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Risk Factors for Postoperative Complications in Preterm Infants with Surgical Necrotizing Enterocolitis and Associated Outcomes

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Abstract

Background: We aim to determine clinical risk factors for postoperative complications in preterm infants with surgical necrotizing enterocolitis (NEC) or spontaneous intestinal perforation (SIP).

Methods: A retrospective cohort study of preterm infants with surgical NEC or SIP to compare clinical factors between those with and without postoperative complications.

Results: 78/109 (71.5%) infants had any complication following surgical NEC. Adhesions (20/35, 57.1%) and wound infection (6/35, 17.1%) were the most common single surgical complications. Patients with a single surgical complication (35/66, 53%) were significantly less likely to be exposed to antenatal steroids, more frequently had a jejunostomy, needed a central line longer, and had a longer length of stay than those without any surgical complication. Infants with >1 surgical complication (43/71, 60.5%) included mainly females, and had AKI more frequently at NEC onset, lower weight z-scores and lower weight for length z- scores at 36 weeks PMA than those without any complications.

On multinomial logistic regression, antenatal steroids exposure (OR 0.23 [CI 0.06, 0.84]; p=0.027) was independently associated with lower risk and jejunostomy 4.81 (1.29, 17.9) was independently associated with higher risk of developing a single complication. AKI following disease onset (OR 5.33 (1.38, 20.6), P=0.015) was independently associated with >1 complication in surgical NEC/SIP infants.

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Author Contribution:

PMG designed the study; PMG, RR, PPG and IP collected, and MAYA analyzed the data. PMG, MAYA, PP, ML and all the authors reviewed data analysis and modified the article. All the authors approved the manuscript.

Conflicts of interest: The authors disclose no conflicts.

Conclusion: Infants with postoperative complications following surgical NEC were more likely to be female, have additional morbidities, and demonstrate growth failure at 36 weeks PMA than those without surgical complications. There was no difference in mortality between those with and without surgical complications.

Keywords

Necrotizing enterocolitis; Outcomes; Preterm infants; Surgical Complications

Category of study:

Clinical science

Introduction

Necrotizing enterocolitis (NEC) affects 3–10% of preterm infants with a birth weight ≤1500 grams [1, 2]. Despite advances in neonatal intensive care, NEC remains a leading reason for surgical intervention, severe clinical course, and mortality in preterm infants [3–7]. The need for surgical intervention in NEC is associated with increased resource utilization and cost of care due to prolonged hospitalization [8, 9]. Spontaneous intestinal perforation (SIP) is also a intestinal disease of preterm infants that requires surgical intervention. Infants with SIP had no significant difference in postoperative, brain injury and survival outcomes than those with NEC diagnosis confirmed on intestinal histology as reported in our recent study [10].

Infants with surgical NEC/SIP are managed with either a primary peritoneal drain (PD) or laparotomy, as debate continues over which operation is best despite recent randomized trials [11, 12]. Gastrointestinal (GI) postoperative complications are frequent in neonates that survive surgery for NEC. Strictures, intestinal failure, and bowel obstruction were the most common GI complications after surgery in a recent meta-analysis [13]. Unfortunately, few studies have comprehensively evaluated potential risk factors for postoperative complications in preterm infants with surgical NEC/SIP.

Our previous retrospective cohort studies have reported the demographics, clinical outcomes, and systemic morbidities in preterm infants with NEC [14–18]. In this study, we sought to determine risk factors for postoperative complications in preterm infants following surgical NEC or SIP. Therefore, we compared the demographics, clinical factors, and growth of preterm infants with surgical NEC/SIP that had any complication, a single complication, and more than a single complication to those that did not have a postoperative complication.

Methods:

Population and Study Design:

This retrospective study was conducted at the University of Mississippi Medical Center (UMMC) Neonatal Intensive Care Unit (NICU). UMMC NICU is a Level IV unit with 900–1000 admissions yearly and referrals from the entire state. The UMMC Institutional Review Board approved this retrospective study with a waiver of informed parental consent. Inclusion criteria were infants diagnosed with either NEC (Bell stage III) requiring

surgery, or spontaneous intestinal perforation (SIP) [19]. Data were collected for infants admitted between January 2013 and December 31, 2018. 109 cases of surgical NEC or SIP (N=72)/SIP (37) were included in the study. Neonates diagnosed with medical NEC, congenital heart disease, congenital kidney anomaly and intestinal atresia were excluded from the analysis.

Demographic and Clinical Information:

Demographic data collected included birth weight (BW), gestational age (GA), appropriate for GA status (AGA), race, sex, mode of delivery, out born status, and Apgar score ≤6 at 5 min. Maternal information collected included chorioamnionitis, antenatal steroids, and pregnancy-induced hypertension (PIH). Postnatal data included patent ductus arteriosus (PDA), frequency of PDA surgical ligation, mechanical ventilation, inotrope (dopamine) use 24 hours after NEC onset, hematological information, ibuprofen /indomethacin treatment (before NEC), 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:

NEC was defined using Bell's criteria[19], and a diagnosis of NEC was made on abdominal X-ray findings including portal venous gas, pneumatosis, and pneumoperitoneum. Bell stage III/surgical NEC frequency was gathered [19]. In addition, we recorded information on the age at NEC diagnosis and fulminant NEC [20]. Fulminant NEC was defined as a severe subtype with death occurring within 48 hours of disease onset with pan-intestinal necrosis seen on laparotomy.

