의학석사 학위논문

A Scoring System for Predicting Disease Progression in Necrotizing Enterocolitis

괴사성 장염의 진행을 예측하는 점수체계의 개발

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이 논문을 의학석사 학위논문으로 제출함
2019 년 10 월

서울대학교 대학원
의학과 외과학전공
박웅기

박웅기의 의학석사 학위논문을 인준함
2020 년 1 월

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Abstract

A Scoring System for Predicting Disease Progression in Necrotizing Enterocolitis

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Background: Necrotizing enterocolitis (NEC) is the most common and one of the most dangerous gastrointestinal emergencies in neonates, with a high mortality rate and serious long term morbidities. Despite the improvement of intensive neonatal care, the incidence of NEC and accompanied morbidity and mortality have remained unchanged. The aim of this study is to fine the risk factors of disease progression and overall, to construct a scoring system to predict patients at risk.

Methods: We retrospectively reviewed the data of 43 medical NEC patients from January 2003 to November 2016. Patients were divided into 2 groups: non-progression group and progression group. The clinical and laboratory findings were compared. Using the factors that were significant in multivariate analysis, a scoring system to predict disease progression was constructed. Additionally, an external validation was performed on 28 patients.

Results: Among 43 medical NEC patients, 18 patients required surgical intervention despite medical treatment because of disease progression. The progression group had younger gestational age (GA), lower peak platelet (PLT) levels, and higher peak C-reactive protein (CRP) levels. A 10-point scoring system consisted with these factors was constructed and over 5-points had a 94.4% sensitivity and 76% specificity. In addition, the external validation showed 87.5% sensitivity and 80% specificity.

Conclusion: We constructed a novel scoring system to predict disease progression in NEC patients. This scoring system is useful in

early detection of patients at risk of disease progression and may help clinicians decide timely surgical intervention.

Keywords : Necrotizing enterocolitis, Gestational age, Platelet count, C-reactive protein, Scoring system

Student Number : 2018-28262

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Introduction

Necrotizing enterocolitis (NEC) is an inflammatory disease involving the intestine associated with hypoxia and ischemia [1-3]. It is the most common and one of the most dangerous gastrointestinal emergencies in neonates with a mortality rate between 20%-30%, and serious long term complications may follow even after surgery [2, 4-6]. Short bowel syndrome due to the portion and length of bowel resected, and bowel stricture are complications related to the surgery itself. In addition, compared to medical NEC patients, the inflammation and ischemia is more extensive, resulting in neurodevelopmental delay.

NEC started to become reported only after modern intensive neonatal care took place. Since then, there has been a lot of improvement in intensive neonatal care. However, the incidence of NEC and accompanied morbidity and mortality have remained unchanged [1, 3, 4]. This may result from the fact that advances in intensive neonatal care led to higher proportion of premature

neonates surviving which increases the proportion of neonates at risk. In addition, the fact that the etiology of NEC remains unclear also may be the cause [7].

Nevertheless, efforts to prevent NEC and studies regarding risk factors and biomarkers of predicting NEC have been published [2, 8–13]. Some of the possible factors and markers researched include calprotectin, intestinal fatty acid binding protein, and proteomics. Breast–milk feeding and nonaggressive enteral feeding were discovered to be safe and efficient methods to prevent NEC [3].

As mentioned above, many studies have researched preventive methods and factors of disease prediction. This is because after NEC occurs, patients unfortunately experience complications of some degree, and therefore, preventing the disease is most important. However, it is also important to manage medical NEC patients so that they do not require surgical intervention. There are only a few studies regarding this concern and validation of these factors is needed.

The aim of this study is to find the risk factors of disease progression to NEC requiring surgical intervention and overall, to construct a scoring system to predict patients at risk.

