 weeks (IQR: 24.3–29.3) and a median BW of 767.5 g (IQR: 640–1,125). The study had34.8% (32/92) females and predominantly African–American (77.2% [71/92]) infants. Fifty-six infants (60.9%) were outborn. 69.5% (64/92) infants were born by Cesarean section, and 72.2% (65/90) received antenatal steroids. Additional full demographic, maternal, and clinical information has been summarized in ►Table 1.

The infants with moderate to severe BPD had a later age of NEC onset (13 [7, 23] vs. 5 days [2, 1]; $p = 0.001$), less fulminant NEC (5.6 [4/71] vs. 33.3% [7/21]; $p = 0.002$), significantly higher frequency of PDA (67.6 [48/71] vs. 28.6% [6/21]; $p = 0.001$) before NEC, had more central line days (59 [IQR: 36, 93] vs. 30.5 days [IQR: 14.5, 60]; $p = 0.01$), higher rate of cholestasis (71.8% [51/71] vs. 42.1% [8/21]; $p = 0.015$), had more antenatal steroids (80% [56/71] vs. 45% [9/21]; $p = 0.002$), younger GA (25.2 weeks [IQR 24, 27] vs. 31.6 weeks [IQR 28.4, 32.6]; $p < 0.001$), had lower BW (710 [IQR: 620, 911] vs. 1,600 grams [IQR: 1030, 2095]; $p < 0.001$), and had more severe AKI (67.6% [48/71] vs. 28.6% [6/21]; $p = 0.001$) compared to infants with non/mild BPD.

Infants with moderate to severe BPD were more likely to require invasive ventilation (76.3 [54/71] vs. 42.9% [9/21]; $p = 0.020$) at day 7 after birth and for a longer duration (7.5 [IQR: 4, 15] vs. 1.5 days [IQR: 1, 4]; $p = 0.003$) compared to infants with non/mild BPD.

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In addition, the infants with moderate to severe BPD received significantly longer invasive support (40.5 [IQR: 12, 59] vs. 6 days [IQR: 2, 13]) and noninvasive respiratory support (51 [IQR: 25, 93] vs. 5 days [IQR: 4, 8.5]; p 0.001) and needed higher FiO_2 following surgical NEC compared to the non/mild BPD infants. In addition, those infants with moderate to severe BPD following NEC were discharged on home oxygen more frequently than infants with non/mild BPD (38.1 [16/42] vs. 0% [0/11]; $p = 0.023$). Additional details of this data are summarized in ►Tables 2 and 3.

Postoperatively, those with moderate to severe BPD took significantly longer median time to reach full feeds (73.5 [IQR: 32,106] vs. 58 days [IQR: 42, 65]; $p = 0.024$) and needed parenteral nutrition for a longer period (109 [IQR: 77, 147] vs. 55 days [IQR: 19, 70]; $p < 0.001$). Those with moderate to severe BPD had significantly higher surgical morbidity (46.5% [33/71] vs. 14.3% [3/21]; $p = 0.008$) and a higher rate of intestinal failure (62.5 [40/79] vs. 13.3% [2/79]; $p < 0.001$) compared to those with non/mild BPD. The preterm infants with moderate to severe BPD had significantly lower median length at postnatal 36 weeks GA (41.2 [IQR: 39, 43.6] vs. 44.3 cm [IQR: 42.5, 48.4]; $p = 0.003$) compared to infants with non/mild BPD. Those infants with moderateto severe BPD had significantly more postnatal use of steroids (67.6 [48/71] vs. 38.1% [8/21]; $p = 0.015$) and a longer median length of hospitalization (161 [IQR: 112, 186] vs. 64 days [IQR: 20, 91]; $p < 0.001$) than those with non/mild BPD (►Table 4).

The preterm infants with moderate to severe BPD had greater percent inflammation ($p = 0.038$) and numerically lower mean necrosis score (1.5 ± SD = 1.3 vs. 2.2 ± SD = 1.3; $p = 0.04$) on intestine histopathology compared to the non/mild BPD group following surgical NEC (►Table 5).

