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Predictive factors related to surgical decision-making in neonates with necrotizing enterocolitis

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Original Article

Abstract

BACKGROUND: Necrotizing enterocolitis (NEC) is more common in neonates. This study aimed to determine the predictive factors in the decision-making about surgery in neonates with NEC.

METHODS: This retrospective cohort study was performed in Ali Asghar Children's Hospital in Tehran, Iran. All neonates hospitalized due to NEC from 2018 to 2020 were enrolled in this study. We compared the study variables such as demographic, clinical, laboratory, radiography, and sonography variables in neonates who underwent surgery with neonates without surgery. Statistical analysis was conducted by SPSS and R software.

RESULTS: There was no statistically significant difference between the two groups regarding age at hospitalization, sex, gestational age, and birth weight ($P > 0.05$). Comparison of laboratory, clinical, and radiography findings showed that there were significant statistical differences in terms of C-reactive protein (CRP), prothrombin time (PT), international normalized ratio (INR), sodium (Na), procalcitonin (PCT), skin discoloration of the abdominal wall, presence of portal venous gas (PVG), pneumoperitoneum, ascites, and fixed intestinal loop between two groups ($P < 0.05$). The results also showed that existence of skin discoloration of the abdominal wall, high level of CRP, PVG, pneumoperitoneum, ascites, and fixed intestinal loop were predictive factors for the decision of surgery.

CONCLUSION: The abdominal color change, high level of CRP, PVG, pneumoperitoneum, ascites, and fixed intestinal loop are predictive factors for the decision of surgery in neonates with NEC.

KEYWORDS: Necrotizing Enterocolitis; C-Reactive Protein; Neonate

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Introduction

Necrotizing enterocolitis (NEC) is an acute inflammatory bowel disease that is more common in premature infants.[1,2] In 2018, the disease incidence was 7% in the United States (US), 8% in Canada, 4% in Japan, and 3% in Sudan.[3-6] The global incidence of the disease was reported at 7% using a meta-analysis study conducted in 2019.[7] The underlying cause of NEC is unknown, but it is more common in infants with gastrointestinal (GI) vascular problems.[2,8] Risk factors for the disease include prematurity, formula feeding, intestinal ischemia, hypoxia, and bacterial colonization, which stress the intestinal mucosa and disrupt the host defense mechanism.

In some cases, NEC causes uncontrollable inflammation of the intestinal wall and intestinal necrosis.[9,10] Clinical findings are divided into three stages based on the Bell's index: in the first stage, there is suspicion of NEC and symptoms include abdominal distention, gastric retention, blood in the stool,

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and nonspecific symptoms include lethargy, mild nutrition, bradycardia, apnea, vomiting, decreased urination, hypothermia, and radiographs show dilation of the ileus pattern in the intestine.[11] In the second stage, in addition to the previous cases, acidosis, thrombocytopenia, electrolyte disturbance, abdominal tenderness, discoloration of the abdominal wall, and in the presence of air in the intestinal wall, ascites and a fixed intestinal loop may be seen. In the third stage, in addition to the previous cases, hypotension, severe electrolyte disturbance, disseminated intravascular coagulation (DIC), neutropenia in ultrasound, the possibility of gas in the portal vein, and the accumulation of gas in the intestinal tract by bacteria also cause pneumatosis intestinalis (PI).[12,13] Symptoms occur between 4-10 days after feeding, but symptoms also appear from 4 hours to 30 days later.[14] Possible laboratory findings include anemia, leukopenia, leukocytosis, metabolic acidosis, electrolyte imbalance, and in severe cases, DIC or thrombocytopenia occurs. The most important treatment measures include discontinuation of oral feeding, initiation of broad-spectrum antibiotics, resuscitation with intravenous (IV) fluids, requesting necessary tests, and radiography and abdominal ultrasound.[15] In severe and complicated cases of NEC disease, surgical intervention is required, including peritoneal drainage and laparotomy, and depending on the severity of the disease and the extent of intestinal damage, resection of the necrotic intestine and anastomosis or ostomy implantation is performed.[16] Understanding the factors that can lead to the decision to have surgery will be essential in predicting the course of the disease and improving the prognosis of infants.[16] So far, scattered studies with small sample sizes in different countries have been conducted on the prognostic factors of the decision to operate on infants with NEC. A study conducted in India on 22 infants with NEC showed that factors such as acidosis (low pH) and shock had a higher chance of requiring surgery than others and factors such as birth weight, gestational age, serum electrolytes, blood sugar, and other measured parameters did not increase the risk of surgery.[17] Although some studies have linked the sonographic and radiological findings of neonates with NEC to the surgical outcome, a study in the US has shown negative radiological results in neonates and focal intestinal perforation (FIP) for their surgical decision can be misleading and should be used with caution.[18-20] In another study, the effect of portal venous gas (PVG) on the possibility of surgery in infants with NEC was investigated. This study showed that the presence of PVG was not related to the need for neonatal surgery and the decision for neonatal surgery should be based on the severity of the NEC and not the presence of PVG.[21] International studies have each measured the impact of a particular radiological or clinical and laboratory feature on the likelihood of surgery, or whether the target population was only preterm infants, whose findings were inconsistent and conflicting results have been reported so far. Despite the importance of this issue, no comprehensive study has been conducted in Iran to investigate the prognostic effect of all radiological, laboratory, and clinical features in neonatal surgery decision-making. This study aimed to determine the predictive factors involved in the timely surgery decision in patients with NEC.

