

# Predictive factors and clinical practice profile for strictures post-necrotising enterocolitis

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## Abstract

Intestinal stricture is a severe and common complication of necrotizing enterocolitis (NEC), causing severe and prolonged morbidity. Our goal was to investigate the clinical predictors for strictures developing after NEC and evaluate the management outcome of the post-NEC strictures to better orient their medicosurgical care.

A total of 188 patients diagnosed with NEC with identical treatment protocols throughout the period under study were retrospectively reviewed from 4 academic neonatal centers between from January 1, 2011, and October 31, 2016. Clinical predictive factors and clinical outcomes, including demographic information, clinical management, laboratory data, histopathology of resected bowel segment, and discharge summaries, were evaluated on the basis of with post-NEC strictures or not.

Of the involved variables examined, the late-onset NEC [risk ratio (RR), 0.56; 95% confidence interval (95% CI), 0.41–0.92;  $P < 0.001$ ], cesarean delivery (RR, 1.42; 95% CI, 0.98–2.29;  $P = 0.026$ ), and first procalcitonin (PCT) (onset of symptoms) (RR, 1.82; 95% CI, 0.98–3.15;  $P = 0.009$ ) were the independent predictive factors for the post-NEC strictures. C-reactive protein (CRP), white blood cell (WBC), and plateletcrit levels were markedly higher on infants with stricture and elevated levels were maintained until the stricture was healed. Infants with intestinal stricture had significantly longer times to beginning enteral feeds ( $23.9 \pm 12.1$ ), than infants without intestinal stricture ( $18.6 \pm 8.8$ ) ( $P = 0.023$ ). The median age at discharge was also significantly higher in the group with stricture ( $P = 0.014$ ).

This retrospective and multicenter study demonstrates that the early-onset NEC and cesarean delivery conferred protection over the post-NEC stricture. Infants with post-NEC stricture need prolonged hospitalization.

**Abbreviations:** CRP = C-reactive protein, MMP = Metalloproteinases, NEC = Necrotising enterocolitis, NICU = Neonatal intensive care unit, PCT = procalcitonin, PS = propensity score, WBC = White Blood Cell.

**Keywords:** necrotizing enterocolitis, PCT, postnatal ages, post-NEC strictures

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## 1. Introduction

Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal tract disease frequently affecting premature infant with an incidence of 3% to 5%, depending on the gestational age (GA) of infant at birth,<sup>[1,2]</sup> and mortality rate of as high as 50%.<sup>[3,4]</sup> Although most cases of NEC are managed conservatively, with optimum medical treatment, bowel rest, abdominal decompression, parenteral nutrition, as well as antibiotics treatment, surgical consultation should be done at the beginning of NEC treatment.<sup>[5]</sup> Emergency surgical intervention is considered in condition with deteriorating clinical condition and intestinal perforation.<sup>[6,7]</sup>

Strictures is a well-known common complication of NEC during posthealing process, affecting about 20% of NEC survivors.<sup>[8]</sup> After the acute episode of NEC, strictures develop at a variable period irrespective of the mode of management, which is associated with severe and prolonged morbidity (septicemia, perforation, intestinal obstruction) and morbidity secondary to intestinal strictures.<sup>[9]</sup> The ischemic injury to the inner muscular layer of the intestine plays an important role in the pathogenesis of NEC.<sup>[10]</sup> When it is asymptomatic for the post-NEC strictures, the treatment is always controversial.<sup>[11]</sup> This is in part owing to the paucity of high-grade literatures describing the natural history of intestinal strictures following NEC. Correctly identifying the stricture state over the other at the time of presentation does need to be acknowledged, by which, we may be able to optimize our surgical and therapeutic approach to this group of patients.