Methods

Patient selection

A retrospective single center study was conducted at Seoul National University Children's Hospital. The objective of this study was to find out the usefulness of a scoring system to predict disease progression from NEC requiring medical treatment to NEC requiring surgical intervention. Patients diagnosed as NEC from January 2003 to November 2016 were selected. All data collection and analysis were performed after approval of the Institutional Review Board.(IRB No. 1902-036-1009)

A total of 186 patients were diagnosed as NEC. From these patients, patients who were transferred from other hospitals after diagnosis and treatment, patients with no definite necrosis on operative record, patients who already had bowel perforation at the time of diagnosis, and patients diagnosed as NEC stage Ia according to the modified Bell's criteria were excluded.

Non-progression group was defined as meeting the modified Bell's criteria stage Ib or higher and did not progress to surgery. Progression group was defined as need for surgical treatment despite medical treatment. In addition, operative records were reviewed to determine definite necrosis and/or bowel perforation. Patients who underwent surgery but did not have evidence of necrosis were excluded. Overall, 43 patients were enrolled in this study and 18 patients received surgical intervention due to disease progression (Figure 1).

Data collection

Clinical data of both maternal and patients were collected. Maternal data included age at delivery, multiple gestations, the type of delivery, predisposing factors, and cause of prematurity. Patient data included sex, gestational age (GA), age at diagnosis, corrected age at diagnosis, birth weight, one- and five-minute Apgar scores. Patient's systolic blood pressure (SBP) at the time of diagnosis, data

of comorbidities including respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP) were also collected. Death at the time of discharge, length of hospital stay was recorded as well.

In addition, we collected serial data of the patient's abdominal circumference (AC) and several laboratory findings. Laboratory findings included pH, complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine (Cr), and C-reactive protein (CRP) levels. Findings were recorded at the time of diagnosis, and times closest to 12, 24, 36, 60hours after diagnosis in the non-progression group. In the progression group, findings were recorded at the time of diagnosis, times closest to 12, 24, 36, 60hours, plus 24hours up to the time of surgery henceforth. The data collection up to 60hours in the non-progression group was based on the median time of diagnosis to surgery in the progression group (median time 64hours).

Statistical analysis

Statistical analyses comparing the medical group and surgical group were performed. Continuous variables were compared using student t-test and Mann-Whitney test. Receiver operating characteristic (ROC) curves were used to appoint a cutoff value for statistically significant continuous variables. Categorical variables were compared using chai square method or fisher's exact test. Logistic regression analysis was performed for multivariate analyses.

To evaluate the role of risk scoring system, ROC curves, area under the curve (AUC) and 95% confidence intervals were estimated. In addition, we performed an external validation using patient data of Seoul National University Bundang Hospital (SNUBH).

All analyses were performed using SPSS 23 and R statistics (ver.3.6.1). P value under 0.05 was considered statistically significant. In addition, to simplify the number of factors, factors with $p \leq 0.002$ were included for multivariate analyses.

Results

Demographic data of mother and patient

The demographic data of the patient and mother are listed on table 1. The mean age of the mother at the time of delivery was 32.56 ± 3.61 years. 24 mothers (55.8%) experienced multiple gestations and 17 mothers (39.5%) received vaginal delivery. When considering comorbidities, 11 mothers (25.6%) had pre-eclampsia and one mother (2.3%) had gestational diabetes mellitus (DM). In addition, 32 mothers (74.4%) had antenatal steroid administration and 16 mothers (37.2%) had antenatal antibiotics administration.

25 of the patients (58.1%) were male and the mean gestational age was 27.86 ± 2.85 weeks. The mean body weight at birth was 836.42 ± 314.97g and 19 patients (44.2%) were small for gestational age. The 1 minute and 5 minute Apgar score were 3.70 ± 1.98 and 6.00 ± 1.69 each. There were 6 mortalities and all of them happened in the disease progression group (33.3%).

Comparison of the characteristics between the non-progression group and the progression group

The characteristics and comorbidities were compared between the non-progression group and disease progression group (Table 2). The mothers in the disease progression group had significantly higher rate of multiple gestations compared to the mothers of the non-progression group. Otherwise there were no differences in maternal characteristics between the two groups.