Spontaneous Intestinal Perforation (SIP) definition:

SIP was defined as pneumoperitoneum on an abdominal x-ray, or intestinal perforation on intestinal pathology with less than 5 cm of bowel resected and no necrosis nor inflammation on histopathology. Patients were classified as either 'simple' SIP who recovered after placement of a peritoneal drain (PD) as the primary intervention, compared to 'complex' SIP patients who required secondary intervention with exploratory laparotomy after PD placement.

At UMMC, preterm infants with pneumoperitoneum who weighed less than 1 kg at NEC diagnosis and were hemodynamically unstable were treated initially with a PD at the bedside but may later have received laparotomy with ostomy and mucous fistula creation. The decision for laparotomy after PD placement was based on clinical deterioration. Reanastomosis was usually performed at least 6 weeks after the initial laparotomy. Information describing the type of stoma (ileostomy, jejunostomy or colostomy) as also recorded.

Kidney Function Data:

The Modified Neonatal Staging Criteria described in Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI was used to determine the incidence of kidney injury [21–25].

Outcomes Data:

Postoperative information such as postoperative ileus days (defined as the number of days NPO after bowel surgery), time to reach full feeds (defined as tolerating ≥ 120 mL/kg/day), total parenteral nutrition days, length of stay, and hospital mortality were recorded. We defined mortality as death due to any reason before hospital discharge. We also recorded information on intestinal failure (defined as parenteral nutrition >90 days) and surgical complications.

Surgical complications

Surgical complications were classified as strictures, fistulas (enterocutaneous), wound dehiscence (dehiscence of skin and subcutaneous tissue), surgical site infections (SSIs), adhesions requiring surgical intervention and perforations. Adhesion data recorded was recorded from surgical notes. SSIs included any superficial or deep infection including abscesses.

Growth Data:

Anthropometric variables including weight, length, weight-for-length, and respective z-scores at 36 weeks post menstrual age using sex-specific Fenton growth charts were recorded.

Statistical Methods:

Demographic and clinical factors in infants with surgical NEC or SIP were compared between infants with and without surgical complications to look for factors associated with an increased risk of complications. Continuous data were summarized as median (1^{st} quartile, 3^{rd} quartile) with Mann-Whitney U or Kruskal-Wallis tests for differences. Categorical data were summarized as counts and percentages, and the group differences were tested with Chi-squared (or Fisher's exact tests when cell counts are below 5). Variables which showed statistical significance were entered into the multinomial logistic regression model to assess their association with the categories of complication frequencies. No complication group was set as the reference level. Multinomial logistic regression was done including antenatal steroids, female sex, peritoneal drain, jejunostomy and AKI by serum creatinine in the model. Of note, data were not complete for all variables; thus, for each analysis only patients with complete data were included. A p-value < 0.05 was considered statistically significant for all analyses. All analyses were performed in R statistical software (version 4.2.2; The R Foundation for Statistical Computing).

Results:

Whole Cohort:

The analysis included 109 infants with either surgical NEC or SIP. 78 Infants (78/109,71.5%) had at least one surgical complication following surgical NEC or SIP. Adhesions were the most common surgical complication (56/78, 71.8%), followed by wound dehiscence 28/78 (35.9%). Infants with any surgical complication received assisted ventilation significantly more frequently following NEC (93.8% vs. 73.3%, p=0.018) and

had a central line longer (62.0 [IQR 41.0;106] vs. 50.5 [IQR 31.5;65.2], p= 0.048) compared to those without any surgical complication. In addition, infants with any surgical complications had significantly lower weight z- scores (−1.80 [−2.17; −1.19] vs. −1.11 [−1.64; −0.8], p=0.024) and weight for length percentile z- scores (−1.38 [−1.79; −0.42] vs. −0.74 [−123; --0.07], p=0.04) at 36 weeks PMA than those without any surgical complication. The two groups did not demonstrate significant differences in maternal and infant demographics, NEC features, need for parenteral nutrition, length of stay, nor mortality. The data have been summarized in Table 1–3.

To better understand what clinical factors might be associated with an increased risk of postoperative complications, we performed subgroup analyses comparing patients with no complications (n=31) to those with only one complication (35/78) and subsequently patients with no complication to those with more than on complication(n=43).

Single surgical complication vs. no surgical complication:

Sixty-six infants with surgical NEC/SIP were included in this analysis, 35 of which (35/66, 53%) had only one surgical complication. Adhesions (20/35,57.1%) and SSIs (6/35,17.1%) were the most common surgical complications. Those with only one complication had lower exposure to antenatal steroids (17/35, 53.1% vs. 25/31, 83.3 %, p=0.023), had a jejunostomy more frequently (15/35, 42.9% vs. 5/31,16.1%, p=0.037), received assisted ventilation more frequently following NEC onset (28/28, 100 % vs. 22/30, 73.3 %, p=0.01), required a central line longer (median 66.5 [41.2;106] vs. 50.5 [31.5;65.2] days, p=0.046), and had a significantly longer median length of stay (median 170 days [IQR 84.5;209] vs. 108 [IQR 74.0;138], p= 0.016) than those without any single surgical complication. The two groups had no significant difference in mortality or growth at 36 weeks PMA. The data are summarized in Tables 1–3.

More than one surgical complication vs. no surgical complication:

Seventy-four infants with surgical NEC/SIP were included in this analysis. Forty-three (43/74, 58.1%) infants had more than one surgical complication. Those with more than one surgical complication were more often females (p=0.015), developed AKI following NEC onset more frequently (32/39, 82.1% vs. 15/30, 50%, p=0.010) using KDIGO criteria, received Penrose drain therapy more often (25/41, 61% vs. 10/30, 33.3%;p=0.039) and had lower median weight z scores (−1.83 [−2.19; −1.12] vs. −1.11 [−1.64;−0.81], p=0.029) and lower median weight for length z- scores (−1.52 [−1.85;−0.26] vs. −0.74 [−1.23;−0.07], p=0.040) at 36 weeks Post menstrual age than those without any complications. The data have been summarized in Tables 1–3.