On multivariable logistic regression analysis, lower BW (adjusted OR = 0.3, [95% confidence interval (CI): 0.1–0.5]; $p = 0.001$), the presence of PDA (adjusted OR = 10.3, [95% CI: 1.6–65.4]; $p = 0.0136$), and longer parenteral nutritional days (adjusted OR = 8.8, [95% CI: 2.0–43.0]; $p = 0.005$) were associated with higher odds of moderate to severe BPD. The multivariable logistic regression model results for factors associated with moderate to severe BPD are summarized in ►Table 6. Surgical morbidity was an independent risk factor for moderate to severe BPD after removing BW from the regression model (adjusted OR = 6, [95% CI: 1.2–38.7]; $p = 0.034$).

Discussion

Approximately three-fourths (77%) of infants following surgical NEC had moderate to severe BPD in this cohort. Those with moderate to severe BPD had significantly lower GA, BW, and a higher rate of PDA. In addition, these infants had late NEC onset and severe clinical course postoperatively compared to infants with non/mild BPD. Infants with moderate to severe BPD following NEC needed higher respiratory support for a longer duration, received parental nutrition and central line support for longer periods of time, had more AKI, intestinal failure, cholestasis, achieved enteral feeds >120 mL/kg later, and more often went home on oxygen support. These findings indicate a higher degree of lung compromise by NEC with a more severe inflammatory process and associated multisystem

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morbidity. We also noticed infants with moderate to severe BPD had poor linear growth at 36 weeks following NEC, as shown in a few reports.[26–28]

In this cohort, preterm infants with moderate to severe BPD had more severe AKI (67.6 vs. 28.6%) following NEC. AKI appears not to be an isolated event but instead reflects remote multiorgan dysfunction involving the lungs, heart, liver, intestines, and brain through an inflammatory mechanism involving neutrophil migration and cytokine expression increased oxidative stress as shown in animal models.[29] A recent study has also shown that AKI was associated with higher odds of BPD in preterm infants born between 29 and 32 weeks of gestation.[30] The fluid overload in an oliguric state or decreased renal function caused by AKI may affect the lung mechanics and exacerbate the BPD in preterm infants with surgical NEC.

In our cohort, surgical morbidity, especially wound dehiscence, was significantly and independently associated with moderate to severe BPD, but only after removing BW from the multivariable regression model (OR = 6.7, [95% CI: 1.2–38.7]; $p = 0.034$). This exploratory analysis, was not prespecified. It suggests that a greater severity of underlying intestinal pathology and requirement for a second surgery may be associated with higher odds of moderate to severe BPD. We hypothesize that the stresses of the second laparotomy, including anesthesia, sedation, paralytic agents, blood products, and assisted ventilation, expose the underlying preterm lung to additional oxidative, hypoxic, and inflammatory injury in preterm infants with surgical NEC. The consequences of a second laparotomy need further study, as well as the contribution of BW in understanding these associations.

Those with moderate to severe BPD had higher inflammatory percent involvement but less necrosis on intestinal pathology. We previously reported that incomplete resection of inflamed intestine was associated with longer hospital stay and mortality than complete resection.[31] The reasons and mechanisms leading to greater severity of BPD in preterm infants are still not fully understood. Toll-like receptor 4 activation by LPS has been associated with NEC in animal model studies.[32–34] Jia et al, have shown that TLR4 expression in the lung gradually increases during postnatal development and its association with NEC-associated BPD.[35] They have demonstrated that mice and humans with NEC-associated lung inflammation express higher pulmonary TLR4 than age-matched controls. The intestinal epithelial TLR4 activation induced high-mobility group box 1 release from the intestine, which activated pulmonary epithelial TLR4, leading to the induction of the neutrophil recruiting CXCL5 and the influx of proinflammatory neutrophils to the lung. The aerosolized administration of a carbohydrate TLR4 inhibitor prevented CXCL5 upregulation and blocked NEC-induced BPD in mice model.[35]

The adult models of intestinal injury have shown that there is cross-talk and homeostasis between the intestinal and respiratory systems via various pathways involving the microbiome, immune system, and metabolites.[14] The studies have shown that intestinal dysbiosis modulates the gut immune tolerance and response by affecting the alteration of dendritic cell priming of the T cells, involving various cytokines.[15] In addition, short-chain fatty acids, such as propionate produced by intestinal bacteria, can modulate lung inflammation in a mice model.[36] A multicenter clinical study has demonstrated that infants

