

Imaging manifestations of neonatal necrotizing enterocolitis to predict timing of surgery

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ABSTRACT

Background. To find the predictor of optimal surgical timing for neonatal necrotizing enterocolitis (NEC) patients by analyzing the risk factors of conservative treatment and surgical therapy.

Methods. Data were collected from 184 NEC patients (Surgery, n=41; conservative treatment, n=143) between the years 2015 and 2019. Data were analyzed by univariate analysis, and multivariate binary logistic regression analysis.

Results. Univariate analysis showed that statistically significant differences between the surgery and conservative treatment groups. The results of multivariate Logistic regression analysis indicated intestinal wall thickening by B-ultrasound and gestational age were independent factors to predict early surgical indications of NEC ($p<0.05$). The true positive rate, false positive rate, true negative rate and false negative rate in the diagnosis of necrotic bowel perforation guided by DAAS (Duke abdominal X-ray score) ≥ 7 and MD7 (seven clinical metrics of metabolic derangement) ≥ 3 were 12.8%, 0.0%, 100.0% and 87.2%, respectively.

Conclusions. In summary, the ultrasound examination in NEC children showing thickening intestinal wall and poor intestinal peristalsis indicated for early operation.

Key words: necrotizing enterocolitis, abdominal X-ray, abdominal ultrasound, operation timing.

Necrotizing enterocolitis (NEC) is a severe intestinal disease, mainly manifested by abdominal distension. NEC is an acquired disease resulting in intestinal mucosal damage, mucosal ischemia and hypoxia, local or diffuse necrosis of the colon and small intestine.^{1,2} In traditional NEC treatment, taking the intestinal perforation as the absolute indication of surgery will miss the opportunity for treatment and increase the risk of postoperative death. Previous studies have shown that early surgical intervention before intestinal perforation or full-thickness necrosis of intestinal wall

significantly improves therapeutic efficacy and reduces the probability of mortality and complications.³ Meanwhile, early surgical intervention also effectively controls systemic metabolic disorders, and reduces postoperative complications such as intestinal stenosis.^{4,5} However, the evidence of pneumoperitoneum on plain radiography is the only absolute criteria for operative intervention⁶, and the single surgical indication may lead to limitations in clinical application. In this study, we provide an approach for clinicians to predict the best surgical timing by comparing X-ray, ultrasound, and the related factors such as abdominal X-ray score (DAAS score) and metabolic disorder score (MD7 score), and finally guide NEC children to be transferred to surgical treatment before intestinal perforation due to inadequate conservative treatment.

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Material and Methods

Research object

All cases were collected from 273 children with NEC who were hospitalized in the Children's Hospital of the Capital Institute of Pediatrics in China from January 2015 to December 2019. Among them, 184 cases met the inclusion criteria, including 41 cases in the surgical group and 143 cases in the non-surgical group.

Inclusion criteria

1) Meet the revised Bell's NEC II or III clinical diagnostic criteria⁷, and the X-ray features suggests of NEC, including pneumatosis, portal venous gas, gasless abdomen, or fixed dilated loops.⁸

2) Complete clinical case records were necessary which included onset time, weight, metabolic disorder indicators, abdominal x-rays, abdominal ultrasound, and surgical records.

Exclusion criteria

1) Children with severe complications who died within 48 hours after admission.

2) Child who needed surgery but had been refused by their guardian.

3) Newborns with gastrointestinal malformations.

Grouping Standard

1) Surgery group: 41 children who met the NEC diagnostic criteria and underwent surgery were included in the surgery group, consisting of 23 cases with intestinal perforation and 18 cases without perforation.

2) Conservative treatment group: 143 children who met the NEC diagnostic criteria without surgery and received conservative treatment.

Research methods

Research content

Imaging of ultrasonography, and metabolic disorder scores of children with NEC were recorded. Duke abdominal X-ray score (Duke

abdominal assessment scale, DAAS) was calculated; seven clinical metrics of metabolic derangement (MD7) were combined to evaluate the best time for NEC surgery.

1) Basic information: gender, age of onset, weight of onset.