Our aim is to evaluate the pattern of post-NEC intestinal strictures and define the clinical profile and predictive factors of strictures following the acute NEC in 4 surgical neonatal units. In

**Table 1****Baseline characteristics of eligible patients with post-NEC strictures according to surgical or conservative management.**

Post-NEC strictures	Surgical (30)	Conservative (53)	P
Eligible patients, N	46	142	
Incidence of stricture, N (%)	65.2%	37.3%	0.001
Median time interval between NEC and diagnosis of the intestinal stricture	37 ± 25 days	23 ± 19 days	0.013
Stricture location, N (%)			
Terminal ileum	13	15	
Ascending colon	12	16	
Transverse colon and descending colon	9	29	
Multiple strictures	4	7	
Duration of PN, days, Mean ± SD	63 ± 28	47 ± 23	0.075
NICU length of stay, days, Mean ± SD	37.2 ± 16.3	25.4 ± 13.9	0.088
90 ds parenteral nutrition depend, N (%)	2 (6.7%)	5 (9.4%)	0.504

NEC=necrotizing enterocolitis, NICU=newborn intensive care unit, PN=parenteral nutrition.

comparison to the previous studies,<sup>[6,12]</sup> we have collected a sizeable number of infants for better predicting development of post-NEC strictures and their medicosurgical care.

## 2. Methods

This was a retrospective study of the hospital-based cohort in 4 newborn intensive care units (NICUs) at Yongchuan Hospital, Children's Hospital of Chongqing Medical University, Sanxia Hospital, and Jinan maternity and child care hospital from January 1, 2011, to October 31, 2016. The electronic medical records for demographic information, clinical management, laboratory data, histopathology of resected bowel segment, and discharge summaries were reviewed. The study protocol was approved by the local ethics committee and the Institutional Review Board in the 4 institutions (IRB No. CHMU2016-062) and performed in accordance with the ethical standards prescribed by the Helsinki Declaration of the World Medical Association.

NEC was defined using Bell's criteria and modified by Walsh and Kliegman.<sup>[13]</sup> On the basis of previous used cutoff,<sup>[14,15]</sup> we set early-onset NEC as occurring at <10 days of age and late-onset NEC occurring at ≥10 days. Eligible for inclusion were infants with a diagnosis of NEC admitted to the neonatal unit during the study period. Exclusion criteria included infants with acute pulmonary bacterial infection, gastrointestinal anomalies (aprotia, intestinal atresia, or Hirschsprung disease), and severe cardiac dysfunction and infants who died during acute NEC.

The symptoms for suspected intestinal stricture include food intolerance, recurrent abdominal distension, high gastric aspirates, radiological features of intestinal obstruction. All patients with a suspected stricture were subjected to a contrast enema (CE) to confirm the stricture and its location. All infants with NEC were followed up in the hospital's outpatient clinic until at least 3 months of corrected age.

### 2.1. Statistical analysis

Results data were subjected to statistical comparisons using SPSS Software (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp. Released 2013, Armonk, NY). Categorical and continuous variables for demographic, health care characteristics, and laboratory measurement were reported as frequencies (percentages) and means ± SDs, respectively. Univariate comparative analyses are subjected to Chi<sup>2</sup> test for qualitative variables, and the Student *t* test for quantitative variables. Multivariable logistic regression analysis was performed to identify independent clinical predictors for the outcome of post-NEC strictures. The

relative risks for postoperative variables were assessed using cross-tabulation [odds ratio (OR)] or multivariate logistic regression analysis [risk ratio (RR)]. The statistical significance was evaluated using a 2-tailed 95% confidence interval (CI), and a *P* value less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