Regression:

We performed a multinomial logistic regression between infant characteristics and the groups related to number of complications in surgical NEC/SIP patient cohort (n=91) using multinomial logistic regression. When comparing no complications to one complication, the use of antenatal steroids was associated with lower odds of having one complication (OR 0.23 [0.06; 0.84], p=0.027) and the presence of a jejunostomy was associated with an

increased odds of having one complication (OR 4.81 [1.29;17.9], p=0.019). On the other side, having AKI as measured by serum creatinine is associated with higher odds (OR 5.33 [1.38; 20.6], P=0.015) of experiencing more than one complication in surgical NEC/SIP infants. The data are summarized in Table 4.

Discussion:

In our surgical NEC/SIP cohort, 53% of infants had a single complication, and 60.5% had more than one complication. More than one surgical complication was seen more frequently in females than in males compared to infants without complication. However, there was no difference in mortality in infants between those with no complications, one complication, or more than one complication. Those with more than one complication had significantly lower growth z scores for weight and weight for length at 36 weeks, most likely due to higher energy demands not met by daily nutrition.

AKI was more common in those infants with more than one complication, secondary to an inflammatory injury, fluid imbalance, and administration of nephrotoxic antibiotics in preterm infants with surgical necrotizing enterocolitis. Thus, the association with AKI could reflect more severe NEC which might make infants at higher risk for surgical complications. The AKI following surgical NEC is most likely caused by blood and fluid loss in the intestine or via ostomy leading to hypotension affecting the renal perfusion. The association between AKI and nephrotoxic antibiotic exposure has been reported in many studies [26–28].

Those infants with single complications stayed in the hospital 62 days longer than those without surgical morbidity. The longer hospitalization is likely due to the inability to reach full feeds, inadequate growth, and parenteral nutrition dependency, as evidenced by longer central line days and a second surgery in infants with surgical complications such as adhesions. Interestingly, this trend was not seen when comparing infants with no complications to those infants with multiple complications.

A metanalysis of 58 studies that including 4260 patients noted Strictures in 24% (95% CI 17%, 31%) of surviving patients, recurrence of NEC in 8% (95% CI 3%,15%), intestinal failure in 13% (95% CI 7%,19%) and adhesion ileus in 6% (95% CI 4%,9%) [13]. Strictures were more common following enterostomy (30%; 95% CI 23%,37%) than after primary anastomosis (8%; 95% CI 0%, 23%) and occurred more often after enterostomy without bowel resection than with bowel resection. However, significant heterogeneity in the weighted average frequency of all sequelae was noted (I^2 range: 38%−90%) [13].

This study had similar findings in terms of the breakdown of complications. We found a high incidence of adhesions requiring surgical intervention and wound complications. Interestingly, when comparing patients without complications to those with any complication, few risk factors that increased the odds of a postoperative complication were evident. As one might expect, having any complication was associated with a longer need for mechanical ventilation, use of a central line for longer, and a lower weight for z score at 36 weeks of gestation. To better define potential risk factors, we elected to perform subgroup

analyses between patients with no complication and those with only one complication and those with more than one complication. We suspected that risk factors for developing more than one complication may become apparent in such an analysis. This demonstrated that being exposed to antenatal steroids was associated with a mild decreased risk in developing only one complication, but the association did not hold when comparing no complication to more than one complication. The significance of this is unclear. One could imagine that receiving antenatal steroids may reduce the risk of pulmonary or other complications. While the comparison between no complications and more than one complication was not statistically significant, the trend of a lower percentage of complications was still there. Similarly incongruent was the use of peritoneal drain which seemed to be associated with an increased risk of more than one complication, but not only one complication. Although, one may suspect that using a peritoneal drain alone may result in a higher rate of stricture or adhesion requiring a second operation; thus, a peritoneal drain may put you at risk for multiple complications as opposed to only one complication. Once again, the presence of a jejunostomy was associated with higher likelihood of one complication, but not multiple. Certainly, a jejunostomy, which typically is a high output ostomy, puts infants at risk for dehydration, malnutrition, intestinal failure, AKI, and wound complications. The trend continued in that those infants with a jejunostomy did have a higher percentage of more than one complication, but it did not reach the level of statistical significance which may be due to the overall small sample size.

Finally, in multinomial regression, we found that antenatal steroids seemed to still be associated with a decreased odds of a single complication and jejunostomy associated with an increased odd of a single complication. One would expect these associations to hold true when comparing no complication to more than one complication, but they did not. It is unclear the significance of this finding, but we suspect the relatively small sample size played a role. Regardless, surgeons can glean that infants that did receive steroids may be at slightly lower risk of postoperative complications. Moreover, as most surgeons already do, we should avoid jejunostomies in these infants, if possible, in order to potentially reduce the odds of a complication. Finally, the multinomial regression for no complications vs. multiple complications, only AKI was associated with a higher odd of more than one complication. This is likely due to the severity of the underlying NEC/SIP disease with deranged physiology. With this information, surgeons may be able to better counsel parents about the risk of postoperative complications in surgical NEC/SIP.