2) Indicators of metabolic disorders: blood culture, blood pressure, platelets, pH, blood sodium, rod-shaped granulocytes, and neutrophils.

3) Abdominal X-ray: intestinal dilatation, gas accumulation, thickening of the intestinal wall, gas accumulation in the intestinal wall, gas accumulation in the portal vein, and pneumoperitoneum signs.

4) Abdominal ultrasound: intestinal dilatation, thickening of the intestinal wall, intestinal wall ischemia, poor intestinal motility, gas accumulation in the intestine wall, and gas accumulation in the portal vein. The representative images of abdominal ultrasound are shown in Figure 1.

5) DAAS scoring method: Based on the abdominal X-ray examination of children with NEC, the 184 children with NEC included in the study were scored using the DAAS scoring standard developed by Coursey et al.⁹ The specific criteria are as follows: 0 point, the intestinal cavity inflation is normal; 1 point, the intestinal cavity inflation is mildly dilated; 2 points, the intestinal cavity inflation is moderately dilated, or the intestinal cavity inflation is normal but with stool-like penetrating shadow; 3 points, the intestinal cavity is inflated with local and moderate expansion of the intestinal loop; 4 points, there is intestinal loop separation or local thickening of the intestinal wall; 5 points, there are multiple separated bowel loops; 6 points, intestinal wall gas accumulation, and there is suspected of abnormal abdominal clinical signs; 7 points, fixed or persistent dilatation of bowel loops; 8 points, clinically diagnosed or with intestinal wall gas; 9 points, there is portal vein gas; 10 points, there is pneumoperitoneum.

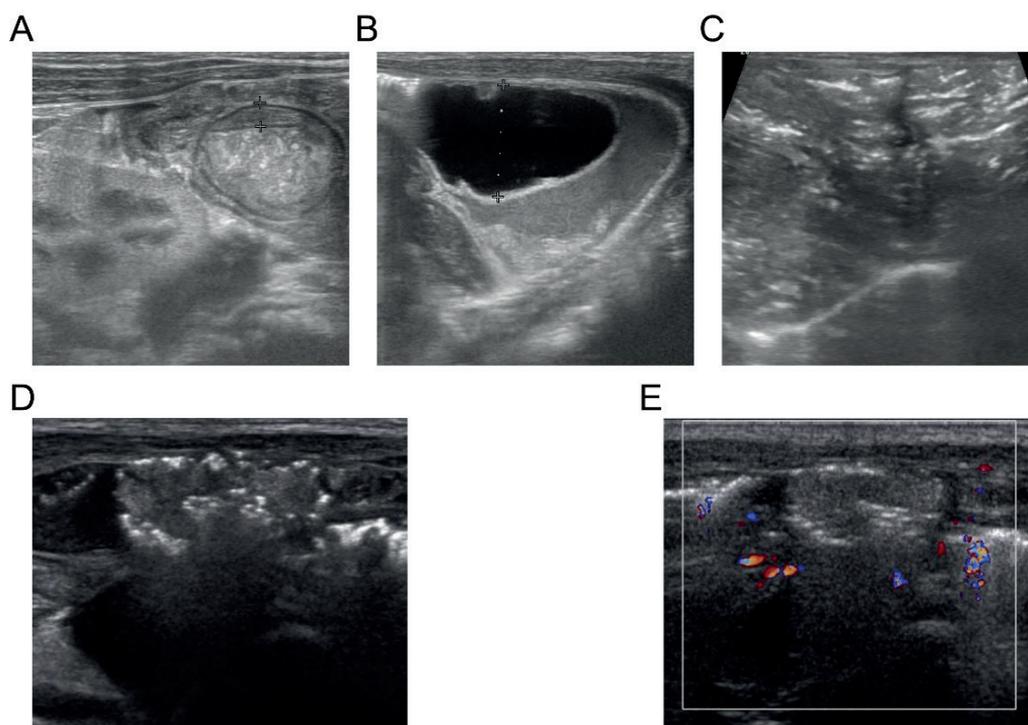


Fig. 1. The representative ultrasound images. A. Intestinal wall edema; B. Dilated bowel with seroperitoneum; C. Hepatic portal venous gas; D. Pneumatosis intestinalis; E. Intestinal ischemia.