Methods

This retrospective cohort study was performed in Ali Asghar Children's Hospital in Tehran, Iran, from 2018 to 2020. This study was conducted after the approval of the Ethics Committee of Iran University of Medical Sciences, Tehran, and the infants entered the study after the verbal permission of the parents (IR.IUMS.FMD.REC.1398.470).

In this study, no sampling was performed,

and all infants admitted to Ali Asghar Children's Hospital between 2018 to 2020 whose parents had allowed their infant to participate in the study, were included. All neonates hospitalized due to NEC that underwent or did not undergo surgery, regardless of gender and time of onset of symptoms, were included in the study. Criteria for inclusion of patients in the study were defined as a neonate with NEC whose disease was diagnosed by a pediatrician and confirmed by relevant tests and imaging devices. Patients who refused to cooperate were excluded from the study. To collect data and record the values of the variables, a checklist was prepared, and demographic characteristics, results of clinical and laboratory tests, and imaging devices (radiography and sonography) of the patients were collected with this questionnaire. Laboratory variables were white blood cell (WBC), platelets, and neutrophils count, magnesium (Mg), calcium (Ca), creatinine (Cr), urea, sodium (Na), potassium (K), etc. Clinical variables included discoloration of the abdominal wall and abdominal distention. Imaging variables (radiography and sonography) included the PVG, the PI, pneumoperitoneum, ascites, and the fixation loop.

Quantitative findings were reported as mean and standard deviation (SD), and qualitative findings as frequency and percentage. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the normality of data distribution. Quantitative variables were compared between the two groups if the data distribution was normal using an independent t-test and if this hypothesis was not confirmed using the Mann-Whitney U test. Chi-square test was used to compare the frequency of qualitative variables between the two groups, and if at least one of the cells was zero or there was a frequency of at least 20% less than 5 in the cross table, Fisher's exact test was used. The obtained data were analyzed by SPSS statistical software (version 25, IBM Corporation, Armonk, NY, USA). Besides, the value of raw odds ratio (OR) was obtained using logistic regression fitting for each variable; in the next step, since the number of variables was higher than the sample size, stepwise (forward) logistic regression was used for multiple analyses, and to obtain the most influential variables, all variables were entered into the model at this stage, and then the analysis was done. To analyze variables with scattered data with low frequency or zero cells, penalized logistic regression was used, which applies an acceptable model to the model's validity and partially prevents the influence of scattered data in the analysis. To analyze this model, logistf package was used in R software. Moreover, for stepwise (forward) logistic regression analysis, the brglm package was used in R software despite the scattered data, which uses the Bayesian approach for scattered data coverage. In addition, the value of model prediction ability was obtained using important variables obtained from stepwise (forward) logistic regression analysis using receiver operating characteristic (ROC) curve and the area under the curve (AUC). In all tests, a significance level of < 0.05 was considered.