When comparing the patient characteristics, the mean gestational age was 28.65 ± 2.86 weeks in the non-progression group and 26.75 ± 2.51 weeks in the disease progression group (p=0.029). In addition, there was a significant difference in birth weight between the two groups (p=0.014). The patients of disease progression group had a more severe stage of bronchopulmonary dysplasia compared to the patients of the non-progression group (p=0.011). None of the

non-progression group patients died while 6 patients (33.3%) of the disease progression group died.

Comparison of clinical and laboratory variables

To find out the factors associated with disease progression, we analyzed and compared various clinical and laboratory factors between the two groups (Table 3, 4). At the time of diagnosis, disease progression group significantly needed more mechanical ventilation (p=0.002), use of inotropes (p=0.006) and use of bicarbonates (p=0.003). In addition, the mean systolic blood pressure at diagnosis was significantly lower in the progression group (p=0.005). The disease progression group tended to have a higher rate of bacteremia (27.8%) compared to the non-progression group (4%) at the time of diagnosis, but it was not statistically significant (p=0.067).

The laboratory data at the time of diagnosis, peak value within 60 hours and before surgery, and the change of value between diagnosis

and peak value were collected and analyzed. At the time of diagnosis, the pH level and hemoglobin (Hb) level was significantly lower in the progression group (p=0.003, p=0.011). In addition, the ALT level was significantly higher in the progression group (p=0.026). However, there was no significant difference in the platelet (PLT) count or CRP level at the time of diagnosis between the two groups.

When comparing the peak values, there was significant difference in minimum Hb level (p=0.004), minimum PLT count (p=0.002), and maximum CRP level (p=0.006). However, there was no difference in peak pH level.

In addition, we compared the change of each variable. The difference in AC (p=0.004), pH (p=0.049), and CRP level (p=0.006) were significantly different between the non-progression group and the progression group.

Our study's objective was to construct a scoring system. Therefore, for easy application of the scoring system, we performed a ROC curve for each significant continuous variable to analyze them

in categorical variables. The optimal cutoff values and ROC curves are listed on table 5 and figure 2.

The total number of statistically significant variables were 14. To design a simple and accurate scoring system, we performed a logistic regression analysis on variables with $p \leq 0.002$ and 3 variables were statistically significant (Table 6).

Construction of a scoring system

To construct a scoring system, we used the parameter estimates of the 3 variables that were statistically significant in multivariate analysis. The scoring system was constructed into a 10-point scale (table 7). According to the ROC curve, the optimal cutoff point of the scoring system was 5 points, with a 94.4% sensitivity and 76% specificity (Table 8, Figure 2).

We additionally performed an external validation on SNUHBH patients. A total of 28 patients (20 non-progression patients and 8 progression patients) were included for validation. As a result, our

scoring system predicted disease progression with an 87.5% sensitivity and 80% specificity (Table 8, Figure 2).

Discussion

There have been many studies regarding the prevention, early diagnosis and outcomes of NEC. The outcome of the disease itself and also the outcome and characteristics of medical NEC compared to surgical NEC are well known [5, 6, 14-16]. In addition, the long-term outcomes of NEC survivors have been researched as well [5, 6]. Recently, studies have focused on finding the risk factors of occurrence or progression, non-invasive early diagnostic tools and markers, and eventually factors of disease prevention [12, 13, 17-19]. It would be best to prevent the disease, but these factors are not yet definite. Therefore, at this point, studying the factors of disease progression and minimizing the morbidity and mortality associated with surgical intervention is also very important.

In this study, we analyzed the risk factors of disease progression in NEC. We collected the clinical and laboratory data of both mother and the patient. Especially, we analyzed not only the laboratory data at the time of diagnosis, but also serial data up to the time of surgery. The

well known risk factors such as gestational age, low birth weight were statistically significant in univariate analysis [20, 21]. In addition, clinical variables such as mechanical ventilation support, use of inotropes or bicarbonates, systolic blood pressure at diagnosis were significant factor of disease progression in univariate analysis. Bhatt, D. et al., reported that 1 minute Apgar score, use of inotropes, mean blood pressure, and sepsis were significant factors of predicting intestinal failure of death in surgical NEC patients [22]. Apgar scores were not significant in our study. In a retrospective study including 64 SGA infants with Bell's stage II NEC, Luo, L. et al. reported that CRP elevation after NEC diagnosis increased the risk for deterioration of NEC [19]. In our study, the maximum CRP level higher than 2.67 within 60 hours of diagnosis was associated with increased risk of disease progression. Overall, metabolic derangement and variables related to inflammation and infection were important factors of disease progression.