6) MD7 assessment method: NEC children included in the study were scored by the frequency of occurrence of seven metabolic disorders¹⁰, including positive blood culture, hypotension, thrombocytopenia, acidosis and hyponatremia that can't be corrected over 48 hours, increased band neutrophils, and neutropenia. The occurrence of one disorder was scored as 1 point, and the MD7 score ranged from 0 to 7.

Procedure

Univariate analysis of all indicators in the surgical group and non-surgical group was performed at first. After that, multivariate logistic regression analysis was performed on those with statistical significance to find out the relevant factors of NEC early surgical treatment and predict the best time for early surgery.

Statistical analysis

Data was analyzed by SPSS22.0 software and expressed as the number of cases and

percentages. The data which conformed to the normal distribution or approximately was expressed by the mean \pm standard deviation ($\bar{x} \pm S$); the data comparison between groups was performed by X^2 test, and t test was used for normal distribution. Binary logistic stepwise regression analysis was used for multivariate analysis, and the results were shown by modified odds ratios (OR), and 95% confidence intervals (95% confidence intervals, 95% CI). $p < 0.05$ was considered statistically significant.

Result

Research object status

184 cases of NEC were eventually incorporated into the diagnosis, of which 89 cases were ruled out. Finally, there were 41 cases in the surgical group and 143 cases in the conservative treatment group.

The single factor analysis

Research object analysis

There was no significant difference in gender and age of onset between the surgical group and the conservative treatment group ($p>0.05$). The difference between the number of weeks of pregnancy and weight at onset was statistically significant ($p<0.05$) (Table I).

X-ray results

X-ray analysis showed that there were statistically significant differences between the surgical group and conservative treatment group in thickening of the intestinal wall, pneumoperitoneum ($p<0.05$). But there were no statistically significant differences in intestinal dilatation, intestinal wall gas accumulation and portal gas accumulation ($p>0.05$), as shown in Table II.

Abdominal ultrasound results

B-scan ultrasound analysis showed that there were statistically significant differences between the surgical group and conservative treatment group in intestinal wall thickening and intestinal peristalsis weakening ($p<0.05$). There was also no statistical significance in intestinal flatulence, intestinal wall gas accumulation ($p>0.05$), as shown in Table III.

Multivariable Logistic regression analysis

As shown above, nine factors related to NEC surgery were found by the single factor analysis: gestational age, body weight at onset, X-ray separated bowel loops, X-ray pneumoperitoneum, ultrasound intestinal wall thickening, ultrasound intestinal peristalsis weakening. The above indicators were included in the multivariate stepwise Logistic regression analysis and the results are shown in Table IV.

Table I. Comparison of general conditions between the surgery and the conservative treatment group.

Survey items	Factors	Surgery, n(%)	Conservative treatment, n(%)	χ^2	p value
Gender	Male	21 (51.22)	80 (55.94)	0.287	0.592
	Female	20 (48.78)	63 (44.06)		
Gestational age	<32 week	13 (31.71)	19 (13.29)	14.358	0.001
	32 week~	19 (46.34)	48 (33.57)		
	≥ 37 week	9 (21.95)	76 (53.15)		
The weight of onset	<1500 g	7 (17.07)	12 (8.39)	12.901	0.002
	1500 g~	24 (58.54)	51 (35.66)		
	≥ 2500 g	10 (24.39)	80 (55.94)		
Days of onset	<7 day	15 (36.59)	26 (18.18)	0.096	0.953
	7 day~	11 (26.83)	36 (25.17)		
	≥ 14	15 (36.59)	51 (35.66)		

Table II. Comparison of physical examination between surgery and conservative treatment group.

Clinical feature	Surgery, n(%)	Conservative treatment, n(%)	χ^2	p value
Intestinal dilatation	11 (100)	58 (56.64)	2.563	0.109
Intestinal wall thickening	5 (58.54)	55 (12.59)	10.004	0.002
Intestinal wall gas accumulation	7 (82.93)	18 (32.87)	0.546	0.460
Portal gas accumulation	3 (12.20)	3 (11.89)	2.752	0.097
Pneumoperitoneum	12 (4.90)	0 (0)	44.774	0.000

Table III. Comparison of abdominal ultrasound results between surgery and conservative treatment group.

