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Clinical Correlates of Cholestasis in Preterm Infants with Surgical Necrotizing Enterocolitis

Parvesh Mohan Garg[1,2,3], **Isabella Pittman**[2], **Joe Yi**[4], **Victoria G Weis**[5], **Ricardo Jorge Rodriguez**[1], **Mitchell R Ladd**[6], **Jessica L Rauh**[6], **Anna Greene McDonald**[7], **Cherrie Welch**[1], **Muralidhar Hebbur Premkumar**[8], **Padma P Garg**[2], **Akhil Maheshwari**[3,9]

[1]Department of Pediatrics/Neonatology, Atrium Health Wake Forest Baptist, Wake Forest School of Medicine, Winston Salem, North Carolina, United States of America

[2]Department of Pediatrics, University of Mississippi Medical Center, Jackson, Mississippi, United States of America

[3]Global Newborn Society, Clarksville, Maryland, United States of America

[4]Frank Porter Graham Child Development Institute, University of North Carolina at Chapel Hill, NC, United States of America

[5]Department of Regenerative Medicine, Wake Forest School of Medicine, Winston Salem, North Carolina, United States of America

[6]Department of Pediatric Surgery, Atrium Health Wake Forest Baptist, Wake Forest School of Medicine, Winston Salem, North Carolina, United States of America

[7]Department of Pathology, Atrium Health Wake Forest Baptist, Wake Forest School of Medicine, Winston Salem, North Carolina, United States of America

[8]Texas Children Hospital, Baylor College of Medicine, Houston, Texas, United States of America

[9]Louisiana State University Health Sciences Center – Shreveport, LA, United States of America

Abstract

Background: We sought to investigate the clinical determinants and outcomes of cholestasis in preterm infants with surgical necrotizing enterocolitis (sNEC).

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Corresponding Author: Parvesh Mohan Garg, Department of Pediatrics/Neonatology, Atrium Health Wake Forest Baptist, Wake Forest School of Medicine, Winston Salem, North Carolina, United States of America, Phone: +1 252 364 5800, gargparvesh@hotmail.com.

Author's Contributions

PMG, PPG, and AM designed the study. PMG, IP, JY, VGW, RJR, ML, CW, MHP, PPG, AGM, JLL, and AM analyzed the data and wrote the paper. All the authors contributed and approved the paper.

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Supplementary Materials

All the Supplementary Table is available online on the website of https://www.newbornjournal.org/.

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Methods: Retrospective comparison of clinical information in preterm infants who developed cholestasis vs those who did not.

Results: Sixty-two (62/91, 68.1%) infants with NEC developed cholestasis at any time following the onset of illness. Cholestasis was seen more frequently in those who had received ionotropic support at 24 hours following sNEC diagnosis (87.1% vs 58.6%; $p = 0.002$), had higher mean C-reactive protein levels 2 weeks after NEC diagnosis ($p = 0.009$), had blood culture-positive sepsis [25 (40.3%) vs 4 (13.8%); $p = 0.011$], received parenteral nutrition (PN) for longer durations (108.4 ± 56.63 days vs 97.56 ± 56.05 days; $p = 0.007$), had higher weight-for-length z scores at 36 weeks' postmenstrual age [−1.0 (−1.73, −0.12) vs −1.32 (−1.76, −0.76); $p = 0.025$], had a longer length of hospital stay (153.7 ± 77.57 days vs 112.51 ± 85.22 days; $p = 0.024$), had intestinal failure more often (61% vs 25.0%, $p = 0.003$), had more surgical complications (50% vs 27.6%; $p = 0.044$), and had >1 complication (21% vs 3.4%; $p = 0.031$). Using linear regression, the number of days after surgery when feeds could be started [OR 15.4; confidence interval (CI) 3.71, 27.13; $p = 0.009$] and the postoperative ileus duration (OR 11.9, CI 1.1, 22.8; $p = 0.03$) were independently associated with direct bilirubin between 2 and 5 mg/dL (mild–moderate cholestasis) at 2 months of age. The duration of PN was independently associated with direct bilirubin >5 mg/dL (severe cholestasis) at 2 months of age in these patients.