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who developed NEC had elevated interleukin (IL)-1β, IL-6, IL-8, and IL-10, monocyte chemoattractant protein-1/CC-motif ligand-2, macrophage inflammatory protein-1β/CC-motif ligand-3 and C-reactive protein, creating a pro-inflammatory state.[37] In an extension of that study, the overall cytokine pattern generated suggests that BPD might be associated with impairment in the transition from innate immune response mediated by neutrophils to the adaptive immune response mediated by T-lymphocytes.[38]

Limitations

Limitations include that this study is a single-center retrospective albeit consecutive experience, perhaps reducing the study's generalizability. UMMC had an NEC rate of 12.8%, higher than other centers in the VON 2019 data. In our cohort, most neonates with surgical NEC are African American, likely due to the race distribution in Mississippi and the patient population of the UMMC. Between 2018 and 2020, 43% of infants born in Mississippi were African American, and approximately 60% of UMMC patients self-identify as African American. Since 2017, UMMC has used donor breast milk for infants less than 34 weeks when the mother's breast milk was not available. As per VON 2020 data, in infants with less than 1,500 grams, UMMC's exclusive breast milk usage rate is low (18 vs. 58%) compared to all VON network hospitals. In this cohort, sample size limits our ability to detect associations between clinical factors, NEC, BPD, and outcomes. Multiple comparisons yield a higher probability of Type I errors. Our study is observational, retrospective, and descriptive. Thus, causality cannot be established with or without formal adjustment for multiple comparisons. Given the limited availability of prior information on factors correlating BPD status in neonates with surgical NEC, our study is exploratory. It should be considered hypothesis generating with regard to the level of evidence provided.

Conclusion

In conclusion, three-fourths of preterm infants had moderate to severe BPD following surgical NEC. Infants developing moderate to severe BPD were significantly more likely to have a PDA. Surgical NEC infants with moderate to severe BPD were more likely to experience longer postoperative morbidity, acute kidney injury, intestinal failure, greater surgical complications, poor linear growth, require greater respiratory support, and longer length of hospitalization. Further research is required to identify and develop lung protection strategies in preterm infants with surgical NEC. Improved risk prediction for the development of BPD in surgical NEC infants from the postoperative time until discharge might help target lung protection strategies. Given the relative infrequency of surgical NEC, larger multicenter prospective and translational studies with adequate sample size are required to develop sound evidence-based risk stratification strategies, including inflammatory, metabolomics, nutritional, intestinal/lung microbiome, and genomic data in preterm infants with surgical NEC. Our study suggests the need to understand the inflammatory surge better and develop immunomodulatory strategies in preterm infants with surgical NEC.

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Key Points

- Three-fourths of preterm infants experienced severe lung injury following surgical NEC.
- The infants with severe moderate/severe BPD were most likely associated with greater duration of postoperative morbidity.
- There is need to understand and develop lung protective strategies in infants with surgical NEC.

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Table 1

Demographic and clinical features of neonates with surgical NEC stratified by BPD status