Our study is limited by its single-center, retrospective design, and a predominantly African American cohort. The relatively small sample size reduces generalizability of these results, and the statistical power limits findings detecting associations between clinical factors and surgical complications in preterm infants with surgical NEC. Further, multiple comparisons yield a higher probability of type I errors.

In conclusion, we attempted to use a retrospective cohort to identify clinical factors that put preterm infants at risk of postoperative complications in surgical NEC/SIP. Unfortunately, despite a high percentage of complications in these infants, clear risk factors were hard to define likely due to the overall small sample size. While not consistent between risk of one complication and more than one complication, we did find that antenatal steroids

seem to be associated with lower odds of one complication. The presence of a jejunostomy seemed to be associated with higher odds of one complication. The presence of AKI by serum creatinine was associated with a higher risk of more than one complication. This information may help guide surgeons in counseling parents about the risks of surgery in infants with surgical NEC/SIP. Regardless, multicenter prospective trials will be needed to better understand the risk factors associated with postoperative complications in this cohort as well as the sequelae of these complications Moreover, multicenter studies would also help determine the impact of surgical complications on short and long-term physical and neurodevelopmental outcomes.

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Table 1.

Demographics and the clinical outcomes infants any complication and with and without single surgical complication in surgical NEC/SIP cohort

	N	Total (N = 109)	No complications (N = 31)	Any complication (N = 78)	p value	N	Total (N = 66)	No complication (N = 31)	Single Complication (N = 35)	p value	N	Total (N = 74)	No complications (N = 31)	>1 Complication (N = 43)	p value
Prenatal Information															
Pregnancy-induced hypertension, n (%)	106	31 (29.2)	11 (36.7)	20 (26.3)	0.41	64	22 (34.4)	11 (36.7)	11 (32.4)	0.92	72	20 (27.8)	11 (36.7)	9 (21.4)	0.25
Chronic hypertension, n (%)	95	15 (15.8)	6 (22.2)	9 (13.2)	0.35	58	11 (19.0)	6 (22.2)	5 (16.1)	0.8	64	10 (15.6)	6 (22.2)	4 (10.8)	0.3
Chorioamnionitis, n (%)	105	12 (11.4)	5 (16.7)	7 (9.33)	0.32	64	7 (10.9)	5 (16.7)	2 (5.88)	0.24	71	10 (14.1)	5 (16.7)	5 (12.2)	0.73
Antenatal Steroid Use, n (%)	100	71 (71.0)	25 (83.3)	46 (65.7)	0.12	62	42 (67.7)	25 (83.3)	17 (53.1)	**0.023**	68	54 (79.4)	25 (83.3)	29 (76.3)	0.68
Infant Demographics															
Gestational Age (weeks, median, IQR)	109	25.4 [24.0;27.3]	26.0 [24.4;27.3]	25.3 [23.8;27.2]	0.49	66	26.1 [24.2;27.5]	26.0 [24.4;27.3]	26.3 [24.0;27.7]	0.89	74	25.3 [24.0;27.1]	26.0 [24.4;27.3]	25.1 [23.6;26.9]	0.31
Small for gestational age, n (%)	106	37 (34.9)	8 (26.7)	29 (38.2%)	0.37	65	19 (29.2)	8 (26.7)	11 (31.4)	0.88	71	26 (36.6)	8 (26.7)	18 (43.9)	0.22
Sex, n (%)	109				**0.052**	66				0.44	74				**0.015**
Female		42 (38.5)	7 (22.6)	35 (44.9)			19 (28.8)	7 (22.6)	12 (34.3)			30 (40.5)	7 (22.6)	23 (53.5)	
Male		67 (61.5)	24 (77.4)	43 (55.1)			47 (71.2)	24 (77.4)	23 (65.7)			44 (59.5)	24 (77.4)	20 (46.5)	
Ethnicity, n (%)	107				0.33	64				0.78	73				0.15
African American		84 (78.5)	22 (73.3)	62 (80.5)			49 (76.6)	22 (73.3)	27 (79.4)			57 (78.1)	22 (73.3)	35 (81.4)	
Caucasian		20 (18.7)	8 (26.7)	12 (15.6)			15 (23.4)	8 (26.7)	7 (20.6)			13 (17.8)	8 (26.7)	5 (11.6)	
Mode of delivery Vaginal	109	75 (68.8)	24 (77.4)	51 (65.4)	0.32	66	22 (33.3)	7 (22.6)	15 (42.9)	0.14	74	19 (25.7)	7 (22.6)	12 (27.9)	0.8
Birth Weight (g, median, IQR)		34 (31.2)	7 (22.6)	27 (34.6)		66	778 [632;988]	780 [640;958]	775 [615;1000]	0.9	74	710 [620;934]	780 [640;958]	690 [610;905]	0.2

	N	Total (N = 109)	No complications (N = 31)	Any complication (N = 78)	p value	N	Total (N = 66)	No complication (N = 31)	Single Complication (N = 35)	p value	N	Total (N = 74)	No complications (N = 31)	>1 Complication (N = 43)	p value
Outborn, n (%)	109	730 [620;940]	780 [640;958]	710 [605;938]	0.39	66	43 (65.2)	22 (71.0)	21 (60.0)	0.5	74	48 (64.9)	22 (71.0)	26 (60.5)	0.49

Table 2.

