



Analysis of Postoperative Outcomes and Extrauterine Growth Retardation in Preterm Infants with Necrotizing Enterocolitis: A Retrospective Study

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Abstract

Objective High mortality and extrauterine growth retardation (EUGR) remain serious problems in preterm infants after necrotizing enterocolitis (NEC) surgery. This study investigated the risk factors for mortality and EUGR in preterm infants after NEC surgery.

Study Design The risk factors were analyzed retrospectively by univariate analysis and multivariate logistic regression analysis in 52 preterm infants, who underwent NEC surgery and were hospitalized in neonatology department of Shanghai Children's Hospital between May 2014 and December 2021. Patients were divided into survival and death groups. Survivors were divided into two groups according to whether EUGR occurred when they achieved full enteral feeding after surgery.

Results The mortality of preterm infants after NEC surgery was 26.9% (14/52). About 55.3% (21/38) of survivors developed postoperative EUGR. (1) Age at surgery, proportion of shock, and intestinal perforation differed significantly between the survival and death groups ($p = 0.001$, 0.005 , and 0.02 , respectively). Shock ($p = 0.02$, odds ratio [OR] = 8.86, 95% confidence interval [CI]: 1.43–55.10) and intestinal perforation ($p = 0.03$, OR = 6.12, 95% CI: 1.16–32.41) were significant risk factors for death. (2) Compared with the non-EUGR group, proportion of preoperative EUGR, postoperative 1-week calories, and parenteral nutrition time differed significantly in EUGR group ($p = 0.001$, 0.01 , and 0.04 , respectively). Preoperative EUGR ($p = 0.02$, OR = 18.63, 95% CI: 1.77–196.42) was a significant risk factor for postoperative EUGR.

Conclusion Shock and intestinal perforation are significant risk factors for death in preterm infants after NEC surgery. Survivors are prone to EUGR, and preoperative EUGR is a significant risk factor. In addition, adequate caloric intake and achievement of full enteral feeding as soon as possible may be beneficial to improve EUGR of preterm infants after NEC surgery.

Keywords

- ▶ extrauterine growth retardation
- ▶ necrotizing enterocolitis
- ▶ outcomes
- ▶ preterm infants
- ▶ surgery

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Key Points

- Shock and intestinal perforation are risk factors for death in preterm infants after NEC surgery.
- Preoperative EUGR is a risk factor for postoperative EUGR in preterm infants after NEC surgery.
- Active correction of shock and avoiding intestinal perforation may help improve the outcomes.

Necrotizing enterocolitis (NEC) is a severe gastrointestinal disease characterized by inflammation and necrosis of the intestine.¹ NEC is common in neonates, especially in preterm infants, and is one of the leading causes of critical gastrointestinal disease and death in preterm infants.² NEC in preterm infants usually occurs at 30 to 32 weeks of corrected gestational age (GA). Immature intestinal immunity and intestinal dysregulation play important roles in the pathogenesis.³ Twenty to forty percent of NEC neonates require surgical treatment due to failure of medical treatment or intestinal perforation.² Neonates treated with NEC surgery, especially preterm low birth weight (LBW) infants, have a high mortality and long-term complication rate.⁴ Survivors may be affected by the intestinal failure or short bowel syndrome and have difficulty resuming enteral feeding, or even have extrauterine growth retardation (EUGR).⁵ EUGR in neonates is commonly defined as a weight less than the tenth percentile of intrauterine growth expected for postmenstrual age, with a weight less than the third percentile indicating severe growth retardation.⁶ Studies have confirmed that EUGR impairs neurological development and increases the risk of obesity, metabolic syndrome, and cardiovascular disease in children.^{6,7} In this study, we retrospectively analyzed the clinical data to identify the risk factors for mortality and EUGR of preterm infants after NEC surgery, which is critical for improving the prognosis of these patients. We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist.

Materials and Methods

Study Design and Patient Population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Shanghai Children's Hospital (2022RY062). This study is retrospective analysis of clinical data of preterm infants who underwent NEC surgery and were admitted to the neonatology department of Shanghai Children's Hospital between May 2014 and December 2021. Inclusion criteria: (1) Met the modified Bell staging criteria for NEC.⁸ (2) Treated with NEC surgery. (3) GA at birth less than 37 weeks. Exclusion criteria: (1) Treated with NEC surgery at other hospitals. (2) Incomplete clinical data. Shedding criteria: Transferred to other departments or hospitals for further treatment before full enteral feeding. The clinical data of 315 NEC neonates were collected, and 52 cases were finally included in this study (→Fig. 1). Fifty-two cases were divided into survival and death groups according to the clinical outcomes. Survivors were divided into EUGR and non-EUGR groups according to whether EUGR occurred when they achieved full enteral feeding after surgery.