Conclusion: Cholestasis was seen in 68% of infants following surgical NEC. The most likely contributive factors are intestinal failure and subsequent PN dependence for longer periods. Our data suggest that identification and prevention of risk factors such as sepsis and surgical complications and early feeds following NEC surgery may improve outcomes.

Keywords

Anthropometric; Adhesions; Bell's criteria; Cholestasis; Farnesoid X; Fenton growth; Fish oil-containing lipid emulsion; Fistula; Ileocecal valve; Intralipids; Infant; Intestinal failure; Liver X receptors; Logistic regression; Necrotizing enterocolitis; Neonate; Outcome; Parenteral nutrition; Perforations; Pneumoperitoneum; Pneumatosis; Portal venous gas; Preterm; Premature; Soybean oil–medium chain triglycerides–olive oil–fish oil; Surgical site infection; Stricture; Term-equivalent age; Weight-for-length; Wound dehiscence; z-scores

Introduction

Necrotizing enterocolitis (NEC) affects 6–10% of very-low-birth-weight premature infants[1,2] and surgical disease remains a leading cause of death in almost 40–50% of these patients.[3] Nearly 13–45% of infants with surgical NEC develop intestinal failure,[4,5] which is associated with prolonged hospitalization and higher economic burden.[6]

Short bowel syndrome secondary to surgical NEC in preterm infants is associated with a longer hospital stay, growth failure, cholestasis, and liver injury.[7] Cholestasis is frequently seen in these infants, affecting 42–85%.[8–11] Bowel length and preservation of the ileocecal valve are the major predictors of weaning from PN.[5] The duration of parenteral nutrition (PN) following surgical NEC is an independent clinical risk factor for cholestasis.[8] Thus, while these are well-known risk factors for cholestasis following surgical necrotizing enterocolitis (sNEC), other clinical predictors of cholestasis after sNEC are not well-studied. African American infants show a higher prevalence of surgical NEC and its associated

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mortality,[12] although the clinical predictors of cholestasis in African American preterm infants with surgical NEC need further study.

We have previously published systemic morbidities and clinical outcomes in preterm infants with sNEC.[13–17] In these reports, we investigated the clinical determinants and outcomes of cholestasis in these patients. We compared clinical information in preterm infants with and without cholestasis in a sNEC cohort. The associations between clinical factors and outcomes were assessed with univariate and multivariable logistic regression analyses. We now compared the clinical determinants and outcomes of cholestasis in preterm infants with sNEC.

Methods

Study Design

The study was conducted at the University of Mississippi Medical Center (UMMC) Neonatal Intensive Care Unit, a Level IV unit with 900–1000 admissions yearly and referrals from the entire state. The UMMC Institutional Review Board approved the study with a waiver of informed parental consent. All infants admitted between January 2013 and December 31, 2018, with a diagnosis of NEC (Bell stage III), were included in the study.[18] Neonates diagnosed with medical NEC, isolated ileal perforation, kidney anomalies, congenital heart disease, and intestinal atresia were excluded from the analysis.

Clinical Information

Demographic data collected included birth weight (BW), gestational age (GA), appropriate for GA status (AGA), race, sex, mode of delivery, outborn status (referred from other hospitals), and Apgar score ≤6 at 5 minutes. Maternal information collected included clinically diagnosed chorioamnionitis, antenatal steroids, and pregnancy-induced hypertension (PIH). Neonatal data included patent ductus arteriosus (PDA), respiratory support, inotrope (dopamine) use 24 hours after NEC onset, hematological information, ibuprofen/indomethacin treatment (before NEC), and frequency of cholestasis (direct bilirubin >2 mg/dL) at any time after NEC diagnosis. Sepsis-related variables included blood culture-proven sepsis at NEC onset and duration/type of antibiotics.