The initial status of the patients in both the non-progression group and progression group was medical NEC according to the Bell's

criteria. However, in 18 patients (42%), disease progressed and needed surgical intervention. In addition, many clinical and laboratory variables were significantly different between the two groups. This implies the necessity of a more refined criteria for the diagnosis and management of NEC. Thus, approaches to propose an alternative diagnostic criterion have been made [9, 23].

Finally, we constructed a scoring system for predicting disease progression in NEC. Out of the many factors, GA<28 weeks, minimum PLT count<201*103/㎕, and maximum CRP level>2.67mg/dL were statistically significant in multivariate analyses and using these 3 variables, a scoring system to predict disease progression was made. There have been studies regarding the factors associated with deterioration of NEC, and in some studies a prediction model was proposed.

Khalak, R. et al. proposed a scoring system for predicting the need for surgery in NEC patients. In this prospective, multicenter study including 100 NEC patients with Bell's stage II or greater, a scoring system consisted of physical examination results (total score of 8

points) was applied. In result, a score of 3 or higher predicted the need for surgical intervention and death with an 88% sensitivity and 81% specificity [24]. We also analyzed the abdominal circumference but it was not statistically significant. Likewise, Bhatt, D et al., predicted intestinal failure of death in surgical NEC patients by applying a hybrid model consisted of 4 clinical patient factors and Tepas, J.J., 3rd et al. suggested that metabolic derangement parameters can be used to determine the timing of surgery in NEC [22, 25].

On the other hand, a study including 157 NEC patients, used laboratory findings for a scoring system to predict NEC totalis [4]. This study used elevated Cr, elevated phosphorus, and thrombocytopenia for the scoring system. However, in our analyses, Cr and other laboratory findings such as liver function panels were not factors associated with disease progression. Furthermore, in a case control study of 779 newborns, Palatnik, A. et al. reported a prediction model for detection of early-onset neonatal sepsis and mortality using both maternal and patient's clinical variables [26].

Compared with these prediction models described above, our study analyzed the clinical and laboratory findings of the patient and also the clinical data of the mother. In addition, to find out the factors of disease progression, we thought that analyses of serial data after diagnosis were also very important. Therefore, we compared variables at the time of diagnosis, peak values during the chosen time interval, and their change of value. From these variables, we picked out 3 significant variables to make a quick, easy to apply scoring system (94.4%sensitivity, 76% specificity). These distinct features make our scoring system a novel prediction model. Finally, we applied this scoring system on an external group for validation and obtained similar results (87.5% sensitivity, 80% specificity).

This study has some limitations. This was a single center retrospective study, including 43 patients. Furthermore, the external validation group also had only 28 patients. Although our scoring system showed suitable results in both the study group and external group, application on a larger sample size may be needed for more concrete results.

Conclusion

We constructed a novel scoring system to predict disease progression in NEC patients. This scoring system is useful in early detection of patients at risk of disease progression and may help clinicians decide timely surgical intervention.

Table 1. Demographic data of the mother and patient

Characteristics	Total patients (n=43)
Maternal characteristics	
Age at delivery, years (mean ± SD)	32.56±3.91
Vaginal delivery, n	17(39.5%)
Multiple gestations, n	24(55.8%)
Pre-eclampsia, n	11(25.6%)
Gestational DM, n	1(2.3%)
Antenatal use of steroids, n	32(74.4%)
Antenatal use of antibiotics, n	16(37.2%)
Infant characteristics	
Male	25(58.1%)
Gestational age, weeks (mean ± SD)	27.86±2.85
Age at diagnosis, weeks (mean ± SD)	2.71±1.87
Postmenstrual age at diagnosis, weeks (mean ± SD)	30.57±3.07
Birth weight, g (mean ± SD)	836.42±314.97
Small for gestational age, n	19(44.2%)
Apgar score 1min (mean ± SD)	3.70±1.98
Apgar score 5min (mean ± SD)	6.00±1.69
Length of stay, days (mean ± SD)	81.70±42.99
Mortality, n	6(14%)
Comorbidities	
RDS	21(48.8%)
PDA	35(81.4%)
BPD	
Mild, Moderate	20(46.5%)
Severe	8(18.6%)
IVH	
Grade I, II	6(14%)
Grade III, IV	4(9.3%)
ROP	10(23.3%)