Results

In this study, 63 neonates with NEC were studied, of which 16 patients underwent surgery with a doctor's diagnosis, and 47 patients were not candidates for surgery. The mean and SD of age of patients in the surgical group was 24.81 ± 24.45 days, and the mean and SD of age of patients in the non-surgical group was 16.60 ± 13.21 days. According to the independent t-test, there was no significant difference between the mean ages of the two groups ($P = 0.56$). Besides, the mean and SD of gestational age in the surgical group was 31.31 ± 4.04 weeks, and the mean and SD of gestational age in the non-surgical group was 30.68 ± 2.59 weeks.

Table 1. Demographic characteristics of neonates with necrotizing enterocolitis (NEC) participating in the study by two groups of the surgical group and non-surgical group

Variables	Surgical group (n = 16) (mean ± SD)	Non-surgical group (n = 47) (mean ± SD)	P
Age (day)	24.81 ± 24.45	16.60 ± 3.21	0.21
Maternal gestational age (week)	31.31 ± 4.04	30.68 ± 2.59	0.47
Weight (g)	1784.38 ± 709.88	1455.72 ± 524.79	0.05

There was no significant difference between the mean gestational age (P = 0.47). The mean and SD of birth weight of patients in the surgical group was 1784.38 ± 709.88 g, and the mean and SD of patients in the non-surgical group was 1455.72 ± 524.79 g (Table 1).

There was no significant difference between patients' mean weight in the two groups (P = 0.05). Moreover, nine patients (56.2%) in the surgical group and 28 patients (56.20%) in the non-surgical group were men, and according to the results of the chi-square test, the genus distribution was similar in the two groups (P = 0.81) (Table 2).

Table 2. Comparison of laboratory characteristics of neonates with necrotizing enterocolitis (NEC) between surgical and non-surgical groups

Variables	Group	Mean ± SD	P
CRP	Surgical	69.88 ± 43.39	< 0.01*
	Non-surgical	11.77 ± 21.83	
pH	Surgical	7.17 ± 0.15	< 0.01*
	Non-surgical	7.34 ± 0.11	
WBC	Surgical	820000.00 ± 5388.01	0.42
	Non-surgical	1030000.00 ± 10174.41	
Lymph	Surgical	48.06 ± 19.97	0.56
	Non-surgical	50.83 ± 15.12	
PLT	Surgical	10200000 ± 99486.46	0.10
	Non-surgical	15700000 ± 119848.51	
PT	Surgical	24.26 ± 19.38	< 0.01*
	Non-surgical	15.44 ± 3.74	
PTT	Surgical	52.44 ± 21.28	0.07
	Non-surgical	44.19 ± 13.41	
INR	Surgical	2.11 ± 0.81	0.02*
	Non-surgical	1.69 ± 0.53	
Sodium	Surgical	130.31 ± 7.49	< 0.01*
	Non-surgical	134.71 ± 4.19	
Potassium	Surgical	3.73 ± 1.44	0.61
	Non-surgical	3.95 ± 1.74	
BUN	Surgical	14.31 ± 7.42	0.67
	Non-surgical	12.38 ± 17.75	
Creatinine	Surgical	1.01 ± 0.93	0.17
	Non-surgical	0.71 ± 0.67	
Calcium	Surgical	8.32 ± 0.76	0.73
	Non-surgical	8.39 ± 0.73	
Magnesium	Surgical	1.85 ± 0.21	0.44
	Non-surgical	1.89 ± 0.19	
Nutrition	Surgical	44.62 ± 18.46	0.41
	Non-surgical	40.62 ± 16.07	

*P < 0.05

CRP: C-reactive protein; WBC: White blood cell; PLT: Platelet count; PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio; BUN: Blood urea nitrogen; SD: Standard deviation

The results showed a statistically significant difference between the mean of C-reactive protein (CRP), pH, prothrombin time (PT), international normalized ratio (INR), and Na in the surgical and non-surgical groups ($P < 0.05$), so that the mean CRP of 58.11 mg/l ($P < 0.01$), mean PT of 8.82 seconds ($P < 0.01$), and mean INR of 0.42 ($P = 0.02$) in the surgical group were more than the non-surgical group and mean of pH was 0.17 ($P < 0.01$). Na was 4.4 mEq/l ($P < 0.01$) in the surgical group which was lower than the non-surgical group. The median of procalcitonin (PCT) in surgical patients was 2.56 ng/ml and in the control group, it was 0.48 ng/ml; there was a significant difference between the two groups in terms of this variable ($P = 0.02$) (Table 2).