There are 188 preterm infants following NEC diagnosis eligible for analysis. Among the acute of NEC infants, 46 infants (24.5%) required early surgical treatment after a median time period of 7 days (range: 2–19). Ninety-six infants (51.1%) needed assisted ventilation and/or hemodynamic support by fluid expansion and/or the administration of vasoactive amines. Twenty-five infants (23.3%) were assessed with Bell's stage 3 disease (Table 1). The strictures were symptomatic following the reestablishment of feeding after a time period of 23 ± 7 days and confirmed on a contrast study when presence of symptoms of intestinal obstruction or the routine contrast study before re-establish gastrointestinal continuity after reversal of stomas. Intestinal strictures developed in 30 of 46 (65.2%) of the surgically managed infants and 53 of 142 (37.3%) in the conservatively treated infants (*P*=0.001). The median time interval between NEC and diagnosis of the intestinal stricture was 23 ± 19 days in medically treated NEC patients versus after 37 ± 25 days in surgically treated NEC patients (*P*=0.013). The strictures following NEC were mainly located in the transverse and descending colon in the conservatively treated NEC patients, whereas they were located in the terminal ileum and ascending colon in the patients undergoing surgical intervention (Table 1).

### 3.2. Risk and predictive factors for post-NEC strictures

The baseline clinical and biological features of the infants with NEC according to with or without strictures are presented in Table 2. The 2 groups were not significantly different with respect to some demographic features, such as sex, maternal age, birth weight (BW), or weight at diagnosis. No differences of clinical status of patients, such as vasopressor use at onset of NEC, respiratory support before or at the time of referral, transfusion pre-NEC strictures, and enteral feeding, etc, were found between the 2 groups, which suggested that the study population reasonably represented the spectrum of neonates with NEC in our institutions (Table 1).

To assess independent clinical predictors of intestinal stricture, multivariable logistic regression analyses (Table 2) were

**Table 2****Baseline variables (onset of NEC) of eligible patients according to with and without post-NEC strictures (multivariate logistic regression).**

Post-NEC strictures	With (83)	Without (105)	P	Risk ratio (95% CI)
Male:female	47:36	59:46	0.535	
Gestational age, wk	29.9±1.6	31.2±2.2	0.055	0.72 (0.53–0.91)
Birth weight, g	1979.7±549.7	2095.4±573.1	0.078	0.68 (0.51–0.86)
weight at diagnosis	2016.4±569.4	2317.3±612.8	0.062	0.58 (0.47–0.84)
Cesarean delivery, n (%)	56 (67.5)	85 (81.0)	0.026	1.42 (0.98–2.29)
SGA infant, n (%)	8 (9.6)	14 (13.3)	0.292	
Maternal age, years	29.1±3.3	28.4±3.1	0.314	
Congenital anomalies, n (%)	38 (45.8)	55 (52.4)	0.226	
Late-onset NEC (occurring at ≥10 days of age), n (%)	55 (66.3)	51 (48.6)	0.000	0.56 (0.41–0.92)
Bell's stage 3	13 (15.7%)	12 (11.4)	0.263	
Transfusion preoperation, % (n)	4 (7.5)	10 (9.5)	0.174	
Vasopressor use at enrollment, n (%)	21 (39.6)	25 (23.8)	0.473	
Enteral feeding, n (%)	52 (62.7)	68 (64.8)	0.441	
Corticosteroids, n (%)	22 (26.5)	20 (19.0)	0.149	
Apgar score at 5 min	8.2±1.1	8.5±1.1	0.134	
Respiratory support, n (%)	23 (27.7)	18 (17.1%)	0.059	0.77 (0.52–0.98)
First platelet count (onset of symptoms), 10 <sup>9</sup> /L	263.1±47.8	278.5±51.3	0.109	0.69 (0.51–0.86)
Hemoglobin, g/L	121.4±25.3	129.2±28.2	0.231	
First WBC (onset of symptoms), 10 <sup>9</sup> /L	15.6±2.3	13.8±2.8	0.018	1.66 (0.97–2.86)
First PCT (onset of symptoms) (ng/mL, normal value: 0–0.5)	5.8±0.9	5.1±1.0	0.009	1.82 (0.98–3.15)
First CRP (onset of symptoms) (mg/L, normal value: 0–10)	16.8±7.6	13.9±6.8	0.058	1.74 (0.92–2.95)
Albumin (g/L, normal range, 35–50)	31.1±4.5	32.3±5.4	0.136	
Prealbumin (g/L, normal range, 0.20–0.40)	0.26±0.03	0.28±0.03	0.185	