Demographics and the clinical outcomes infants with and without a single surgical complication in surgical NEC/SIP cohort

	N	Total (N = 109)	No complications (N = 31)	Any complication (N = 78)	p value	N	Total (N = 66)	No complications (N = 31)	1 complication (N = 35)	p value	N	Total (N = 71)	No complications (N = 34)	>1 Complication (N = 43)	p value
NEC Disease Features															
Age of NEC onset (days, median, IQR)	109	11.0 [7.00;23.0]	10.0 [4.50;24.0]	12.0 [7.00;23.0]	0.4	66	11.5 [7.00;25.0]	10.0 [4.50;24.0]	13.0 [7.00;25.0]	0.29	74	10.5 [6.00;21.8]	10.0 [4.50;24.0]	11.0 [6.50;20.5]	0.63
Clinical Presentation, n (%)	107				0.71	66				0.51	72				0.18
Abdominal Distension		98 (91.6)	29 (93.5)	69 (90.8)			58 (87.9)	29 (93.5)	29 (82.9)			69 (95.8)	29 (93.5)	40 (97.6)	
Bloody Stools		6 (5.61)	2 (6.45)	4 (5.26)			6 (9.09)	2 (6.45)	4 (11.4)			2 (2.78)	2 (6.45)	0 (0.00)	
Feed Intolerance		3 (2.80)	0 (0.00)	3 (3.95)			2 (3.03)	0 (0.00)	2 (5.71)			1 (1.39)	0 (0.00)	1 (2.44)	
Radiologic Findings, n (%)															
Pneumatosis	108	42 (38.9)	8 (26.7)	34 (43.6)	0.16	65	27 (41.5)	8 (26.7)	19 (54.3)	**0.045**	73	23 (31.5)	8 (26.7)	15 (34.9)	0.63
Portal venous gas	108	7 (6.48)	3 (10.0)	4 (5.13)	0.39	65	5 (7.69)	3 (10.0)	2 (5.71)	0.66	73	5 (6.85)	3 (10.0)	2 (4.65)	0.4
Pneumoperitoneum	108	62 (57.4)	18 (60.0)	44 (56.4)	0.9	65	38 (58.5)	18 (60.0)	20 (57.1)	0.99	73	42 (57.5)	18 (60.0)	24 (55.8)	0.91
Penrose drain, n (%)	106	51 (48.1)	10 (33.3)	41 (53.9)	0.09	65	26 (40.0)	10 (33.3)	16 (45.7)	0.45	71	35 (49.3)	10 (33.3)	25 (61.0)	**0.04**
Spontaneous intestinal perforation (SIP), n (%)	109	32 (29.4)	8 (25.8)	24 (30.8)	0.78	66	17 (25.8)	8 (25.8)	9 (25.7)	0.99	74	23 (31.1)	8 (25.8)	15 (34.9)	0.56
Complex SIP with Penrose drain, n (%)	29	14 (48.3)	3 (42.9)	11 (50.0)	0.99	16	8 (50.0)	3 (42.9)	5 (55.6)	0.99	20	9 (45.0)	3 (42.9)	6 (46.2)	0.99
Fulminant necrosis, n (%)	108	10 (9.26)	1 (3.33)	9 (11.5)	0.28	65	7 (10.8)	1 (3.33)	6 (17.1)	0.11	73	4 (5.48)	1 (3.33)	3 (6.98)	0.64
Presence of ileocecal valve, n (%)	105	76 (72.4)	20 (66.7)	56 (74.7)	0.56	63	43 (68.3)	20 (66.7)	23 (69.7)	0.99	72	53 (73.6)	20 (66.7)	33 (78.6)	0.39
Jejunostomy, n (%)	109	34 (31.2)	5 (16.1)	29 (37.2)	0.05	66	20 (30.3)	5 (16.1)	15 (42.9)	**0.037**	74	19 (25.7)	5 (16.1)	14 (32.6)	0.19