The results of comparing the frequency of clinical features related to the neonates participating in the study showed that abdominal color change was significantly different between the two groups, so that abdominal color change appeared in 13 (81.2%) infants who underwent surgery, while it did not appear in any of the children who did not have surgery. This difference was statistically significant ($P < 0.01$). In addition, the mean duration of hospitalization in patients who underwent surgery was 32.62 ± 48.69 days and for patients who did not undergo surgery, it was 22.93 ± 19.44 days, and the difference in the mean length of hospitalization was not statistically significant between the two groups ($P = 0.41$) (Table 3).

Comparing the frequency of imaging characteristics (radiography and sonography) related to the neonates showed that PVG was found in 4 (25%) neonates who underwent surgery. At the same time, it was not seen in any of the children who did not have surgery. It is statistically significant ($P < 0.01$). 13 (81.2%) neonates who underwent surgery had PI, and for neonates who did not undergo surgery, this number was 3 (6.4%) neonates ($P < 0.01$). In terms of pneumoperitoneum, 13 (81.2%) infants who underwent surgery had this complication, and for infants who did not have any surgery, this number was 1 (2.1%) infant ($P < 0.01$). Ascites also appeared in 10 (62.5%) infants who underwent surgery, while it did not appear in any children who did not have surgery ($P < 0.01$). 5 (31.2%) infants who underwent surgery had a fixation loop ($P < 0.01$) (Table 4).

By controlling the effect of other variables, the odds for surgery in infants with PVG were 16.95 times higher than in infants without PVG [OR = 16.95, 95% confidence interval (CI): 5.31-56.43]. The results showed that by controlling the effect of other variables, the odds of surgery in infants with a fixation loop was 5.56 times higher than in infants without a fixation loop. It was statistically significant (OR = 5.56, 95% CI: 2.42-11.02). By controlling the effect of other variables, per unit increase in CRP increased the chance of surgery in infants by 1.05 times (OR = 1.05, 95% CI: 1.01-1.13). By controlling the effect of other variables, the chance of surgery in infants who had abdominal discoloration was 12.19 times higher than in infants who did not have abdominal discoloration, and this increase was statistically significant (OR = 12.19, 95% CI: 3.56-21.98).

Table 3. Comparison of the frequency of clinical features of neonates with necrotizing enterocolitis (NEC) between the surgical and the non-surgical groups

Variables	Group	Surgical [n (%)]	Non-surgical [n (%)]	P
Abdominal distention	No	0 (0)	5 (10.60)	0.31
	Yes	16 (100)	42 (89.04)	
Abdominal color change	No	3 (18.81)	47 (100)	< 0.01*
	Yes	13 (81.20)	0 (0)	

Table 4. Comparison of frequency of imaging characteristics (radiography and sonography) of neonates with necrotizing enterocolitis (NEC) between surgical and non-surgical groups

Variables	Group	Surgical [n (%)]	Non-surgical [n (%)]	P
PVG	No	12 (75.00)	47 (100)	< 0.01*
	Yes	4 (25.00)	0 (0)	
PI	No	3 (18.80)	44 (93.60)	< 0.01*
	Yes	13 (18.20)	3 (6.40)	
Pneumoperitoneum	No	3 (18.80)	46 (97.90)	< 0.01*
	Yes	13 (18.20)	1 (2.10)	
Ascites	No	6 (37.50)	47 (100)	< 0.01*
	Yes	10 (62.50)	0 (0)	
Fixation loop	No	11 (68.80)	47 (100)	< 0.01*
	Yes	5 (31.20)	0 (0)	

P < 0.05

PVG: Portal venous gas; PI: Pneumatosis intestinalis

Besides, by controlling the effect of other variables, the pneumoperitoneum and also the presence of ascites increased the chance of surgery in neonates with NEC 27.02 times (OR = 27.02, 95% CI: 11.12-43.46) and 29.12 times (OR = 29.12, 95% CI: 10.15-52.50), respectively (Table 5).