	N	Overall n (%)/median (IQR) N = 92	Non/mild BPD n (%)/median (IQR) N = 21	Moderate to severe BPD n (%)/median (IQR) N = 71	p-Value
Pregnancy-induced hypertension	92	27 (29.3)	8 (38.1)	19 (26.8)	0.31
Maternal chronic hypertension	79	14 (17.7)	3(16.7)	11 (18.0)	1
Chorioamnionitis	91	9 (9.9)	0 (0.00)	9 (12.9)	0.11
Antenatal steroids	90	65 (72.2)	9 (45.0)	56 (80.0)	**0.002**
Gestational age (wk)	92	26.2 (24.3, 29.3)	31.6 (28.4, 32.6)	25.2 (24, 27)	**<0.001**
Birth weight (g)	92	767.5 (640, 1,125)	1,600.0 (1,030.0, 2,095.0)	710.0 (620.0, 911.0)	**<0.001**
Small for gestational age	92	30 (32.6)	7 (33.3)	23 (32.4)	0.93
Gender (female)	92	32 (34.8)	5 (23.8)	27 (38.0)	0.22
Ethnicity	92				0.34
Caucasian		17 (18.5)	2 (9.5)	15(21.1)	
African American		71 (77.2)	18 (85.7)	53 (74.6)	
Latino		2 (2.2)	1 (4.8)	1 (1.4)	
Other		2 (2.2)	0 (0.00)	2 (2.8)	
Mode of delivery	92				0.38
C-section		64 (69.6)	13 (61.9)	51 (71.8)	
Vaginal		28 (30.4)	8 (38.1)	20 (28.2)	
Apgar's score <6 at 5 min	91	28 (30.8)	4 (19.0)	24 (34.3)	0.18
Outborn	92	56 (60.9)	12(57.1)	44 (62.0)	0.69
Patent ductus arteriosus	92	54 (58.7)	6 (28.6)	48 (67.6)	**0.001**
Patent ductus arteriosus, indomethacin treated	92	12 (13.0)	0 (0.00)	12 (16.9)	0.06
Patent ductus arteriosus, surgically ligated	92	5 (5.4)	0 (0.00)	5 (7.0)	0.58
Central line present (d)	87	52 (30, 80)	30.5 (14.5, 60)	59.0 (36.0, 93.0)	**0.010**
Positive blood culture sepsis	92	31 (33.7)	8 (38.1)	23 (32.4)	0.62
CRP on day of NEC onset (mg/L)	79	3.2 (1.2, 8)	2.6 (0.9, 4.6)	4.7 (1.4, 8.5)	0.08
CRP at 24 h after NEC onset (mg/L)	72	8 (3, 19.4)	5.4 (1.6, 17.0)	8.5 (3.0, 19.8)	0.16
CRP at 48 h after NEC onset (mg/L)	60	14.9 (3.3, 21.9)	7.8 (3.3, 20.3)	15.5 (3.9, 22.0)	0.39
CRP at 96 h after NEC onset (mg/L)	64	7.2 (4.1, 15.6)	5.4 (4.3, 24.5)	7.6 (4.1, 15.5)	0.93
CRP at 1 wk after NEC onset (mg/L)	64	5.3 (2.9, 8.2)	7.4 (6.8, 10.4)	4.8 (2.5, 8.0)	0.07

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	N	Overall n (%)/median (IQR) N = 92	Non/mild BPD n (%)/median (IQR) N = 21	Moderate to severe BPD n (%)/median (IQR) N = 71	p-Value
CRP at 2 wk after NEC onset (mg/L)	61	3.4 (1.9, 5.7)	8.1 (3.1, 14.7)	3.4 (1.7, 5.3)	**0.03**
Cholestasis at NEC onset	90	59 (65.6)	8 (42.1)	51 (71.8)	**0.015**
AKI by serum creatinine	92				0.24
No AKI		46 (50.0)	14 (66.7)	32 (45.1)	
Stage 1		19 (20.7)	3(14.3)	16 (22.5)	
Stage 2		12 (13.0)	3(14.3)	27 (38.0)	
Stage 3		15 (16.3)	1 (4.8)	8(11.3)	
AKI by urine output	92				**0.011**
No AKI		47 (51.1)	14 (66.7)	33 (46.5)	
Stage 1		4 (4.3)	1 (4.8)	3 (4.2)	
Stage 2		28 (30.4)	1 (4.8)	27 (38.0)	
Stage 3		13 (14.1)	5 (23.8)	8(11.3)	
Severe AKI vs. non-severe AKI Stage 2/3 vs. 0/1	92	54 (58.7)	6 (28.6)	48 (67.6)	**0.001**

Abbreviations: AKI, acute kidney injury; BPD, bronchopulmonary dysplasia; CRP, C-reactive protein (mg/L); IQR, interquartile range; NEC, necrotizing enterocolitis.

Note: Categorical variables are presented as count (percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with lung injury were evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate, otherwise Fisher-Freeman-Halton Exact test was used with low expected cell counts. Bold values are statistically significant.

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Table 2

NEC features and surgical morbidity in preterm infants with of surgical NEC stratified by BPD status