Treatment of Necrotizing Enterocolitis

Medical principles: Stop feeding to allow rest for the intestine and prevent further injury, while correcting disorders of water, electrolytes, acid-base balance, and reducing systemic inflammatory reactions. Provide appropriate nutritional

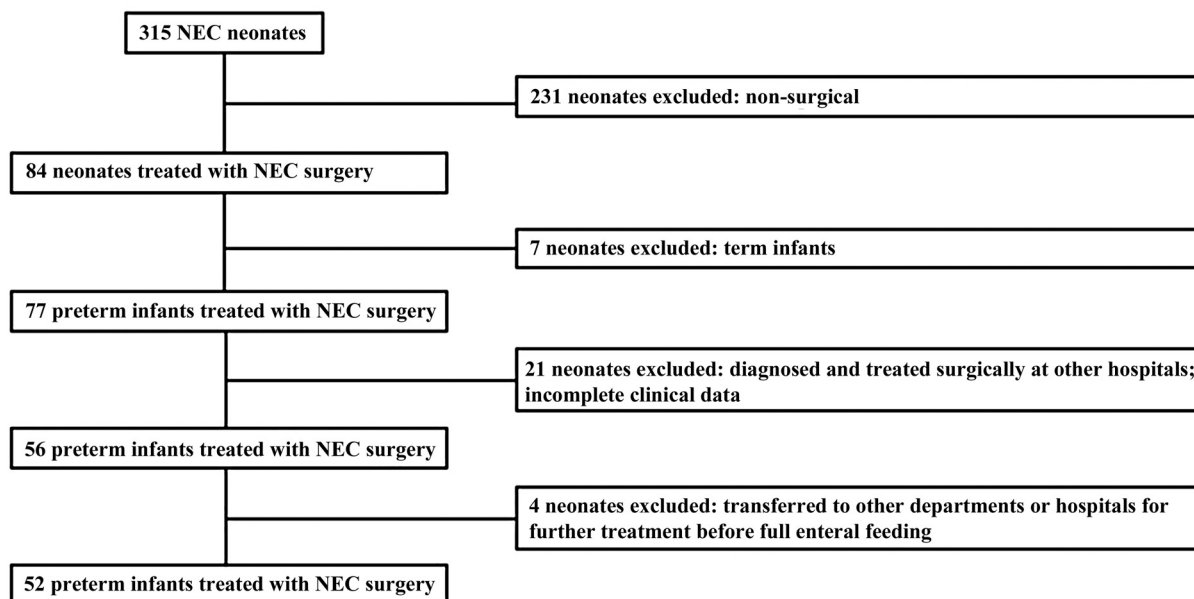


Fig. 1 Flowchart of the procedure to enroll neonates in the study. NEC, necrotizing enterocolitis.

support to achieve normal growth and development, promote residual intestinal compensation, and reduce complications associated with intestinal resection and parenteral nutrition (PN).^{8,9}

Indications for surgical treatment: Failure of medical treatment or intestinal perforation.^{8,9}

Observation Items

General clinical information: GA at birth, BW, and sex.

Preoperative indicators: Age at surgery, intestinal perforation, sepsis, shock, presence of EUGR, mechanical ventilation, the time interval between diagnosis of NEC, and surgery.

Postoperative indicators: Surgical procedures, time and formula of refeeding, postoperative 1-week calories, postoperative PN time, and complications (cholestasis, liver enzyme abnormalities, and hypertriglyceridemia).

Statistical Analysis

SPSS 22.0 statistical software was used to analyze the data. Normally distributed data were expressed as mean \pm standard deviation ($x \pm s$), and *t* test was used for comparison. Non-normally distributed data were expressed as quartiles M (P_{25} , P_{75}), and nonparametric test was used. Count data were expressed as the number of cases and percentages, and the chi-squared test was used. Logistic regression analysis was used for multivariate analysis. A *p*-value less than 0.05 was statistically significant.