NEC Information

The diagnosis of NEC was based on abdominal X-ray findings, including portal venous gas, pneumatosis, and pneumoperitoneum and the cases were classified using Bell's criteria.[18] Data on the age at NEC diagnosis and frequency of Bell stage III/surgical NEC were compiled.[18,19]

Histopathological Evaluation

Hematoxylin- and eosin-stained resected intestinal tissue sections were evaluated by a team of a board-certified gastrointestinal pathologists and a senior pathology trainee for necrosis, inflammation, hemorrhage, and reparative changes.[20]

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Cholestasis

We recorded the data on cholestasis (direct bilirubin >2 mg/dL) at the time of NEC onset[21] and every week up to 2 months thereafter. We defined mild–moderate cholestasis as a direct bilirubin between 2 and 5 mg/dL. Severe cholestasis was defined as a direct bilirubin >5 mg/dL.

Postoperative and Outcome Data

We also recorded information on intestinal failure (parenteral nutrition >90 days) and surgical morbidity. Postoperative information such as postoperative ileus days (defined as the number of days infants were NPO after bowel surgery), time to reach full enteral feeds (≥120 mL/kg/day), total parenteral nutrition days, length of stay, and hospital mortality were measured. We defined mortality as death due to any reason before hospital discharge. Surgical morbidity/complications were defined as stricture, fistula, wound dehiscence, surgical site infection (including abscess), adhesions, and perforations. If an infant had more than one abovementioned complication at any time following NEC were grouped into more than 1 surgical complication cohort.

Somatic Growth

We tracked anthropometric variables, including weight, height, weight-for-length, head circumference, and respective z-scores using sex-specific Fenton growth charts at 36 weeks postmenstrual age.

Brain Growth

Per our hospital practice, we obtained brain MRI without contrast in all VLBW infants when clinically indicated at a corrected age of 36 weeks or before discharge. The most common reason for not obtaining MRI was death or transfer to a different center for bowel transplantation. All term-equivalent age (TEA) MRI scans were scored independently by two pediatric neuroradiologists who were unaware of the initial MRI reading and the diagnosis of cholestasis. We used a 8-scale scoring system for white and gray matter injury developed by Woodward et al.[22]

Statistical Methods

Demographic and clinical information in preterm infants with and without cholestasis in the surgical NEC cohort were compared. Continuous data were summarized as median (1st quartile, 3rd quartile) with Mann–Whitney U or Kruskal–Wallis tests for differences. Categorical data were summarized as numerical counts and percentages. Variability was quantified using standard deviations (SDs). Group differences were tested with Chi-squared or Fisher's exact tests. Variables with significant association (p-value less than 0.05) in univariate analysis were candidates for the multivariable models.

A multinomial logistic regression was conducted to assess the potential risk of cholestasis associated with the following variables: pressor support 24 hours after NEC, indomethacin use, time to surgery from NEC onset, TPN days, postoperative ileus days, and time to reach full feeds. Simple linear regression was conducted to assess the predictors for persistent

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cholestasis at 2 months following the surgical NEC with the following continuous variables: length of stay, time to reach full feeds, TPN days, and length of postoperative ileus. A generalized linear regression using a binomial distribution was conducted on mortality, time to reach full feeds, intestinal failure, surgical complication, a single-surgical complication, more than one surgical complication, and white matter injury. A p-value < 0.05 was considered statistically significant for all the analyses. All analyses were performed in SPSS and SAS 9.4.