	N	Overall n (%)/median (IQR) N = 92	Non/mild BPD n (%)/median (IQR) N = 21	Moderate-to-severe BPD n (%)/median (IQR) N = 71	p-Value
Clinical presentation	92				0.80
Abdominal distension		83 (90.2)	19 (90.5)	64 (90.1)	
Bloody stools		7(7.6)	2 (9.5)	5 (7.0)	
Feeding intolerance		2(2.2)	0 (0.00)	2 (2.8)	
Pneumatosis	92	41 (44.6)	13 (61.9)	28 (39.4)	0.06
Pneumoperitoneum	92	51 (55.4)	12 (57.1)	39 (54.9)	0.85
Portal venous gas	92	6(6.5)	2 (9.5)	4(5.6)	0.61
Age of NEC onset (d)	92	10 (5, 23)	5 (2, 10)	13.0 (7.0, 23.0)	**0.001**
Fulminant NEC	92	11 (12.0)	7(33.3)	4(5.6)	**0.002**
Present of Penrose drain	89	38 (42.7)	5 (25.0)	33 (47.8)	0.06
Surgery <48 h	92	62 (67.4)	17 (81.0)	45 (63.4)	0.13
Time to surgery (h)			21 (4.5, 48)	51.5 (24, 232)	**0.001**
Length of bowel resected (cm)	89	12.7 (4.3, 28.8)	27.5 (6.15, 44.95)	12.0 (4.3, 24.9)	0.05
Region of bowel resected	84				0.82
Small bowel resected		53 (63.1)	11 (57.9)	42 (64.6)	
Large bowel resected		4 (4.8)	1(5.3)	3 (4.6)	
Combined large and small bowel resected		27 (32.1)	7 (36.8)	20 (30.8)	
Presence of ileocecal valve	91	65 (71.4)	13 (61.9)	52 (74.3)	0.27
Surgical morbidity (infection, adhesions, strictures, and dehiscence)	92	36 (39.1)	3(14.3)	33 (46.5)	**0.008**
More than one surgical morbidity (infection, adhesions, strictures, dehiscence)	92	12 (13.0)	1(4.8)	11 (15.5)	0.28
Adhesions	92	15 (16.3)	1 (4.8)	14 (19.7)	0.17
Wound dehiscence	92	14 (15.2)	0 (0.00)	14 (19.7)	**0.034**
Wound infection	92	6(6.5)	1 (4.8)	5 (7.0)	1
Stricture	92	8(8.7)	0 (0.00)	8 (11.3)	0.19
Fistula	92	6(6.5)	1 (4.8)	5 (7.0)	1
Compartment syndrome	92	2 (2.2)	1(4.8)	1 (1.4)	0.40
Intestinal failure	79	42 (53.2)	2(13.3)	40 (62.5)	**<0.001**

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Abbreviations: BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; IQR, interquartile range.

Note: Categorical variables are presented as count (percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with lung injury were evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate; otherwise, Fisher–Freeman–Halton exact test was used with low expected cell counts. Bold values are statistically significant.

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Table 3

Ventilation, oxygenation, and anthropometric data in infants with surgical NEC classified by BPD

Variable	N	Overall n (%)/median (IQR) N = 92	Non/mild BPD n (%)/median (IQR) N = 21	Moderate-to-severe BPD n (%)/median (IQR) N = 71	p-Value
Day 7 FiO_2	51	28 (21, 40)	23.0 (21.0, 46.0)	29.0 (22.0, 36.0)	0.58
Day 7 ventilation mode	52				**0.02**
Room air		4(7.7)	3(21.4)	1 (2.6)	
Intubated		35 (67.3)	6 (42.9)	29 (76.3)	
CPAP		5 (9.6)	3(21.4)	2 (5.3)	
HFNC		5 (9.6)	2 (14.3)	3 (7.9)	
Noninvasive (NIMV)		3 (5.8)	0 (0.00)	3 (7.9)	
Mode of ventilation outborn	36				1
Intubated		35 (97.2)	4 (100.0)	31 (96.9)	
NIMV		1(2.8)	0 (0.00)	1 (3.1)	
FiO_2 admission outborn	37	44 (29, 70)	47.5 (36, 77.5)	44.0 (28.0, 70.0)	0.47
Invasive ventilation duration before NEC	60	7 (3, 13.5)	1.5 (1,4)	7.5 (4, 15)	**0.003**
Non-invasive duration before NEC	32	8 (3.5, 15)	5.5 (2, 8)	9.5 (4, 17)	0.10
FiO2 7 d before NEC	31	25 (21, 40)	25.5 (21, 50)	25.0 (21.0, 38.0)	0.97
Ventilation mode 2 weeks after NEC	78				**<.001**
Room air		12 (15.4)	9 (64.3)	3 (4.7)	
Intubated		54 (69.2)	2(14.3)	52 (81.3)	
CPAP		5 (6.4)	1 (7.1)	4(6.3)	
HFNC		7 (9.0)	2(14.3)	5 (7.8)	
Invasive vent duration after NEC (d)	88	22 (8, 56)	6 (2, 13)	40.5 (12, 59)	**<.001**
Noninvasive duration after NEC	73	41 (11, 71)	5 (4, 8.5)	51.0 (25.0, 93.0)	**<.001**
FiO_2 after 2 weeks of NEC	79	28 (21, 36)	21.0 (21.0, 21.0)	30.0 (24.0, 36.0)	**0.001**
Home O_2	53	16 (30.2)	0 (0.00)	16 (38.1)	**0.02**
Weight at 36 weeks (g)	82	2,085 (1,800, 2,335)	2,332.0 (2,200.0, 2,445.0)	2,030.0 (1,800.0, 2,250.0)	**0.03**
Length at 36 weeks (cm)	81	42 (39, 44)	45.0 (43.0, 48.4)	41.3 (39.0, 43.8)	**0.002**
Weight for length	81	5 (4.5, 5.5)	5.1 (4.5, 5.4)	4.9 (4.5, 5.5)	0.68
Weight centile at 36 weeks	82	8 (2, 19)	18.0 (11.0, 26.0)	6 (2, 18)	0.06
Length centile at 36 weeks	81	2 (0, 10)	19.0 (4.0, 69.0)	2 (0, 9.5)	**0.02**