SD; standard deviation, DM; diabetes mellitus, RDS; respiratory distress syndrome, PDA; patent ductus arteriosus, BPD; bronchopulmonary dysplasia, IVH; intraventricular hemorrhage, ROP; retinopathy of prematurity

Table 2. Comparison of the characteristics between the non-progression group and the progression group

Characteristics	Non-progression group (n=25)	Progression group (n=18)	P Value
Maternal characteristics			
Age at delivery, years (mean ± SD)	31.88±3.64	33.50±4.16	0.183
Vaginal delivery, n	8	9	0.234
Multiple gestations, n	10	14	0.028
Preecampsia, n	7	4	0.736
Gestational DM, n	1	0	1
Antenatal use of steroids, n	19	13	0.779
Antenatal use of antibiotics, n	9	7	0.847
Infant characteristics			

Male	13	12	0.336
Gestational age, weeks (mean ± SD)	28.65±2.86	26.75±2.51	0.029
Age at diagnosis, weeks (mean ± SD)	2.39±1.88	3.16±1.81	0.189
Postmenstrual age at diagnosis, weeks (mean ± SD)	31.05±2.95	29.91±3.20	0.237
Birth weight, g (mean ± SD)	910.25±358.22	733.89±211.64	0.014
Small for gestational age	9	10	0.203
Apgar score 1min (mean ± SD)	3.88±2.35	3.42±1.31	0.446
Apgar score 5min (mean ± SD)	6.24±1.67	5.67±1.72	0.278
Length of stay, days (mean ± SD)	74.44±31.16	91.78±54.87	0.239
Mortality, n	0	6	0.003
Comorbidities			
RDS	9	12	0.067
PDA	19	16	0.284

BPD			0.011
Mild, Moderate	14	6	
Severe	1	7	
IVH			1
Grade I, II	2	4	
Grade III, IV	1	3	
ROP	3	7	0.067

SD; standard deviation, DM; diabetes mellitus, RDS; respiratory distress syndrome, PDA; patent ductus arteriosus, BPD; bronchopulmonary dysplasia, IVH; intraventricular hemorrhage, ROP; retinopathy of prematurity

Table 3. Univariate analysis of the clinical variables

Variables	Non-progression group (n=25)	Progression group (n=18)	P Value
Mechanical ventilator support	12	17	0.002
Use of inotropes	1	7	0.006
Use of bicarbonates	0	6	0.003
Bacteremia	1	5	0.067
AC at diagnosis, cm (mean ± SD)	22.71±3.37	22.36±3.42	0.740
SBP at diagnosis, mmHg (mean ± SD)	66.52±15.93	52.61±14.15	0.005

SD; standard deviation, AC; abdominal circumference, SBP; systolic blood pressure

Table 4. Univariate analyses of the laboratory variables

Variables	Non-progression group (n=25)	Progression group (n=18)	P Value
At diagnosis (mean ± SD)			
pH	7.33±0.07	7.20±0.17	0.003
WBC count, /㎕	13792.00±11926.54	15210.00±13442.34	0.717
Hb level, g/dL	12.75±2.60	10.79±2.05	0.011
PLT count, $*10^3$/㎕	261.68±116.33	204.94±204.60	0.255
CRP, mg/dL	1.31±3.04	3.33±4.65	0.092
AST, IU/L	34.40±23.71	54.78±46.63	0.102
ALT, IU/L	6.84±4.17	23.39±28.72	0.026
Total bilirubin, mg/dL	4.48±3.11	4.08±3.49	0.693
Serum Cr, mg/dL	0.82±0.53	0.94±0.60	0.486