Results

Risk Factors for Cholestasis after sNEC and Outcomes of Cholestasis in sNEC

In our cohort of 91 infants with surgical NEC, 62 (62/91, 68.1%) infants developed cholestasis at some time following the onset of NEC. The patients had a gestational age of 27.2 ± 4 weeks (mean ± SD) and birth weight of 1011 ± 563.9 gms. The majority were male infants (63/91, 69.2%) and of African American ancestry (66/91, 72.5%). Infants with cholestasis received inotropic support more frequently at 24 hours following surgical NEC (87.1% vs 58.6%; $p = 0.002$), had higher mean CRP levels at 2 weeks after the onset of surgical NEC (6.26 ± 5.70 vs 2.23 ± 1.57; $p = 0.009$), and had positive blood culture sepsis more often than those without cholestasis (25 (40.3%) vs 4 (13.8%), $p = 0.011$).

Infants who developed cholestasis received parenteral nutrition (PN) for longer periods (108.4 ± 56.6 days vs 97.56 ± 56 days; $p = 0.007$), had higher weight for length z-scores at 36 weeks postmenstrual age [−1.0 (−1.73, −0.12) vs −1.32 (−1.76, −0.76); $p = 0.025$], and had a longer length of hospital stay (153.7 ± 77.5 days vs 112.51 ± 85 days; $p = 0.024$) when compared with infants with no cholestasis. Infants with cholestasis developed intestinal failure more often (35 (61%) p 6 (25%), $p = 0.003$), had more surgical complications following NEC (31 (50%) vs 8 (27.6%), $p = 0.044$), and had >1 complication (13 (21%) vs 1 (3.4%), $p = 0.031$) than those without cholestasis. The data are summarized in Tables 1 to 3. There was no significant difference in intestinal histopathology, length of bowel resected, and the white matter injury on the brain MRI nor mortality in the two groups.

On multivariable logistic regression modeling, the duration of PN (OR 1.026; CI 1.004–1.050; $p = 0.0235$) and the need for inotropic support for 24 hours following NEC (OR 6.68; CI 1.374–32.562; $p = 0.0186$) were independent risk factors for cholestasis. The data are summarized in Table 4.

Risk Factors and Outcomes of Cholestasis at 2 Months Following NEC

About 52 infants were eligible for the cholestasis analysis at 2 months following surgical NEC. In total, 15/52 (28.8%) infants had complete resolution of cholestasis. Out of 37 infants with persistent cholestasis, 22/52 (42.3%) had direct bilirubin levels between 2 and 5 mg/dL (mild–moderate) and 15/52 (28.8%) had direct bilirubin levels more than 5 mg/dL (severe cholestasis).

Those with resolved cholestasis at 2 months following the onset of surgical NEC had higher birth weight (1192.6 ± 623.8 vs 829±456 gms; $p = 0.024$), higher CRP levels at 48 and 96 hours ($p < 0.05$), and required small bowel resected less often [5/51 (9.8%) vs 28/51

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(54.9%); $p = 0.004$] following surgical NEC. The gestational age, age of surgical NEC onset, length of bowel resection, surgical morbidities, and death were not statistically significant in infants with and without resolved cholestasis at 2 months following onset of the surgical NEC. The data are summarized in Supplementary Table 1.

On multinominal logistic regression, infants with surgical NEC had longer durations of postoperative ileus (11.9, CI 1.1, 22.8; $p = 0.03$), which was independently associated with direct bilirubin levels between 2 and 5 mg/dL (mild–moderate cholestasis) at 2 months of age. The duration of total PN was independently associated with direct bilirubin >5 mg/dL (severe cholestasis) at 2 months of age in infants (OR 37.14; 4.26, and 70.03; $p = 0.0269$). The data are summarized in Table 5.