	N	Total (N = 109)	No complications (N = 31)	Any complication (N = 78)	p value	N	Total (N = 66)	No complications (N = 31)	1 complication (N = 35)	p value	N	Total (N = 71)	No complications (N = 34)	>1 Complication (N = 43)	p value
Ileostomy, n (%)	109	62 (56.9)	20 (64.5)	42 (53.8)	0.42	66	38 (57.6)	20 (64.5)	18 (51.4)	0.41	74	44 (59.5)	20 (64.5)	24 (55.8)	0.61
Colostomy, n (%)	109	11 (10.1)	4 (12.9)	7 (8.97)	0.5	66	7 (10.6)	4 (12.9)	3 (8.57)	0.7	74	8 (10.8)	4 (12.9)	4 (9.30)	0.71
Length of bowel resected (cm, median, IQR)	104	10.7 [4.27;27.4]	9.60 [3.60;15.4]	12.6 [5.15;29.5]	0.15	63	11.0 [5.00;27.2]	9.60 [3.60;15.4]	14.9 [6.20;31.0]	0.07	71	9.70 [3.70;23.5]	9.60 [3.60;15.4]	10.4 [4.00;27.2]	0.43
Region of bowel resected n (%)	100				0.3	60				0.57	67				0.27
Large bowel or both		31 (31.0)	11 (40.7)	20 (27.4)			21 (35.0)	11 (40.7)	10 (30.3)			21 (31.3)	11 (40.7)	10 (25.0)	
Small bowel		69 (69.0)	16 (59.3)	53 (72.6)			39 (65.0)	16 (59.3)	23 (69.7)			46 (68.7)	16 (59.3)	30 (75.0)	
Length of jejunum lost (cm, median, IQR)	97	0.00 [0.00;8.10]	0.00 [0.00;3.50]	1.30 [0.00;9.00]	0.15	60	0.00 [0.00;10.1]	0.00 [0.00;3.50]	2.65 [0.00;23.6]	0.07	67	0.00 [0.00;5.25]	0.00 [0.00;3.50]	0.00 [0.00;5.90]	0.39
Length of ileum lost (cm, median, IQR)	101	3.20 [0.00;9.00]	2.50 [0.00;6.80]	3.50 [0.00;11.0]	0.67	61	3.20 [0.00;7.90]	2.50 [0.00;6.80]	3.70 [0.00;7.90]	0.78	68	3.10 [0.00;9.43]	2.50 [0.00;6.80]	3.35 [0.00;14.7]	0.65
Length of colon lost (cm, median, IQR)	101	0.00 [0.00;1.70]	0.00 [0.00;2.67]	0.00 [0.00;0.70]	0.31	61	0.00 [0.00;2.00]	0.00 [0.00;2.67]	0.00 [0.00;0.70]	0.57	70	0.00 [0.00;1.93]	0.00 [0.00;2.67]	0.00 [0.00;0.42]	0.26
Total small bowel lost, (cm, median, IQR)	109	8.00 [3.20;22.3]	5.90 [2.00;12.3]	8.75 [3.55;25.1]	0.15	66	8.00 [3.50;15.0]	5.90 [2.00;12.3]	9.00 [5.15;27.2]	0.1	74	7.50 [2.22;19.5]	5.90 [2.00;12.3]	8.10 [3.05;24.4]	0.35
Residual small bowel (cm, median, IQR)	109	77.7 [65.0;98.0]	93.8 [69.5;101]	72.0 [64.6;94.9]	**0.051**	66	86.2 [64.2;100]	93.8 [69.5;101]	72.0 [63.6;97.2]	0.14	74	78.8 [66.6;98.0]	93.8 [69.5;101]	71.0 [66.2;92.2]	0.05
Residual colon (cm, median, IQR)	109	24.4 [22.7;27.8]	23.6 [22.5;26.1]	24.4 [22.7;27.8]	0.56	66	24.4 [22.7;27.8]	23.6 [22.5;26.1]	24.4 [22.7;30.2]	0.33	74	23.1 [22.7;24.4]	23.6 [22.5;26.1]	22.7 [22.7;24.4]	0.91
Duration of Penrose drain (days, median, IQR)	51	8.00 [2.00;17.5]	6.50 [2.00;11.5]	8.00 [3.00;20.0]	0.33	26	9.50 [2.00;17.8]	6.50 [2.00;11.5]	10.5 [1.88;21.5]	0.3	35	6.00 [2.50;13.5]	6.50 [2.00;11.5]	6.00 [4.00;16.0]	0.43
Total number of laparotomies (median, IQR)	30	2.00 [2.00;2.75]	2.00 [2.00;2.00]	2.00 [2.00;3.00]	0.17	18	2.00 [2.00;2.00]	2.00 [2.00;2.00]	2.00 [2.00;2.00]	0.42	19	2.00 [2.00;3.00]	2.00 [2.00;2.00]	2.00 [2.00;3.00]	0.12
Surgical Complications															
Morbidity, n (%)	109	78 (71.6)	0 (0.00)	78 (100)		66	35 (53.0)	0 (0.00)	35 (100)		74	43 (58.1)	0 (0.00)	43 (100)	
Wound dehiscence, n (%)	109	28 (25.7)	0 (0.00)	28 (35.9)		66	4 (6.06)	0 (0.00)	4 (11.4)		74	24 (32.4)	0 (0.00)	24 (55.8)	

	N	Total (N = 109)	No complications (N = 31)	Any complication (N = 78)	p value	N	Total (N = 66)	No complications (N = 31)	1 complication (N = 35)	p value	N	Total (N = 71)	No complications (N = 34)	>1 Complication (N = 43)	p value
Wound infection, n (%)	109	14 (12.8)	0 (0.00)	14 (17.9)		66	6 (9.09)	0 (0.00)	6 (17.1)		74	8 (10.8)	0 (0.00)	8 (18.6)	
Stricture, n (%)	109	12 (11.0)	0 (0.00)	12 (15.4)		66	1 (1.52)	0 (0.00)	1 (2.86)		74	11 (14.9)	0 (0.00)	11 (25.6)	
Adhesions, n (%)	109	56 (51.4)	0 (0.00)	56 (71.8)		66	20 (30.3)	0 (0.00)	20 (57.1)		74	36 (48.6)	0 (0.00)	36 (83.7)	
Fistula, n (%)	109	13 (11.9)	0 (0.00)	13 (16.7)		66	3 (4.55)	0 (0.00)	3 (8.57)		74	10 (13.5)	0 (0.00)	10 (23.3)	
Compartment syndrome, n (%)	109	8 (7.34)	0 (0.00)	8 (10.3)		66	1 (1.52)	0 (0.00)	1 (2.86)		74	7 (9.46)	0 (0.00)	7 (16.3)	

Table 3.