Clinical feature	Surgery, n(%)	Conservative treatment, n(%)	χ^2	p value
Intestinal flatulence	4 (9.76)	20 (10.99)	0.503	0.478
Intestinal wall thickening	14 (34.15)	15 (10.49)	13.431	0.000
Intestinal wall gas accumulation	7 (17.07)	22 (15.38)	0.068	0.794
Intestinal peristalsis weakening	12 (29.27)	15 (10.49)	8.974	0.003

Table IV. Multivariable logistic regression analysis of factors related to NEC surgery.

Factor	B value	SE value	Wald value	p value	OR value	OR value 95%CI	
						Lower limit	Upper limit
B-ultrasound intestinal wall thickening	5.119	1.960	6.819	0.009	167.1	3.585	7788.758
Gestational age	-1.592	0.694	4.857	0.028	0.217	0.056	0.844
Constant	2.543	2.345	1.176	0.027	12.715		

Table V. DAAS combined with MD7 score results.

Evaluation index	Number of cases	Conservative treatment	Surgery	
			Intestinal perforation	Intestinal necrosis
DAAS \geq 7				
MD7 \geq 3	5	0	5	0
MD7 <3	21	7	9	5
DAAS<7				
MD7 \geq 3	17	8	3	6
MD7 <3	136	125	5	6

Table VI. DAAS combined with MD7 to guide surgical timing (%).

	True positive rate	False positive rate	True negative rate	False negative rate
DSSA \geq 7	48.7	5.0	95.0	51.3
MD7 \geq 3	53.8	16.9	83.1	46.2
DSSA \geq 7 and MD7 \geq 3	12.8	0.0	100.0	87.2

B-scan ultrasound indicated intestinal wall thickening (OR=167.1, 95%CI: 3.585-7788.758) and gestational age (OR=0.217, 95%CI: 0.056-0.844) were independent factors to predict early surgical indications of NEC (p<0.05).

DAAS and MD7 evaluation results

DAAS and MD7 scores were calculated in 184 NEC children. After surgical treatment, intestinal perforation was confirmed in 5 cases with DAAS \geq 7 and MD7 \geq 3. There were 136

cases with DAAS <7 and MD7 <3, including 125 cases with conservative treatment and 11 cases with surgery, as shown in Table V. The true positive rate, false positive rate, true negative rate and false negative rate in the diagnose of necrotic bowel perforation guided by DAAS \geq 7 and MD7 \geq 3 were 12.8%(5/39), 0.0%(0/140), 100.0%(140/140) and 87.2%(34/39), respectively, as shown in Table VI. These data suggest the sensitivity of DAAS combined with MD7 score in predicting the timing of NEC surgery was poor.

Discussion

NEC is a common digestive disease worldwide. Although previous studies have tried to reveal the pathogenesis of NEC, the NEC process remains unclear. Scholars believe that many risk factors are involved in the pathogenesis of NEC.⁴ The main purpose of surgical treatment for NEC children is to remove the necrotic intestinal tissue as completely as possible to reduce the abdominal inflammatory condition and preserve the intestinal tissue to avoid the occurrence of short bowel syndrome.¹¹ However, this indication is difficult to grasp in clinical work. Pneumoperitoneum, abdominal wall redness, abdominal mass, and intestinal obstruction are considered as indications for early surgical operation.^{12,13} However, traditionally, the pneumoperitoneum on plain radiography is the only absolute criteria for operative intervention, and this makes some NEC children without intestinal perforation miss the therapeutic opportunity, leading to an increased risk of death. In recent years, studies have showed that early surgical intervention before intestinal perforation significantly raises therapeutic efficacy, as well as reduce the probability of mortality and complications.^{5,8}

In the present study, we found that the presence of pneumoperitoneum on abdominal x-rays indicates intestinal perforation, suggesting surgical indications. Meanwhile, our present study suggested that intestinal perforation already existed before pneumoperitoneum was detected, which led to a loss of the predicted power. A previous study showed that the transit time of the entire intestine is prolonged in NEC condition, thus, the continuous X-ray examination describes food transportation throughout the intestine and records the regional dependent effects of NEC damage on intestinal transport in premature infants.¹⁴