Discussion

In our cohort, almost 68% of cases had cholestasis at any time following surgical NEC. Infants with cholestasis were sicker at the time of disease onset as evidenced by the need for inotropic support at 24 hours and the frequency of blood culture-proven sepsis. Infants with cholestasis had a higher incidence of intestinal failure (56.5% vs 20.7%), received PN for longer durations, and were more likely to have >1 surgical complication. Those with cholestasis stayed in the hospital almost 6 weeks longer than those without, although there was no overall increase in mortality than these controls. Unlike other reports,[8] we saw no significant differences in gestational age and birthweight in infants with and without cholestasis. In our cohort of surgical NEC, we also did not find significant differences in the presence of an ileocecal valve, bowel histopathology, and the length of bowel resection. However, patients with cholestasis (direct bilirubin >2 mg/dL) had a higher incidence of bloodstream infections following surgical NEC; in sepsis-associated liver injury, bacterial toxins may have induced pro-inflammatory cytokines and caused ischemic liver injury.[23]

In a retrospective study of 225 infants with NEC/SIP from Finland, investigators found intestinal failure-associated cholestasis (IFAC) in 42% of cases.[9] In multivariate logistic regression analysis, IFAC development was associated with septicemia and repeated surgical procedures. However, there was no increase in overall mortality.[9] We observed similar findings in our cohort; patients with cholestasis had more surgical complications following NEC and a larger number of infants had >1 complication. Infants who needed multiple surgical procedures required PN support for a longer duration with increased risk for cholestasis.

A recent multicenter observational study of 465 preterm infants assessing the risk factors associated with cholestasis indicated that the maximum dose of amino acids, extra uterine growth restriction, feeding intolerance, surgically treated NEC, and longer total hospital stay were independent risk factors for the development of PN-associated cholestasis (PNAC).[24] soybean oil–medium chain triglycerides–olive oil–fish oil (SMOF®) and breastfeeding were protective factors for PNAC. In comparison, in our cohort, the infants with any cholestasis following surgical NEC had longer length of stay on univariate analysis alone. We observed higher weight-for-length ratio most likely due to consistent adequate calories and proteins provided by the PN. However, at our center, we used the Intralipids® as a fat source that

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may have contributed to the cholestasis frequency observed. We did not collect data on the maximum dose of amino acid and dextrose concentration used in preterm infants with cholestasis.

A recent metanalysis by Zou et al.[25] indicated that fish oil-containing lipid emulsion significantly reduced the occurrence of PNAC with a risk ratio (RR) = 0.53, 95% confidence interval (CI) 0.36–0.80, $p = 0.002$. In mice, macrophage-derived interleukin (IL)-1β seems to play a key role in PNAC, activating hepatocyte nuclear factor-kappa B (NF-κB), which in turn interferes with farnesoid X and liver X-receptor signaling to suppress the transcription of bile and sterol transporters, thereby causing cholestasis.[26] Hepatic macrophages and related IL-1β and NF-κB signaling may be new targets for restoring bile and sterol transport to treat or prevent PNAC.

Similar to our study, Duro et al. reported cholestasis in 70% of cases in a predominantly male cohort with a median gestational age of 26 weeks.[8] They identified small-bowel resection or creation of jejunostomy (odds ratio [OR] 4.96, 95% confidence interval [CI] 1.97–12.51, $p = 0.0007$) and duration of PN in weeks (OR 2.37, 95% CI 1.56–3.60, $p < 0.0001$) as independent risk factors for PN-associated liver disease (PNALD) in preterm infants with surgical NEC.[8] Just as in our cohort, the duration of PN was independently associated with cholestasis.

Our study has some important limitations. First, this was a single-center experience, with predominantly African American patients reducing the study's generalizability. Second, the retrospective study design and a small sample size limited our power to detect associations between clinical factors, NEC, and outcomes. Further, the small sample size may have resulted in type-I errors from multiple comparisons. Finally, most of the neonates with surgical NEC were African American. While this is partly due to race distribution in Mississippi, this may also be related to adverse social determinants of health and/or genetic risk for surgical NEC.