Results

General Clinical Information

A total of 52 surgically treated preterm infants with NEC were involved in this study, including 39 male and 13 female infants with a GA of 31.32 ± 2.81 weeks and a BW of $1,672.12 \pm 601.19$ g. Surgical procedures included 14 cases of enterostomy, 14 cases of intestinal resection enteroanastomosis, 16 cases of intestinal resection enterostomy, and 8 cases of abdominal drainage.

Risk Factors for Clinical Outcomes in Preterm Infants after Necrotizing Enterocolitis Surgery

Of the 52 preterm infants, 38 cases (73.1%) were discharged with restored intestinal function after surgery. Fourteen cases (26.9%) died despite aggressive medical and surgical treatment. According to the clinical outcomes, 52 surgically treated preterm infants were divided into survival and death groups. The age of patients in the death group at surgery was younger than that in the survival group, and the difference was statistically significant ($p < 0.05$; **-Table 1, -Fig. 2A**). Compared with the survival group, the proportions of shock and intestinal perforation in the death group were higher, and the difference was statistically significant ($p < 0.05$; **-Table 1, -Fig. 2B-C**). There was no significant difference between the two groups in terms of GA, BW, sex, time interval between diagnosis of NEC and surgery, mechanical ventilation before NEC, and sepsis ($p > 0.05$; **-Table 1**). The results of logistic regression analysis showed that shock and intestinal perforation were independent risk factors for death in preterm infants undergoing NEC surgery ($p < 0.05$; **-Table 2**).

Risk Factors for Postoperative Extrauterine Growth Retardation in Preterm Infants after Necrotizing Enterocolitis Surgery

Among the 38 survivors, the median weight centiles at birth, in the preoperative period and in the postoperative period when they reached full enteral feeding were 55.5, 25, and 6, respectively. The proportions of patients weighing less than 10 centiles at birth, in the preoperative period, and in the postoperative period at full enteral feeds were 13.2% (5/38), 34.2% (13/38) and 55.3% (21/38), respectively. Compared to the weight centiles in the preoperative period, weight centiles in the postoperative period at full enteral feeds were significantly decreased (6 [0, 22] vs. 25 [3.5, 41], $z = -3.86$, $p = 0.00$). In this study, 38 survivors were divided into a non-EUGR group (17 cases, 44.7%) and an EUGR group (21 cases, 55.3%) according to whether EUGR occurred when they achieved full enteral feeding after surgery. Compared with the non-EUGR group, patients in the EUGR group had a higher proportion of

Table 1 Univariate analysis of factors for clinical outcomes

Factors	Survival group (n = 38)	Death group (n = 14)	t/z/ χ^2	p-Value
GA (wk)	31.38 \pm 2.71	31.14 \pm 3.16	0.27	0.79
BW (g)	1,700.66 \pm 556.28	1,594.64 \pm 726.86	0.56	0.58
Sex (male)	73.7% (28/38)	78.6% (11/14)	0.00	1.00
Age at surgery (d)	35.84 \pm 24.39	16.07 \pm 13.23	3.73	0.001
Time interval between diagnosis of NEC and surgery (d)	4.5 (1, 26.75)	2 (1, 6)	1.75	0.08
Mechanical ventilation	44.7% (17/38)	35.7% (5/14)	0.34	0.75
Sepsis	86.8% (33/38)	100.0% (14/14)	/	0.31 ^a
Shock	36.8% (14/38)	85.7% (12/14)	7.92	0.005
Intestinal perforation	21.1% (8/38)	57.1% (8/14)	6.26	0.02

Abbreviations: BW, birth weight; GA, gestational age; NEC, necrotizing enterocolitis.

Note: ^aFisher's exact test.