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Abbreviations: CPAP, continuous positive airway pressure; fiO_2, fraction of inspired oxygen; HFNC, high flow nasal cannula; IQR, interquartile range.

Note: Categorical variables are presented as count (percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with lung injury were evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate, otherwise Fisher–Freeman–Halton exact tests were used with low expected cell counts. Fenton chart used for anthropometric measurement. Bold values are statistically significant.

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Table 4

Postoperative outcomes in preterm infants with surgical NEC stratified based on BPD status

Variable	N	Overall n (%)/median (IQR) N = 92	Non/mild BPD n (%)/median (IQR) N = 21	Moderate-to-severe BPD n (%)/median (IQR) N = 71	p-Value
Postoperative Ileus days (d)	81	13 (9, 17)	9.5 (7, 14)	14.0 (10.0, 20.0)	0.07
Postoperative day at starting enteral feedings (d)	80	14 (10, 18.5)	10.0 (10.0, 14.0)	14.0 (11.0, 21.0)	0.11
Day of attainment of full enteral feedings (120 mL/kg)	67	67 (32, 89)	58.0 (42.0, 65.0)	73.5 (32, 106)	**0.024**
Duration of parenteral nutrition (d)	92	95 (57.5, 140)	55.0 (19.0, 70.0)	109.0 (77.0, 147.0)	**<.001**
Breast milk	92	16 (17.4)	1 (4.8)	15 (21.1)	0.107
Donor milk	92	21 (22.8)	1 (4.8)	20 (28.2)	**0.035**
Formula feeds	92	51 (55.4)	9 (42.9)	42 (59.2)	0.187
Breast milk and formula feeds	92	17 (18.5)	3(14.3)	14 (19.7)	0.753
Assisted ventilation (intubated)	90				**0.009**
Intubated		78 (86.7)	13 (68.4)	65 (91.5)	
High flow nasal cannula		7 (7.8)	2 (10.5)	5 (7.0)	
CPAP		3 (3.3)	2 (10.5)	1 (1.4)	
Room air		2 (2.2)	2 (10.5)	0 (0.00)	
24 h presser support	92	70 (76.1)	14 (66.7)	56 (78.9)	0.249
Postnatal use of steroids	92	56 (60.9)	8 (38.1)	48 (67.6)	**0.015**
Length of stay (d)	92	133 (85, 178)	64.0 (20.0, 91.0)	161.0 (112.0, 186.0)	**<.001**
Death	92	22 (23.9)	8 (38.1)	14 (19.7)	0.083

Abbreviations: BPD, bronchopulmonary dysplasia; IQR, interquartile range; NEC, necrotizing enterocolitis.

Note: Categorical variables are presented as count (percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with lung injury were evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate, otherwise Fisher–Freeman–Halton exact test were used with low expected cell counts. Bold values are statistically significant.