In summary, cholestasis is a common morbidity following surgical NEC and it is most likely secondary to intestinal failure and PN dependence for a longer period. We speculate that identification of risk factors such as sepsis and surgical complication following NEC surgery may allow the development of preventive strategies for cholestasis and improve outcomes. There is a need for large prospective multicenter clinical and translational studies to fully understand the mechanisms, risk factors for, and impact of cholestasis on health and outcomes in premature infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Necrotizing enterocolitis is a major cause of morbidity and mortality in premature infants.
- In a retrospective study, we reviewed the medical records of 91 infants to identify the clinical determinants and outcomes of cholestasis in preterm infants with surgical necrotizing enterocolitis. Sixty-two (62/91, 68.1%) infants with NEC developed cholestasis at any time following the onset of illness.
- Cholestasis was seen more frequently in those who had received ionotropic support at 24 hours following the diagnosis of surgical NEC, had higher C-reactive protein levels, 2 weeks after the diagnosis of NEC, had blood culture-positive sepsis, received parenteral nutrition for longer durations, had higher weight-for-length z-scores at 36 weeks postmenstrual age, had a longer length of hospital stay, had intestinal failure, and had more surgical complications.
- Cholestasis is seen in most infants recovering from surgical NEC. Intestinal failure and subsequent dependence on parenteral nutrition for long periods are important predictors.

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Table 1:

Clinical information of surgical NEC infants with and without cholestasis

	N	Total (N = 91)	No cholestasis (N = 29)	Cholestasis (N = 62)	p-value
Prenatal information					
Chronic hypertension, *n* (%)	75	12 (16.0)	4 (17.4)	8 (15.4)	0.83
Antenatal steroid use, *n* (%)	88	65 (73.9)	18 (66.7)	47 (77.0)	0.31
Infant information					
Gestational age (weeks, mean ± SD)	91	27.2 (4.0)	27.8 (4.0)	27.0 (4.0)	0.35
Birth weight (gm, mean ± SD)	91	1011.0 (563.9)	1112.4 (610.3)	963.6 (539.4)	0.24
Male, *n* (%)	91	63 (69.2)	22 (79.5)	41 (66.1)	0.35
Ethnicity, *n* (%)	91				0.23
African American		21 (23.1)	10 (34.5)	11 (17.7)	
Caucasian		66 (72.5)	48 (77.4)	18 (62.1)	
Latino		2 (2.2)	1 (3.4)	1 (1.6)	
Other		2(2.2)	0 (0.0)	2 (3.2)	
C-section, *n* (%)	91	62 (68.1)	22 (75.9)	40 (64.5)	0.28
Out born, *n* (%)	91	62 (68.1)	18 (62.1)	44 (71.0)	0.40
Ventilation following NEC, *n* (%)	88				0.08
Intubation		78 (88.6)	23 (82.1)	55 (91.7)	
CPAP		7 (8.0)	2 (7.1)	5 (8.3)	
High flow		1 (1.1)	1 (3.6)	0 (0.0)	
Room air		2 (2.3)	2 (7.1)	0 (0.0)	
Patent ductus arteriosus, *n* (%)	91	57 (62.6)	15 (51.7)	42 (67.7)	0.14
Pressor support 24 h after NEC, *n* (%)	91	71 (78.0)	17 (58.6)	54 (87.1)	***0.002***
Indomethacin use, *n* (%)	91	12 (13.2)	1 (3.4)	11 (17.7)	0.06

The presence of bold and italic values signified $p < 0.05$

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Table 2:

NEC disease features in infants with and without cholestasis

	N	Total (N = 91)	No cholestasis (N = 29)	Cholestasis (N = 62)	p-value
NEC disease features					
NEC age of onset (days, median ± SD)	91	17.2 (15.6)	14.7 (15.4)	18.4 (15.7)	0.30
Time to surgery from NEC onset (hours, mean ± SD)	91	243.3 (507.8)	124.0 (407.1)	299.1 (542.6)	0.13
Radiologic findings, *n* (%)	91				
Pneumatosis		51 (56.0)	18 (62.1)	33 (53.2)	0.43
Portal venous gas		6 (6.6)	0 (0.0)	6 (9.7)	0.08
Pneumoperitoneum		45 (49.5)	17 (58.6)	28 (45.2)	0.23
Penrose drain, *n* (%)	87	24 (39.1)	7 (25.9)	27 (45.0)	0.09
Presence of ileocecal valve, *n* (%)	90	61 (67.8)	22 (75.9)	39 (63.9)	0.26
Region of bowel resected *n* (%)	88				0.50
Small bowel		56 (63.6)	19 (70.4)	37 (60.7)	
Large bowel		2 (2.3)	0 (0.0)	2 (3.3)	
Combined large and small bowel		30 (34.1)	8 (29.6)	22 (36.1)	
Length of bowel resected (cm, mean ± SD)	91	23.3 (24.2)	23.6 (26.6)	23.2 (23.2)	0.94
Necrosis grade (mean ± SD)	91	1.6 (1.3)	1.6 (1.3)	1.6 (1.3)	0.81
Inflammation grade (mean ± SD)	91	1.9 (1.0)	1.7 (1.0)	2.0 (1.0)	0.09
Hemorrhage grade (mean ± SD)	91	2.3 (1.2)	2.5 (1.0)	2.2 (1.2)	0.24
Healed, *n* (%)	91	41 (45.1)	10 (34.5)	31 (50.0)	0.12
Sepsis variables					
Positive blood culture sepsis, *n* (%)	91	29 (31.9)	4 (13.8)	25 (40.3)	**0.01**
CRP on the day of NEC (mg/dL, mean ± SD)	77	7.8 (8.7)	5.7 (7.3)	8.8 (9.2)	0.13
CRP 24 hours after NEC (mg/dL, mean ± SD)	72	12.6 (11.3)	8.6 (9.6)	14.5 (11.6)	**0.039**
CRP 48 hours after NEC (mg/dL, mean ± SD)	65	15.0 (11.7)	12.8 (12.8)	16.0 (11.1)	0.32
CRP 96 hours after NEC (mg/dL, mean ± SD)	67	11.4 (11.4)	9.6 (7.8)	11.9 (12.2)	0.50
CRP 1 week after NEC (mg/dL, mean ± SD)	65	9.0 (9.6)	6.6 (6.4)	9.7 (10.3)	0.27
CRP 2 weeks after NEC (mg/dL, mean ± SD)	64	5.3 (5.3)	2.2 (1.6)	6.3 (5.7)	**0.009**
Central line days (days, mean ± SD)	84	60.7 (41.3)	50.4 (34.6)	65.0 (43.4)	0.14

The presence of bold values signified $p < 0.05$

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Table 3:

Postoperative intestinal and outcomes information in infants with and without cholestasis