CRP = C-reactive protein, NEC = necrotizing enterocolitis, PLT = plateletcrit, SGA = small for gestational age, WBC = white blood cell.

conducted and showed that the clinical factors that independently increased the likelihood of intestinal stricture included the late-onset NEC (RR, 0.56; 95% CI, 0.41–0.92;  $P < 0.001$ ), cesarean delivery (RR, 1.42; 95% CI, 0.98–2.29;  $P = 0.026$ ), and elevated first procalcitonin (PCT) (onset of symptoms) (RR, 1.82; 95% CI, 0.98–3.15;  $P = 0.009$ ). Of the intestinal perforations during acute NEC, first C-reactive protein (CRP) (onset of symptoms) posed a borderline risk for development of strictures ( $P = 0.058$ ).

### 3.3. Inflammation follow-up

The inflammatory or immune variables CRP, white blood cell (WBC), and PCT were measured initially on admission and repeated at least once every 24 hours on acute episode of NEC and strictures. At the first few hours of the symptom for stricture, CRP, WBC, and PCT levels were measured as indicated in Table 3.

CRP was markedly higher on infants with stricture and elevated levels were maintained until the stricture was healed. The

mean maximum CRP concentration was also significantly higher in infants who developed stricture ( $P < 0.001$ ). High PCT level when NEC diagnosis was another factor elevated during post-NEC strictures. Mean WBC levels were also high in infants who developed stricture at all time periods, as summarized in Table 3.

### 3.4. Outcome for post-NEC strictures

According to established criteria, a comparison of the outcomes between the 2 groups is summarized in Table 4. There were no differences in the incidence of serum electrolyte imbalance between the 2 groups. The mean hospitalization time in NICU ( $P = 0.078$ ) and the median age at discontinuation of parenteral nutrition ( $P = 0.052$ ) were longer in the group with stricture, but this difference was not significant. Infants with intestinal stricture had significantly longer times to beginning enteral feeds ( $23.9 \pm 12.1$ ), than infants without intestinal stricture ( $18.6 \pm 8.8$ ) ( $P = 0.023$ , Student *t* test) (Table 4). The median age at discharge was

**Table 3****Changes in laboratory variables related with post-NEC strictures (Student *t* test).**

Post-NEC strictures	With (83)	Without (105)	P
PLT, 10 <sup>9</sup> /L			
PLT level at onset of symptoms, mg/L	225.1±166.3	263.4±143.9	0.089
PLT mean minimum, mg/L	128.3±49.8	164.8±57.6	0.084
WBC, 10 <sup>9</sup> /L			
WBC level at onset of symptoms, mg/L	16.4±2.2	14.3±2.5	0.042
WBC mean maximum, mg/L	19.3±4.1	16.1±4.5	0.083
PCT (ng/mL, normal value: 0–0.5)			
PCT level at onset of symptoms, mg/L	6.5±2.6	5.3±2.2	0.007
PCT mean maximum, mg/L	11.8±4.6	8.9±3.8	0.000
CRP (mg/L, normal value: 0–10)			
CRP level at onset of symptoms	18.3±8.9	14.6±7.4	0.013
CRP mean maximum, mg/L	23.6±8.7	21.2±8.4	0.000

CRP = C-reactive protein, NEC = necrotizing enterocolitis, PLT = plateletcrit, WBC = white blood cell.