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Table 5

Histopathological changes in infants with surgical NEC classified by BPD status

	Overall N = 92	Non/mild BPD N = 21	Moderate to severe BPD N=71	p-Value
Necrosis, mean (± SD) Median (IQR)	1.6 (± 1.3) 2 (0, 3)	2.2 (± 1.3) 3(1,3)	1.5 (± 1.3) 1.5 (0, 2)	0.04
Inflammation, mean (±SD) median (IQR)	1.9 (± 1.0) 2 (1,2.5)	1.9 (± 1.3) 2(1,3)	1.9 (± 0.9) 2(1,2)	0.64
Hemorrhage, mean (± SD) Median (IQR)	2.3 (± 1.2) 2(2,3)	2.5 (± 1.5) 3 (2, 4)	2.2 (± 1.1) 2(2,3)	0.34
Reparative change, mean (±SD) Median (IQR)	0.4 (± 0.5) 0(0, 1)	0.3 (± 0.5) 0(0, 1)	0.5 (± 0.5) 0(0, 1)	0.24
Necrosis, n (%)	0(0, 1)	0(0, 1)	0 (0, 0)	0.08
0	23 (29.1)	3(17.6)	20 (32.3)	
< 25%	13 (16.5)	2 (11.8)	11 (17.7)	
25–50%	18 (22.8)	2 (11.8)	16 (25.8)	
50–75%	20 (25.3)	9 (52.9)	11 (17.7)	
> 75%	5(6.3)	1 (5.9)	4(6.5)	
Inflammation, n (%)				0.03
0	5 (6.3)	3(17.6)	2 (3.2)	
< 25%	23 (29.1)	4(23.5)	19 (30.6)	
25–50%	31 (39.2)	3(17.6)	28 (45.2)	
50–75%	14 (17.7)	5 (29.4)	9 (14.5)	
> 75%	6(7.6)	2 (11.8)	4(6.5)	
Hemorrhage, n (%)				0.08
0	6 (7.6)	3(17.6)	3 (4.8)	
< 25%	13 (16.5)	1 (5.9)	12 (19.4)	
25–50%	28 (35.4)	4(23.5)	24 (38.7)	
50–75%	17 (21.5)	3(17.6)	14 (22.6)	
> 75%	15 (19.0)	6 (35.3)	9 (14.5)	
Reparative change, n (%)	33 (41.8)	5 (29.4)	28 (45.2)	0.24

Abbreviations: BPD, bronchopulmonary dysplasia; IQR, interquartile range; NEC, necrotizing enterocolitis; SD, standard deviation.

Note: Categorical variables are presented as count (percentage). Continuous variables are presented as mean (standard deviation) and, if not normally distributed, as median with interquartile range. Continuous measures' statistical associations with lung injury were evaluated with the Kruskal–Wallis test. Differences in categorical measures' associations were tested using the Chi-square test when expected cell counts were adequate, otherwise Fisher-Freeman-Halton exact tests were used with low expected cell counts. Bold values are statistically significant.

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Table 6

Factors associated with moderate-to-severe BPD with multiple logistic regression analysis

Multiple logistic regression (moderate-to-severe BPD vs. non-/mild BPD)				
Effect	**OR**	**95% CI**		**p-Value**
		Lower CL	**Upper CL**	
Birth weight (grams per standard deviation)	0.281	0.078	0.530	**0.0013**
Patent ductus arteriosus (present vs. absent)	10.276	1.614	65.412	**0.0136**
Any surgical morbidity (present vs. none)	4.593	0.748	28.185	0.0996
TPN days (per standard deviation of days)	8.822	1.961	42.992	**0.005**
Severe AKI vs. nonsevere AKI	4.769	0.768	29.609	0.0936

Abbreviations: AKI, acute kidney injury; BPD, bronchopulmonary dysplasia; CI, confidence interval; NEC, necrotizing enterocolitis; OR, odds ratio; TPN, total parenteral nutrition.

Notes: Bold values are statistically significant.

Multiple logistic regression with stepwise selection (entry univariate significance level $p \leq 0.15$) was performed, the retained variables with birth weight are listed above after selection. Candidate variables into the model include:

- Patent ductus arteriosus (present vs. absent).
- NEC age onset (per cohort standard deviation in days).
- Any surgical morbidity (present vs. none).
- TPN days (per cohort standard deviation in days).
- Severe AKI vs. nonsevere AKI.
- Higher degree of inflammation (present vs. absent).
- Time to surgery from NEC onset (per cohort standard deviation in days).
- Combined FiO_2.

Combined FiO_2 is defined as the combination of FiO_2 admission outborn and day 7 FiO_2. Higher degree of inflammation was defined as inflammation involving >25% of the specimen area. The OR and its 95% CI for the continuous variables were expressed as per standard deviation of the variable in the cohort.

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