	N	Total (N = 91)	No cholestasis (N = 29)	Cholestasis (N = 62)	p-value
Postoperative intestinal features					
Time to reach full feeds (days, mean ± SD)	66	71.3 (45.6)	58.1 (47.8)	77.1 (44.0)	0.12
Days of starting feeds (days, mean ± SD)	80	19.3 (17.0)	14.0 (10.0)	21.5 (18.8)	0.08
Days of TPN (days, mean ± SD)	90	97.6 (56.1)	74.7 (48.1)	108.4 (56.6)	**0.007**
Postoperative ileus (days, mean ± SD)	81	17.6 (15.5)	13.4 (10.0)	19.2 (17.0)	0.13
Surgical complication, *n* (%)	91	39 (42.9)	8 (27.6)	31 (50.0)	**0.044**
Single complication, *n* (%)	91	23 (25.3)	6 (20.7)	17 (27.4)	0.49
>1 complication, *n* (%)	91	14 (15.4)	1 (3.4)	13 (21.0)	**0.031**
Wound dehiscence, *n* (%)	91	15 (16.5)	2 (6.9)	13 (21.0)	0.09
Wound infection, *n* (%)	91	8 (8.8)	1 (3.4)	7 (11.3)	0.22
Adhesions, *n* (%)	91	20 (22.0)	4 (13.8)	16 (25.8)	0.20
Fistula, *n* (%)	91	5 (5.5)	0 (0.0)	5 (8.1)	0.12
Intestinal failure, *n* (%)	83	42 (50.6)	6 (25.0)	36 (61.0)	**0.003**
Outcomes					
Weight z-scores @36 weeks	72	−1.67 (−2.1, −0.88)	−1.68 (−2.04, −1.05)	−1.54 (−2.11, −0.87)	0.38
Length z-scores @36 weeks	72	−1.92 (−3.26, −1.30)	−1.67 (−3.66, −1.19)	−2.04 (−3.26, −1.35)	0.30
Weight-for-length z-scores @36 weeks	72	−1.11 (−1.74, −0.194)	−1.32 (−1.76, −0.76)	−1.0 (−1.73, −0.12)	**0.025**
Head circumference z-scores @36 weeks	72	−2.16 (−2.72, −0.98)	−1.92 (−2.82, −0.942)	−2.39 (−2.77, −0.92)	0.30
White-matter injury, *n* (%)	60	28 (46.7)	9 (50.0)	19 (45.2)	0.74
Length of stay (days, mean ± SD)	91	140.5 (81.6)	112.4 (84.2)	153.7 (77.5)	**0.024**
Death	91	22 (24.2)	6 (20.7)	16 (25.8)	0.60

The presence of bold values signified $p < 0.05$

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Table 4:

Regression analysis

N = 65	Exp (B)	95% CI	Significance
Pressor support 24 hours after NEC	6.689	1.374–32.562	**0.0186**
Indomethacin use	4.783	0.352–64.991	0.2397
Time to surgery from NEC onset	1.001	0.999–1.003	0.4012
TPN days	1.026	1.004–1.050	**0.0235**
Days of starting feeds	1.109	0.996–1.235	0.0596
Time to reach full feeds	0.982	0.959–1.005	0.1213
Intercept	0.148		0.1099

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Table 5:

Bivariate analysis of resolved cholestasis

	Direct bilirubin at 2 months of age ≤5 [3]			Direct bilirubin at 2 months of age ≥5 [3]			
	β	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**	**n**
Length of stay[1]	8.39	−34.30, 51.09	0.7000	38.80	−8.18, 85.78	0.1055	53
Mortality[2]	0.74	−1.62, 3.11	0.5385	1.95	−0.35, 4.24	0.0966	53
Achievement of full feeds[2]	−1.79	−4.03, 0.45	0.1174	−1.25	−3.64, 1.14	0.3044	50
Time to reach full feeds[1]	20.54	−8.50, 49.59	0.1657	14.74	−16.92, 46.4	0.3615	43
Days of starting feeds[1]	15.42	3.71, 27.13	**0.0099**	0.67	−12.10, 13.43	0.9185	52
TPN days[1]	21.40	−8.60, 51.40	0.1620	37.14	4.26, 70.03	0.0269	52
Short gut syndrome[2]	1.16	−0.36, 2.68	0.1347	0.72	−0.83, 2.28	0.3627	50
Post-op ileus[1]	11.95	1.10, 22.80	**0.0309**	0.60	−11.23, 12.43	0.9208	52
Surgical complication[2]	0.05	−1.26, 1.35	0.9442	0.54	−0.91, 1.99	0.4656	53
Single complication[2]	0.56	−0.99, 2.11	0.4780	0.98	−0.65, 2.61	0.2392	53
More than 1 complication[2]	−0.55	−2.12, 1.03	0.4957	Low sample size			53
White-matter injury[2]	−0.68	−2.23, 8.88	0.3930	−0.15	−1.92, 1.61	0.8640	38

[1]Continuous outcome uses linear regression;

[2]Binary outcome uses logistic regression;

[3]Reference level direct bilirubin at 2 months of age <2

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