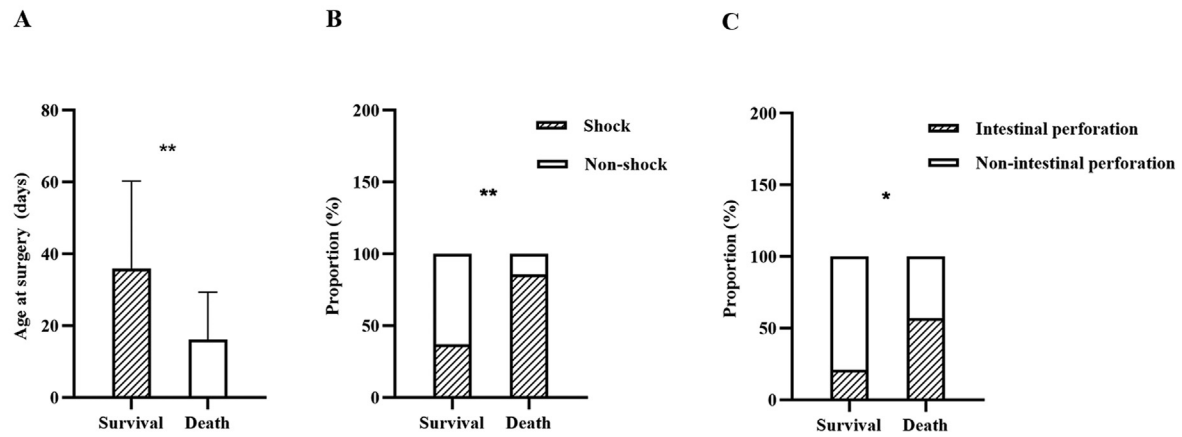


Fig. 2 Univariate analysis of factors for clinical outcomes. (A) Age at surgery in the death group was significantly younger than that in the survival group (** $p < 0.01$). (B) Compared with the survival group, the proportion of shock in the death group was significantly higher (** $p < 0.01$). (C) The proportion of intestinal perforation was significantly higher in the death group than that in the survival group (* $p < 0.05$).

Factors	OR	95%CI	p-Value
Age at surgery (days)	0.95	0.91–1.00	0.06
Shock	8.86	1.43–55.10	0.02
Intestinal perforation	6.12	1.16–32.41	0.03

Abbreviations: CI, confidence interval; OR, odds ratio.

Factors	Non-EUGR group (n = 17)	EUGR group (n = 21)	t/ χ^2	p-Value
GA (wk)	31.03 ± 2.47	31.67 ± 2.91	-0.73	0.47
BW (g)	1,770.88 ± 431.33	1,643.81 ± 645.02	0.70	0.49
Preoperative EUGR	5.9% (1/17)	57.1% (12/21)	-	0.001a
Intestinal perforation	29.4% (5/17)	14.3% (3/21)	-	0.43a
Enterostomy	76.5% (13/17)	57.1% (12/21)	-	0.31a
Intestinal resection	76.5% (13/17)	81.0% (17/21)	-	1.00a
Ileocecal valve	58.8% (10/17)	76.2% (16/21)	-	0.31a
Refeeding time	13.76 ± 5.56	17.19 ± 9.22	-1.35	0.19
Refeeding formula (human milk)	23.5% (4/17)	38.1% (8/21)	-	0.49a
Postoperative 1-week calories (kcal/kg/d)	89.00 ± 16.56	75.99 ± 13.88	2.64	0.01
Postoperative PN (days)	24.00 ± 11.02	34.38 ± 18.20	-2.06	0.04
Cholestasis	64.7% (11/17)	76.2% (16/21)	-	0.49a
Liver enzyme abnormalities	35.3% (6/17)	52.4% (11/21)	-	0.34a
Hypertriglyceridemia	23.5% (4/17)	52.4% (11/21)	-	0.10a

Abbreviations: BW, birth weight; EUGR, extrauterine growth retardation; GA, gestational age; PN, parenteral nutrition.

^aFisher's exact test.

preoperative EUGR, lower calories at 1-week postoperatively, and longer postoperative PN time, with statistically significant differences ($p < 0.05$; ▶Table 3, ▶Fig. 3A–C). No significant differences were found between the two groups in terms of GA, BW, intestinal perforation, surgical procedures, postoperative

refeeding time, refeeding formula, and complications ($p > 0.05$; ▶Table 3). Further logistic regression analysis revealed that preoperative EUGR was an independent risk factor for the development of postoperative EUGR in NEC preterm infants ($p < 0.05$; ▶Table 4).