Peak value within 60hrs/before Surgery			
Maximum AC, cm	23.24±3.29	23.80±3.62	0.6
Minimum pH	7.28±0.06	7.23±0.12	0.101
Minimum Hb level, g/dL	11.79±2.60	9.97±1.20	0.004
Minimum PLT count, $*10^3/\mu\ell$	201.60±101.14	107.44±83.60	0.002
Maximum CRP level, mg/dL	3.32±4.92	10.43±9.10	0.006
Maximum AST level, IU/L	29.20±10.80	149.89±365.74	0.18
Maximum ALT level, IU/L	10.80±6.06	36.83±61.09	0.089
Maximum total bilirubin level, mg/dL	4.03±2.72	4.51±2.94	0.584
Maximum serum Cr level, mg/dL	0.68±0.28	0.83±0.52	0.207
Change in laboratory value			
AC, cm	0.53±0.91	1.44±1.07	0.004
pH	−0.05±0.81	0.04±0.17	0.049

WBC, /㎕	−3675.79±9847.58	754.62±10101.44	0.226
Hb, g/dL	−0.96±2.93	−0.83±1.90	0.872
PLT, $*10^3$/㎕	−60.08±103.35	−97.50±201.99	0.431
CRP, mg/dL	2.01±5.39	7.09±9.86	0.006
AST, IU/L	−5.20±19.27	95.11±372.20	0.269
ALT, IU/L	3.96±6.67	13.44±68.25	0.564
Total bilirubin, mg/dL	−0.45±1.80	0.43±3.29	0.266
Serum Cr, mg/dL	−0.14±0.48	−0.11±0.45	0.8

SD; standard deviation, WBC; white blood cell, Hb; hemoglobin, PLT; platelet, CRP; C−reactive protein, AST; aspartate aminotransferase, ALT; alanine aminotransferase, Cr; creatinine, AC; abdominal circumference

Table 5. Univariate analysis using the cutoff values of continuous variables

Variables	Cutoff value	AUC	P Value
GA	28 weeks	0.702	0.0013
Birth weight	720g	0.722	0.0013
SBP at diagnosis	62mmHg	0.746	0.0136
pH at diagnosis	7.3	0.779	0.0023
Hb at diagnosis	12.5g/dL	0.73	0.0111
ALT at diagnosis	8IU/L	0.79	0.0028
Minimum Hb value	11.1g/dL	0.714	0.0074
Minimum PLT value	$201*10^3/\mu\ell$	0.78	0.002
Maximum CRP value	2.67mg/dL	0.747	0.0011
Change in pH	0.01	0.671	0.0195
Change in AC	0cm	0.75	0.019
Change in CRP	1.18mg/dL	0.617	0.0071

AUC; area under the curve, GA; gestational age, SBP; systolic blood pressure, Hb; hemoglobin, ALT; alanine aminotransferase, PLT; platelet, CRP; C-reactive protein, AC; abdominal circumference

Table 6. Multivariate analysis

Variable	Parameter estimate	P value	Odds ratio	95% CI
GA	3.49	0.0096	32.79	2.34 – 460.03
PLT minimum	2.78	0.0351	16.08	1.21 – 213.06
CRP maximum	3.04	0.0189	20.98	1.65 – 266.12

CI; confidence interval, GA; gestational age, PLT; platelet, CRP; C-reactive protein

Table 7. Scoring system for predicting NEC progression

Variable	Contents	Score
GA	<28 weeks	4
Minimum PLT value	<201k	3
Maximum CRP value	>2.67	3
Total score		10

GA; gestational age, PLT; platelet, CRP; C-reactive protein

Table. 8 Validation of the scoring system (Study group and External group)

Study group

			Predicted group		Total
			Non-progression	Progression	
Original	Count	Non-progression	19	6	25
		Progression	1	17	18
	%	Non-progression	76	24	100
		Progression	0.06	94.4	100