**Table 4****Outcome characteristics in the infants with and without post-NEC strictures (Student *t* test).**

Post-NEC strictures	With (83)	Without (105)	<i>P</i>
Bacterial sepsis, N (%)	11 (13.3)	13 (12.4)	0.213
Albumin transfusion per patients, g	28.1 ± 9.1	19.7 ± 8.5	0.011
Albumin minimum (g/L, normal range, 35–50)	30.2 ± 4.8	31.6 ± 5.2	0.125
Prealbumin minimum (mg/dL, normal range, 20–40)	22.4 ± 3.9	25.5 ± 5.3	0.131
Days to enteral feeds (median)	18.6 ± 8.8	23.9 ± 12.1	0.023
Duration of PN, days, Mean ± SD	48.6 ± 29.8	66.8 ± 38.5	0.103
Mechanical ventilation, a days	13.7 ± 8.2	16.8 ± 9.5	0.015
NICU length of stay, days, Mean ± SD	28.9 ± 14.7	31.9 ± 18.4	0.078
90 days parenteral nutrition depend, N (%)	4 (4.8)	6 (5.7)	0.371
Survival >90 days, N (%)	20 (24.1)	31 (29.5)	0.026
Median age at discontinuation of PN (days)	88 ± 33	84 ± 36	0.052
Median age at discharge, days	94 ± 36	87 ± 35	0.014
Mean weight at discharge, g	4311 ± 467	3536 ± 396	0.002

NEC = necrotizing enterocolitis, NICU = newborn intensive care unit, PN = parenteral nutrition.

also significantly higher in the group with stricture ( $P=0.014$ ; Table 4). No significant differences were found in nutritional variables between the 2 groups within the in-hospital period (albumin and prealbumin). All types of nutritional support were well tolerated in both groups.

In all groups, postoperative nutrition was continued for at least 30 days, and the mean weight at discharge were  $4311 \pm 467$  and  $3536 \pm 396$  g for patients with post-NEC stricture or not, respectively ( $P=0.002$ , Student *t* test). Furthermore, time spent on mechanical ventilation was utilized as a proxy for illness severity throughout the entire hospital stay. Durations of mechanical ventilation were also significantly different between the 2 groups ( $P=0.015$ ). Analysis of liver and kidney function did not demonstrate any alterations related to post-NEC strictures (data not shown).

#### 4. Discussion

This study sets out to investigate the clinical predictors and management results of the post-NEC strictures, which developed during or after medical therapy for NEC. In this retrospective study from 4 medical centers, of the examined clinical predictors for strictures in infants with NEC, late-onset NEC was found to have a major effect on the likelihood of post-NEC strictures, which were the first reported variables related to post-NEC strictures. Furthermore, the cesarean delivery was significantly correlated with the occurrence of strictures. Thus, compared with other observational studies, our study adds some interesting data to predict the development of post-NEC strictures and refine the reliability of the inflammation variables, CRP and WBC.

The identification of predictive factors for post-NEC strictures would permit NEC cases to be managed appropriately; early refeeding after NEC could be introduced at a low risk of stricture, whereas it would be advisable to perform contrast study before the reestablishment of feeding for high-risk infants.<sup>[16–18]</sup> Of the clinical predictors, several variables, such as CRP and WBC, have been reported previously and thus were expected.<sup>[6,19,20]</sup> Also, given that PCT is similar in reflecting the intestinal inflammation as CRP and WBC, we expected it to be predictive. The local intestinal inflammatory response, starting with the activation of mast cells, macrophages, and neutrophils, is thought to contribute to collagen deposition, fibrosis, and wound contraction, which are the pathogenesis of post-NEC strictures.<sup>[21,22]</sup> We examined the kinetics of various markers of inflammation and severity of illness

at the time of acute NEC. In all patients, inflammatory responses and immune variables were significantly increased immediately after NEC diagnosis, and these alterations persisted until the presence of stricture, such as presence of high white cell count during acute NEC, CRP serum concentration >10 mg/L, that appeared to be correlated with the post-NEC strictures, respectively, confirming that inflammation plays a major role in the pathophysiology of NEC. A score system has been established based on clinical, biological, and radiological evaluation.<sup>[2,3]</sup> One of the items in this scoring system was the elevation of CRP levels after the diagnosis of NEC. Our results confirm that the PCT elevation at the onset of symptoms for NEC could be a predictive factor for the occurrence of post-NEC strictures. The prognostic value of other acute phase markers [e.g., tumor necrosis factor alpha, matrix metalloproteinases (MMPs), interleukin 6], which has been shown to contribute to anastomotic edema and postoperative ileus, should be confirmed in the future.