In this study, we found that the predictive ability of surgery reached 90.24% (37/41) in NEC children who received surgical intervention according to the abnormal ultrasound results, including the thickened intestinal wall and

poor intestinal wall ischemia not the intestinal gas accumulation, ascites, and portal gas accumulation. Additionally, we found that the ultrasound examination also revealed the thickening of the intestinal wall in the early stage of NEC lesions, and indicated intestinal wall ischemia and poor intestinal motility in the middle stage, as well as the deterioration of the intestinal wall in the late stage.¹⁵ In recent years, abdominal ultrasound examination has been widely used and become more standardized in the diagnosis and treatment of NEC diseases.¹⁶ Although the ultrasound is important in the early diagnosis of NEC intestinal wall, the examinational power is strongly influenced by the subjectivity of a sonologist, especially, a sonologist with insufficient experience.¹⁷

It was reported that abdominal ultrasound is a non-invasive imaging examination that is increasingly being used in the evaluation of NEC intestinal perforation.¹⁸ Abdominal ultrasound is equipped to measure intestinal wall thickness and evaluate the characteristics of ascites. Cuna et al.¹⁸ reported that the sensitivity of ultrasound mentioned is not high, but the sensitivity of ultrasound for intestinal wall thickening is high. Abdominal ultrasound has a high specificity in bowel lesion severity. For example, the severity of intestinal lesions revealed by ultrasound was earlier than that by X-ray imaging. However, ultrasonic testing is dependent on the capacity of the ultrasound operator. Therefore, it is necessary to improve the skills of sonologist in diagnosing NEC. What's more, Lok et al. reported that sensitivities below 70% and specificities largely above 80% for diagnosing definite NEC, but the timing of the ultrasound is not specified.¹⁹ Most of the ultrasonic testing was performed 4 to 6 hours after the X-ray testing, which is a limit for ultrasound application. Actually, we can increase the frequency of ultrasound examinations and make good use of the non-invasive characteristics of ultrasound examinations to dynamically monitor the degree of intestinal infection in children, so as to find the possibility of intestinal necrosis for the first time.

In our present study, we transferred the subjective abdominal X-ray results into the half quantitative analysis using the DAAS evaluation system. Meanwhile, the incidence frequency of seven metabolic disorders (MD7), which include positive blood culture, hypotension, thrombocytopenia, uncorrected acidosis and hyponatremia over 48 hours, rod nucleocytosis and neutropenia, were selected as the joint evaluation system of the DAAS.¹⁰ The results suggested that the DAAS combined with MD7 evaluation system made a high clinical diagnostic specificity for guiding surgical treatment in NEC children but with low sensitivity. This indicates that it is likely to lead to misdiagnosis and delay the best timing of surgery using the DAAS evaluation system in NEC children, which is mainly due to the rapid progress of NEC and the subjectivity of radiologists in reading the film. Thus, the DAAS combined with MD7 evaluation system were not suitable for the indicator of surgical timing selection in NEC children.

The development of NEC is affected by many factors, the early prevention and detection of high-risk factors are particularly important in the diagnosis and therapy of NEC. Our present study suggests that B-scan ultrasound showing thickening intestinal wall and poor intestinal peristalsis can be used as early surgical indications for children with NEC. The sensitivity of DAAS combined with MD7 score in predicting the timing of NEC surgery was poor. Accurate ultrasound is a better predictor of the timing of NEC surgery than X-ray. Finally, the timing of surgery should be selected according to the actual situation of children with NEC.

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Ethical approval

The study was reviewed and approved by the institutional review committee and involved informed consent. Review date: January 18, 2022. Review location: 2 Yabao Road, Chaoyang District, Beijing, Capital institute of Pediatrics. Multifunctional conference room on the 11th floor of science and Trade Building. Ethics review No SHERSLM2022001.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: LY, LM; data collection: CL; analysis and interpretation of results: LY, YC, LX; draft manuscript preparation: CL, LM. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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