Table 5. Results of multiple logistic regressions fitting in determining predictive factors in timely surgical decision-making in patients with necrotizing enterocolitis (NEC)

Variables	Model a1		Model a2	
	OR (95% CI)	P	AOR (95% CI)	P
Gender (men as reference)	1.15 (0.36-3.61)	0.81	-	-
Age	1.03 (0.99-1.06)	0.21	-	-
Gestational age	1.07 (0.89-1.29)	0.46	-	-
Weight	1.00 (0.07-1.01)	0.52	-	-
CRP	1.06 (1.03-1.08)	0.01*	1.05 (1.03-1.13)	0.01*
pH	1.17 (0.03-0.52)	0.01*	-	-
WBC	1.00 (1.00-1.01)	0.43	-	-
Nutrition	1.01 (098-1.05)	0.40	-	-
Lymph	0.99 (0.96-1.02)	0.55	-	-
PLT	1.00 (1.00-1.01)	0.54	-	-
PT	1.16 (1.01-1.33)	0.04*	-	-
PTT	1.03 (1.99-1.06)	0.11	-	-
INR	2.66 (1.00-7.04)	0.04*	-	-
Sodium	0.87 (0.78-0.96)	0.01*	-	-
Potassium	0.79 (0.43-1.44)	0.44	-	-
BUN	1.01 (0.97-1.04)	0.67	-	-
Creatinine	1.57 (0.77-3.17)	0.21	-	-
Calcium	0.86 (0.39-1.99)	0.73	-	-
Magnesium	0.33 (0.02-5.57)	0.44	-	-
Abdominal distention (reference = non-existence)	4.27 (1.32-7.22)	0.03*	-	-
Abdominal color change (reference = non-existence)	48.49 (0.01-850.00)	0.99	12.19 (3.56-21.98)	0.01*
PVG (reference = non-existence)	34.20 (31.21-37.19)	0.01*	16.95 (5.56-31.43)	0.03
PI (reference = non-existence)	63.55 (11.43-353.42)	0.01*	-	-
Pneumoperitoneum (reference = non-existence)	50.70 (19.09-960.95)	0.01*	27.02 (11.12-43.46)	0.02
Ascites (reference = non-existence)	40.38 (10.01-70.61)	0.01*	29.12 (10.15-52.50)	0.01*
Fixation loop (reference = non-existence)	45.43 (42.47-48.46)	0.01*	5.56 (2.42-11.02)	0.01
Duration of hospitalization	1.01 (0.99-1.03)	0.27		

*P < 0.05; a: Raw logistic model and control group was considered as reference; b: Logistic model (forward) and control group was considered as reference.

OR: Odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval; WBC: White blood cell; BUN: Blood urea nitrogen; PVG: Portal venous gas; INR: International normalized ratio; CRP: C-reactive protein; PT: Prothrombin time; PTT: Partial thromboplastin time; PLT: Platelet count; PI: Pneumatosis intestinalis

According to the results of the previous section, using the ROC curve, the ability of the factors obtained from the multiple logistic model in the previous section was investigated. Considering the factors obtained from multiple logistic regression, the area under the curve (AUC) was equal to 0.92, which indicates the high diagnostic accuracy of these factors in deciding on surgery for neonates with NEC (Figure 1).

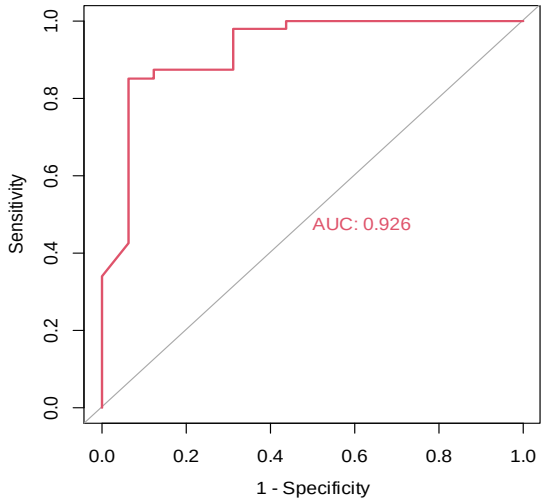

Figure 1. Receiver operating characteristic (ROC) chart to evaluate the ability of factors derived from the logistic model to make timely surgical decisions