Clinical outcomes infants with and without surgical complication in surgical NEC/SIP cohort

	N	Total (N = 109)	No complications (N = 31)	Any complication (N = 78)	p value	N	Total (N = 66)	No complication (N = 31)	1 complication (N = 35)	p value	N	Total (N = 74)	No complications (N = 31)	> 1 Complication (N = 43)	p value
Hemodynamic variables															
Assisted ventilation (intubated), n (%)	95				**0.018**	58				**0.01**	67				0.38
Intubation		83 (87.4)	22 (73.3)	61 (93.8)			50 (86.2)	22 (73.3)	28 (100)			55 (82.1)	22 (73.3)	33 (89.2)	
CPAP		7 (7.37)	5 (16.7)	2 (3.08)			5 (8.62)	5 (16.7)	0 (0.00)			7 (10.4)	5 (16.7)	2 (5.41)	
High flow		2 (2.11)	1 (3.33)	1 (1.54)			1 (1.72)	1 (3.33)	0 (0.00)			2 (2.99)	1 (3.33)	1 (2.70)	
Room air		3 (3.16)	2 (6.67)	1 (1.54)			2 (3.45)	2 (6.67)	0 (0.00)			3 (4.48)	2 (6.67)	1 (2.70)	
Patent ductus arteriosus, n (%)	109	72 (66.1)	20 (64.5)	52 (66.7)	0.99	66	42 (63.6)	20 (64.5)	22 (62.9)	0.99	74	50 (67.6)	20 (64.5)	30 (69.8)	0.82
PDA surgical ligation, n (%)	106	7 (6.60)	2 (6.67)	5 (6.58)	0.99	64	3 (4.69)	2 (6.67)	1 (2.94)	0.6	72	6 (8.33)	2 (6.67)	4 (9.52)	0.99
Pressor support 24 h after NEC, n (%)	104	76 (73.1)	20 (69.0)	56 (74.7)	0.73	63	50 (79.4)	20 (69.0)	30 (88.2)	0.12	70	46 (65.7)	20 (69.0)	26 (63.4)	0.82
Indomethacin use, n (%)	107	16 (15.0)	5 (16.1)	11 (14.5)	0.78	65	7 (10.8)	5 (16.1)	2 (5.88)	0.24	73	14 (19.2)	5 (16.1)	9 (21.4)	0.79
Apgar score 6 at 5 min, n (%)	107	30 (28.0)	9 (30.0)	21 (27.3)	0.97	64	17 (26.6)	9 (30.0)	8 (23.5)	0.76	73	22 (30.1)	9 (30.0)	13 (30.2)	0.99
AKI by serum creatinine present, n (%)	99	64 (64.6)	15 (50.0)	49 (71.0)	0.08	60	32 (53.3)	15 (50.0)	17 (56.7)	0.8	69	47 (68.1)	15 (50.0)	32 (82.1)	**0.010**
AKI by urine output present, n (%)	98	44 (44.9)	12 (46.2)	32 (44.4)	0.99	57	25 (43.9)	12 (46.2)	13 (41.9)	0.96	67	31 (46.3)	12 (46.2)	19 (46.3)	0.99
AKI by urine output and serum creatinine present, n (%)	98	24 (24.5)	7 (26.9)	17 (23.6)	0.94	57	15 (26.3)	7 (26.9)	8 (25.8)	0.99	67	16 (23.9)	7 (26.9)	9 (22.0)	0.86

	N	Total (N = 109)	No complications (N = 31)	Any complication (N = 78)	p value	N	Total (N = 66)	No complication (N = 31)	1 complication (N = 35)	p value	N	Total (N = 74)	No complications (N = 31)	> 1 Complication (N = 43)	p value
Platelet transfusion before NEC onset, n (%)	102	78 (76.5)	21 (70.0)	57 (79.2)	0.46	64	46 (71.9)	21 (70.0)	25 (73.5)	0.97	60	56 (93.3)	25 (92.6)	31 (93.9)	0.99
Blood transfusion before NEC onset, n (%)	90	85 (94.4)	25 (92.6)	60 (95.2)	0.63	57	54 (94.7)	25 (92.6)	29 (96.7)	0.6	50	11 (22.0)	2 (10.5)	9 (29.0)	0.17
Postoperative Intestinal Features															
Postoperative ileus days (days, median, IQR)	83	13.0 [11.0;17.5]	12.0 [9.00;15.0]	13.5 [11.0;18.0]	0.23	64	81.0 [49.5;119]	61.5 [31.8;114]	87.5 [60.8;128]	0.21	52	12.0 [9.75;15.0]	12.0 [9.00;15.0]	13.0 [11.0;15.0]	0.68
Duration of parenteral nutrition (days, median, IQR)	105	81.0 [38.0;118]	61.5 [31.8;114]	84.0 [38.5;120]	0.45	54	14.0 [11.0;18.8]	12.0 [9.00;15.0]	16.0 [12.0;19.5]	0.09	71	71.0 [31.0;116]	61.5 [31.8;114]	82.0 [31.0;117]	0.88
Sepsis Variables															
Positive blood culture sepsis, n (%)	109	36 (33.0)	8 (25.8)	28 (35.9)	0.43	66	21 (31.8)	8 (25.8)	13 (37.1)	0.47	74	23 (31.1)	8 (25.8)	15 (34.9)	0.56
Central line present (days, median, IQR)	95	60.0 [38.0;99.0]	50.5 [31.5;65.2]	62.0 [41.0;106]	**0.048**	54	59.5 [38.0;91.5]	50.5 [31.5;65.2]	66.5 [41.2;106]	**0.046**	65	59.0 [35.0;96.0]	50.5 [31.5;65.2]	62.0 [43.0;106]	0.11
Duration of antibiotics (days median, IQR)	75	10.0 [7.00;14.0]	9.50 [7.00;13.8]	10.0 [6.00;14.0]	0.43	43	10.0 [7.00;14.0]	9.50 [7.00;13.8]	12.0 [7.00;14.0]	0.97	58	9.50 [7.00;12.8]	9.50 [7.00;13.8]	9.00 [5.00;10.5]	0.25
CRP at 24 h after NEC onset (median, IQR)	77	8.70 [3.20;17.7]	10.2 [2.65;18.8]	8.70 [3.70;16.1]	0.93	45	12.6 [3.70;18.5]	10.2 [2.65;18.8]	12.6 [4.80;18.2]	0.6	52	8.00 [2.72;17.0]	10.2 [2.65;18.8]	8.00 [2.72;15.0]	0.56
CRP at 48 h after NEC onset (median, IQR)	68	15.2 [3.95;21.9]	15.4 [3.45;21.7]	14.1 [4.62;22.3]	0.8	43	16.9 [5.00;22.0]	15.4 [3.45;21.7]	18.9 [7.50;23.1]	0.5	47	14.7 [2.85;21.9]	15.4 [3.45;21.7]	7.40 [2.50;21.9]	0.87
CRP at 96 h after NEC	72	8.05 [4.10;17.1]	8.65 [5.53;18.7]	7.80 [3.45;16.1]	0.26	43	8.80 [4.65;19.1]	8.65 [5.53;18.7]	8.80 [3.90;18.9]	0.79	47	6.60 [4.15;15.9]	8.65 [5.53;18.7]	5.80 [3.30;15.3]	0.1