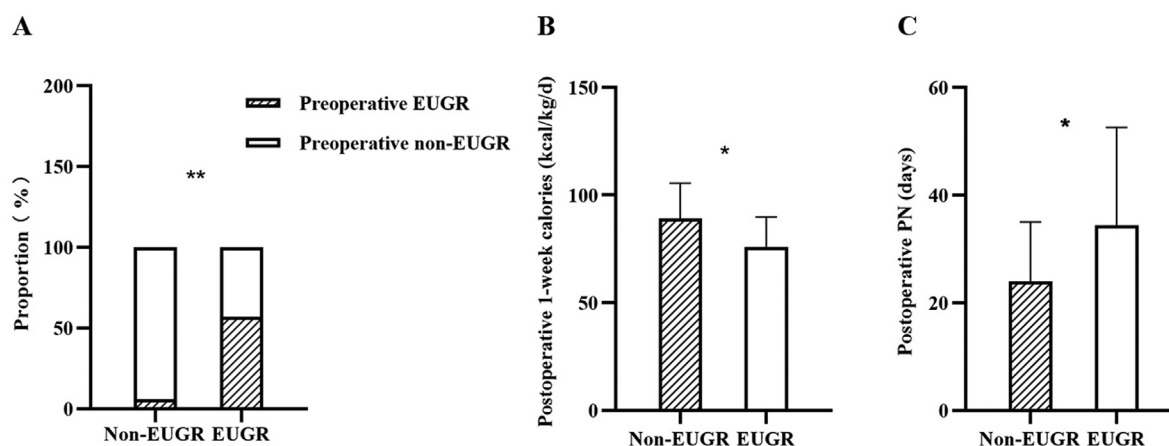


Fig. 3 Univariate analysis of factors for postoperative EUGR. (A) Compared with the non-EUGR group, the proportion of preoperative EUGR in the EUGR groups was higher (** $p < 0.01$). (B) The postoperative 1-week calories were significantly lower in the EUGR group than that in the non-EUGR group (* $p < 0.05$). (C) The duration of PN in the EUGR group was significantly longer compared with the non-EUGR group (* $p < 0.05$). EUGR, extrauterine growth retardation; PN, parenteral nutrition.

Table 4 Logistic regression analysis of factors for postoperative EUGR

Factors	OR	95% CI	p-Value
Preoperative EUGR	18.63	1.77–196.42	0.02
Postoperative 1-week calories (kcal/kg/d)	0.96	0.91–1.02	0.18
Postoperative PN (d)	1.06	0.98–1.16	0.16

Abbreviations: CI, confidence interval; EUGR, extrauterine growth retardation; OR, odds ratio; PN, parenteral nutrition.

Discussion

NEC is a common and fetal gastrointestinal disorder that usually affects the growth and clinical outcomes of preterm infants. Neonates treated with NEC surgery account for a high percentage of NEC patients and have a high mortality rate.² Survivors of NEC surgery are at high risk of imbalanced nutrition, which leads to growth retardation and multiple complications.^{4,10} Studies on the clinical outcomes and postoperative nutritional management of preterm infants after NEC surgery are limited. Our study investigated factors associated with clinical outcomes and postoperative EUGR in preterm infants who underwent NEC surgery. It demonstrates that shock and intestinal perforation are significant risk factors for death in preterm infants after NEC surgery. Preoperative EUGR, lower calories at 1-week postoperatively, and longer postoperative PN time were associated with postoperative EUGR of survivors. Moreover, preoperative EUGR is a significant risk for postoperative EUGR. These results might help clinicians identify NEC patients at high risk of death, and improve prognosis and survival quality.

A total of 52 surgically treated preterm infants were enrolled in this study, of whom 14 died, representing a mortality rate of 26.9%. NEC is a complex disease with high mortality and morbidity. Some studies have reported that the mortality rate of neonates with NEC is approximately 3%, while the mortality rate of neonates requiring surgical intervention is up to 30%.^{2,11} The above results are generally consistent with the mortality rate reported in our study. In our study, no

correlation was found between GA, BW, and sex with the clinical outcomes of preterm infants who underwent NEC surgery. LBW is by far the most commonly reported significant prognostic factor for neonatal NEC, which is consistent with large cohort studies describing a high prevalence of NEC in LBW infants. However, its clinical relevance as an independent prognostic factor for NEC (odds ratio: 0.999–1.001) is controversial and may only be relevant in clinical practice.^{12–17} In addition, some studies have shown that male was a risk factor for death in NEC neonates, while others have found a higher mortality rates in females.¹⁸ Differences in the results of these studies may be influenced by race and sample size.

In this study, shock and intestinal perforation were found to be independent risk factors for death in preterm infants treated with NEC surgery. The two indicators are the main clinical manifestations of stage 3B NEC and reflect the severity of the disease. Previous studies have found that NEC classification is a strong prognostic factor for neonatal NEC survival and that stage 3 NEC is an independent prognostic factor for neonatal NEC survival.^{18,19} Wei et al confirmed that infants who received surgical treatment for NEC without intestinal perforation had a better prognosis compared with the infants who underwent NEC surgical treatment with intestinal perforation.²⁰ Therefore, based on active medical treatment, the severity of the patient's condition should be carefully evaluated, and the timing of surgical treatment should be grasped before shock and intestinal perforation occur in NEC.