Discussion

It is essential to know the factors that can lead to the decision to have surgery. This study aimed to determine the prognostic factors in the timely decision of surgery in NEC. In this study, 63 neonates with NEC were studied, of which 16 patients required surgery (25.4%). There was no statistically significant difference between the two groups in terms of age at hospitalization, gender, gestational age at birth, and birth weight, and the two groups were similar in terms of demographic characteristics. Our study is the first study to examine the laboratory characteristics of neonates with NEC in two groups. Examining the laboratory findings of WBC, platelets, lymphocytes, neutrophils, Mg, Ca, Cr, BUN, K, Na, INR, PTT, and PT in the two groups, we found that the mean CRP, PT, INR, Na, and PCT in the two groups differed, and they were statistically significant. Although the mean of CRP, PT, INR, and PCT in the surgical group was higher than the non-surgical group and this difference was statistically significant, after adjusting the effect of other variables and performing multiple logistic regression, we found that only patients' CRP was a predictor of the need for surgery and PT, INR and PCT levels were not predictors of the need for surgery. We also found that although the mean pH and Na of blood in the surgical group were not significantly lower than the non-surgical group, after adjusting the effect of other variables and performing multiple logistic regressions, the amount of pH and Na were not predictive factors of the need for surgery.

Therefore, among the laboratory factors, only high CRP can be a predictor factor of the need for surgery, which is consistent with the results of other studies in this field.[22,23] The results of a study conducted by Duci et al. showed that high CRP was an independent factor in the severity of NEC and the need for surgery.[23] In addition, the results of another study showed that high CRP levels in 24 hours before and 72 hours after diagnosis of NEC in infants were associated with an increased risk of surgery and death in infants,[22] which is consistent with the results of the present study.

furthermore, in this study, by comparing the clinical characteristics of neonates with NEC in two groups, we found that the surgical group had changed abdominal color; however, the duration of hospitalization was the same in both groups. After adjusting the effect of other variables and performing multiple logistic regressions, we found that the clinical factor predicting the need for surgery was changing of the abdominal color. Comparing the imaging characteristics (radiography and

sonography) of infants with NEC in two groups, we found that in the surgical group, PVG, PI, pneumoperitoneum, ascites, and fixation loop were significantly more observed. Due to the destructive effect of other variables such as clinical and laboratory characteristics, we found that PVG, pneumoperitoneum, ascites, and fixation loop were present after adjusting the effect of these variables and performing multiple logistic regression. Moreover, radiographic and sonographic factors predicted the need for surgery.

Other retrospective studies in recent years have been consistent with the present study. The association of imaging findings such as PVG, PI, pneumoperitoneum, and free fluid in the abdomen has been directly linked to surgery and the worse prognosis of the disease. Factors such as decreased peristalsis, intestinal thickness, perfusion in the intestine, and increased or decreased small intestinal thickness have also been reported as predisposing factors for surgery.[24-26]

But in a study in which 194 infants with NEC were evaluated over a 13-year period in terms of the relationship between PVG and surgery, no association was found between the presence of PVG and surgery.[21] One of the reasons for the discrepancy between the results of this study could be due to the different accuracy of radiologists in this study. Another reason is that the focus of this study was only on the study of the relationship between PVG and surgical outcome and did not adjust the role of other radiological, clinical, and experimental factors. In this study, the presence of PVG was repeated in several stages, including the beginning of the patient's admission, 6 to 8 hours later, or according to clinical need, which leads to higher accuracy of measurement in terms of PVG and reduction of instrumental bias. The results of prospective cohort studies were consistent with the results of retrospective studies, such as the PVG presence of intraperitoneal (IP) air.[24,25] One of the limitations of the present study was the small sample size due to the lack of NEC cases in the hospital during the years under study, which can affect the statistical power of the study.

To better understand the dimensions of the factors influencing the decision of neonatal surgery, a more extensive multicenter study should be performed in specialized pediatric hospitals in the country with more extended periods and more patients to reconcile the results of different studies with fewer patients.

Conclusion

Some radiological and laboratory findings such as the abdominal color change, high CRP, the presence of PVG, pneumoperitoneum, ascites, and the observation of fixation loop have high diagnostic accuracy in deciding on the need for surgery in infants with NEC and can be excellent clinical guides for specialists to make decisions as quickly and accurately as possible for surgery in infants with NEC, regardless of the severity of their disease.

Conflict of Interests

Authors have no conflict of interests.

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