	N	Total (N = 109)	No complications (N = 31)	Any complication (N = 78)	p value	N	Total (N = 66)	No complication (N = 31)	1 complication (N = 35)	p value	N	Total (N = 74)	No complications (N = 31)	> 1 Complication (N = 43)	p value
onset (median, IQR)															
CRP at 1 week after NEC onset (median, IQR)	76	4.60 [2.50;7.70]	6.25 [3.10;8.07]	3.95 [2.28;7.40]	0.25	46	4.85 [3.10;7.90]	6.25 [3.10;8.07]	3.85 [2.87;7.15]	0.31	50	4.95 [2.15;8.00]	6.25 [3.10;8.07]	4.45 [1.77;7.47]	0.3
CRP at 2 weeks after NEC onset (median, IQR)	72	3.35 [1.67;5.73]	3.40 [1.40;5.45]	3.30 [1.90;6.30]	0.47	42	3.55 [1.42;5.70]	3.40 [1.40;5.45]	3.70 [2.35;6.50]	0.4	53	3.00 [1.60;5.70]	3.40 [1.40;5.45]	2.80 [1.92;5.68]	0.63
Cholestasis, n (%)	88	61 (69.3)	16 (57.1)	45 (75.0)	0.15	53	33 (62.3)	16 (57.1)	17 (68.0)	0.6	63	44 (69.8)	16 (57.1)	28 (80.0)	0.09
Weight Percentile (36 weeks) z-score	71	−1.59 [−2.12; −0.92]	−1.11 [−1.64; −0.81]	−1.80 [−2.17; −1.19]	**0.024**	39	−1.32 [−1.92; −0.84]	−1.11 [−1.64; −0.81]	−1.64 [−2.05; −1.31]	0.11	55	−1.59 [−2.12; −0.90]	−1.11 [−1.64; −0.81]	−1.83 [−2.19; −1.12]	**0.029**
Length Percentile (36 weeks) z-score	71	−2.13 [−3.34;−1.50]	−2.11 [−2.52; −1.33]	−2.41 [−3.39; −1.69]	0.21	39	−2.21 [−3.34; −1.33]	−2.11 [−2.52; −1.33]	−2.82 [−3.43; −1.61]	0.24	55	−2.13 [−3.08; −1.50]	−2.11 [−2.52; −1.33]	−2.13 [−3.36; −1.69]	0.29
Weight-for-length (36 weeks) z-score	71	−1.08 [−1.71; −0.26]	−0.74 [−1.23; −0.07]	−1.38 [−1.79; −0.42]	**0.044**	39	−0.97 [−1.50; −0.22]	−0.74 [−1.23; −0.07]	−1.14 [−1.54; −0.64]	0.21	55	−1.08 [−1.74; −0.16]	−0.74 [−1.23; −0.07]	−1.52 [−1.85; −0.26]	**0.040**
Length of Stay (days, median, IQR)	109	117 [72.0;171]	108 [74.0;138]	136 [72.8;179]	0.09	66	116 [81.2;176]	108 [74.0;138]	170 [84.5;209]	**0.016**	74	114 [52.8;161]	108 [74.0;138]	122 [47.0;169]	0.46
Death, n (%)	109	37 (33.9)	8 (25.8)	29 (37.2)	0.36	66	47 (71.2)	23 (74.2)	24 (68.6)	0.81	74	48 (64.9)	23 (74.2)	25 (58.1)	0.23

Table 4:

Association between infant characteristics and the number of complications in surgical patient cohort (n=91) using multinomial logistic regression.

Characteristics	1 complication		> 1 complication	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Antenatal steroids	0.23 (0.06, 0.84)	**0.027**	0.76 (0.20, 2.94)	0.7
Female	1.38 (0.40, 4.77)	0.6	2.56 (0.81, 8.14)	0.11
Penrose drain	1.41 (0.44, 4.51)	0.6	1.90 (0.62, 5.84)	0.3
Jejunostomy	4.81 (1.29, 17.9)	**0.019**	1.97 (0.50, 7.77)	0.3
AKI by serum creatinine	1.15 (0.36, 3.71)	0.8	5.33 (1.38, 20.6)	**0.015**

Note: Reference group for the target variable was set as 0 complication and for antenatal steroids, AKI by serum creatinine, Penrose drain, Jejunostomy was set as ‘No’. ‘Male’ was set as the reference level for Female.

OR represents as odds ratio and CI represents as confidence interval.