Of the 38 surviving preterm infants after NEC surgery in this study, 21 cases (55.3%) developed postoperative EUGR at the

time of full enteral feeding. It has been confirmed that NEC is an independent risk factor for EUGR, and NEC neonates requiring surgical intervention are at higher risk of growth failure at discharge.^{14,21,22} Patients undergoing NEC surgery are at high risk of imbalanced and deficient nutrition due to limited nutrient absorption caused by intestinal failure or short bowel syndrome, and the need for higher energy intake to repair tissues after recovery from surgery.^{5,10} Previous studies showed that EUGR in preterm infants has significant effects on growth and development, especially neurological development, and can lead to impaired neurological development.^{6,21,23} Long-term follow-up results suggested that patients who survive NEC surgery have a poor neurological prognosis and might develop severe neurological developmental disorders, which are critical to the survival quality.^{24–26} Therefore, improving EUGR in preterm infants undergoing NEC surgery is important for their long-term prognosis.

The findings of our study showed that preoperative EUGR, postoperative 1-week calories, and postoperative PN time were correlated with the development of postoperative EUGR in preterm infants after NEC surgery, and preoperative EUGR was an independent risk factor. Preoperative EUGR was closely associated with postnatal growth and development of preterm infants in this study. Prevention of EUGR in preterm infants is an important basis for preventing postoperative growth retardation in NEC patients. The caloric value of 89.0 ± 16.56 kcal/kg/d at 1-week postoperatively was significantly higher in the non-EUGR group than that in the EUGR group in this study, suggesting that a higher caloric intake may be required for postoperative recovery from NEC. The current recommendation for PN caloric requirements in the early postoperative period in Chinese infants after NEC enterostomy is 45 to 55 kcal/kg/d, while some foreign studies suggest that energy requirements in the postoperative recovery phase should be increased to 90 to 120 kcal/kg/d, but these studies are mostly from critically ill neonates and not specific to the particular population after NEC surgery.^{10,27} In this study, the duration of postoperative PN was longer in the EUGR group, but there was no significant difference in the initiation time of enteral nutrition (EN) between the two groups. The duration of PN after NEC surgery correlates with the resection of intestinal tube and ileocecal flap, while the initiation time of refeeding depends on the length of the remaining intestinal tube and the clinical condition of patients.^{2,9} Previous researches revealed that in preterm infants, a long PN period and a late EN initiation are correlated with EUGR.⁷ Human milk is recommended as the preferred feeding formula for postoperative patients because the components of human milk could promote the growth of small intestinal mucosa, regulate intestinal microorganisms, and shorten the PN time.^{2,9,28} However, in clinical practice, lack of human milk or restricted transport conditions often prevents NEC neonates from choosing human milk as a refeeding formula after surgery. Therefore, only 12 of the 38 survivors in this study chose human milk as the refeeding formula, and the correlation between human milk and postoperative EUGR in NEC preterm infants was not determined. The above results suggested that in preterm

infants treated with NEC surgery, preoperative nutritional management is crucial, adequate caloric supply should be ensured postoperatively, and EN should be started as early as possible with appropriate assessment of the intestinal function to shorten the PN time.

Limitations

Our study has some limitations. Since it was a single-center retrospective study, the inherent bias associated with a retrospective study exists. Multicenter or prospective study needs to be performed for further validation. What's more, extrauterine growth and development of preterm infants is a continuous process, and we lack long-term follow-up data after patients are discharged from the hospital.

Conclusion

In conclusion, preterm infants undergoing NEC surgery have a high mortality rate. Shock and intestinal perforation are independent risk factors for death in preterm infants treated with NEC surgery. Active correction of shock and appropriate timing of surgery to avoid intestinal perforation may help improve the clinical outcomes of preterm infants after NEC surgery. Preoperative EUGR is an independent risk factor for the development of postoperative EUGR in preterm infants after NEC surgery. Good preoperative nutritional management, adequate caloric intake in the first week after surgery, and achievement of full enteral feeding as soon as possible may be beneficial in improving postoperative EUGR in preterm infants with NEC.

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Conflict of Interest

None declared.

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