Here in the current research, we observed significant association between late-onset NEC and the occurrence of post-NEC stricture. To our knowledge, this is the first report to identify later NEC as an independent protective factor for post-NEC strictures. In the reviewed literature, there does not appear to be any direct relationship between later NEC and post-NEC strictures. It could be of prognostic significance and are clinically plausible. We previously found that the infants who develop NEC after 10 days of life do influence postoperative outcome survival or other clinically important outcomes (under press). NEC typically occurs in the second to third week of life; however, in very low birth weight infants, it may be delayed for up to 3 months of age. Age of onset is inversely related to GA.<sup>[15]</sup> We hypothesize that late-onset NEC might be a marker of more extensive disease. It has been suggested that when compared with early-onset NEC, late-onset NEC carries an unexplained intrinsic risk for adverse neonatal outcomes overall.<sup>[15,24]</sup> The infants who developed NEC after day of life 14 were at an increased risk of mortality and adverse neurologic outcomes, even after adjusting for maternal factors, GA, and BW,<sup>[25]</sup> which makes it clear that they are dissimilar, with earlier NEC lacking the inflammation and ischemia that is a hallmark of later NEC. Furthermore, later NEC patients tend to present necrosis of their intestines or radiography lesion,<sup>[15]</sup> which was described as the predictor of stricture.<sup>[21]</sup> Patients with radiography lesion might have more extensive intestinal involvement and might benefit from laparotomy and bowel resection.<sup>[26]</sup> Thrombocytopenia and



metabolic acidosis at the time of acute NEC were not predictors of strictures.

There are other factors in the current study that might contribute to the likelihood of post-NEC stricture, the degree of intestinal obstruction and the severity of illness, including congenital anomalies, mechanical ventilation time, and length of hospital stay, which proved to be associated with post-NEC strictures.<sup>[2,6,27]</sup> These factors are difficult to modify given current neonatal intensive care unit (NICU) therapies. Together and individually, they reflect the severity of illness of the infant. As such, they commonly necessitate close clinical monitoring. Furthermore, compared with morbidity of intestinal strictures in Nelson Textbook of Pediatrics,<sup>[5]</sup> the high incidence here in this article might attribute to the certain population of patients. Here, in this research, 25 infants (23.3%) were assessed with Bell's stage 3 disease, reflecting more illness severity; this might account for the current high incidence of intestinal strictures.

Although our study is the largest reported series of post-NEC strictures, it has several limitations. Weaknesses of our study include the retrospective nature, in which we collected the data with an inherent risk of selection bias. Furthermore, the results of this study were based on an intent-to-treat analysis. Infants included in this study were referred from other neonatal units for surgical evaluation and could represent the severe end of NEC spectrum making the observations not applicable to perinatal settings that medically manage infants with NEC. There were a number of infant withdrawals of support, making it difficult to interpret the survival data. The study also takes place over a long time period and outcomes from many patients may not reflect outcomes from current treatment algorithms; there have likely been many practice changes within both the surgery and the neonatology divisions, leading to different care practices between study patients.

## 5. Conclusion

Clinical evidence from the present study suggest that late-onset infants were at an increased risk of post-NEC strictures, thus offering a recent insight into the impact of improved care on the clinical profile and outcomes of post-NEC strictures. Strategies aimed at optimizing systematic screening at late-onset NEC diagnosis through digestive contrast study have the potential to optimize our surgical and therapeutic approach. We acknowledge that these results are based on a homogenous group of patients. It will be necessary to conduct quality investigation in the future to best utilize the limited therapies available.

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