External group

			Predicted group		Total
			Non-progression	Progression	
Original	Count	Non-progression	16	4	20
		Progression	1	7	8
	%	Non-progression	80.0	20	100
		Progression	12.5	87.5	100

Figure 1. Flow chart of patient selection

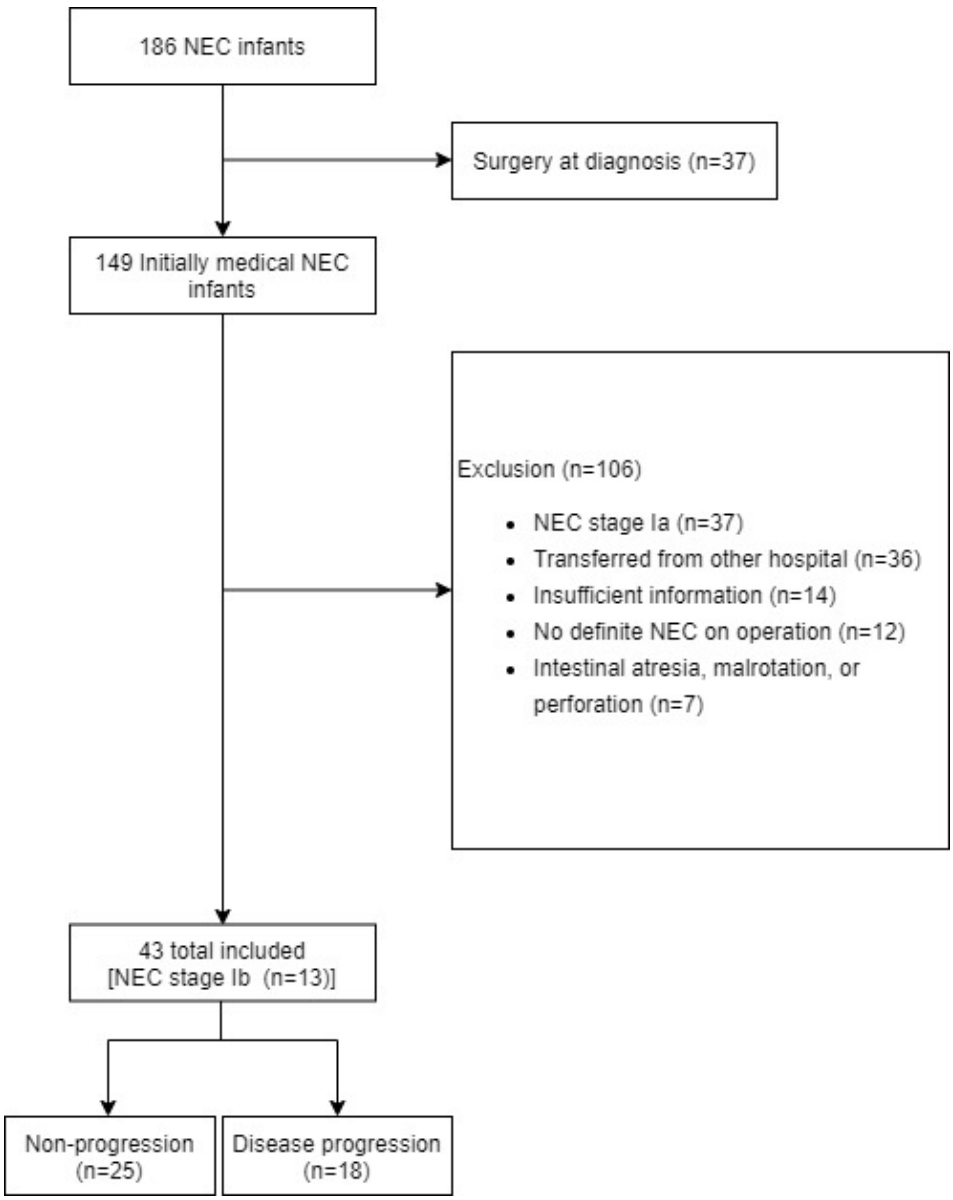


Figure 2. ROC curves of the significant continuous variables

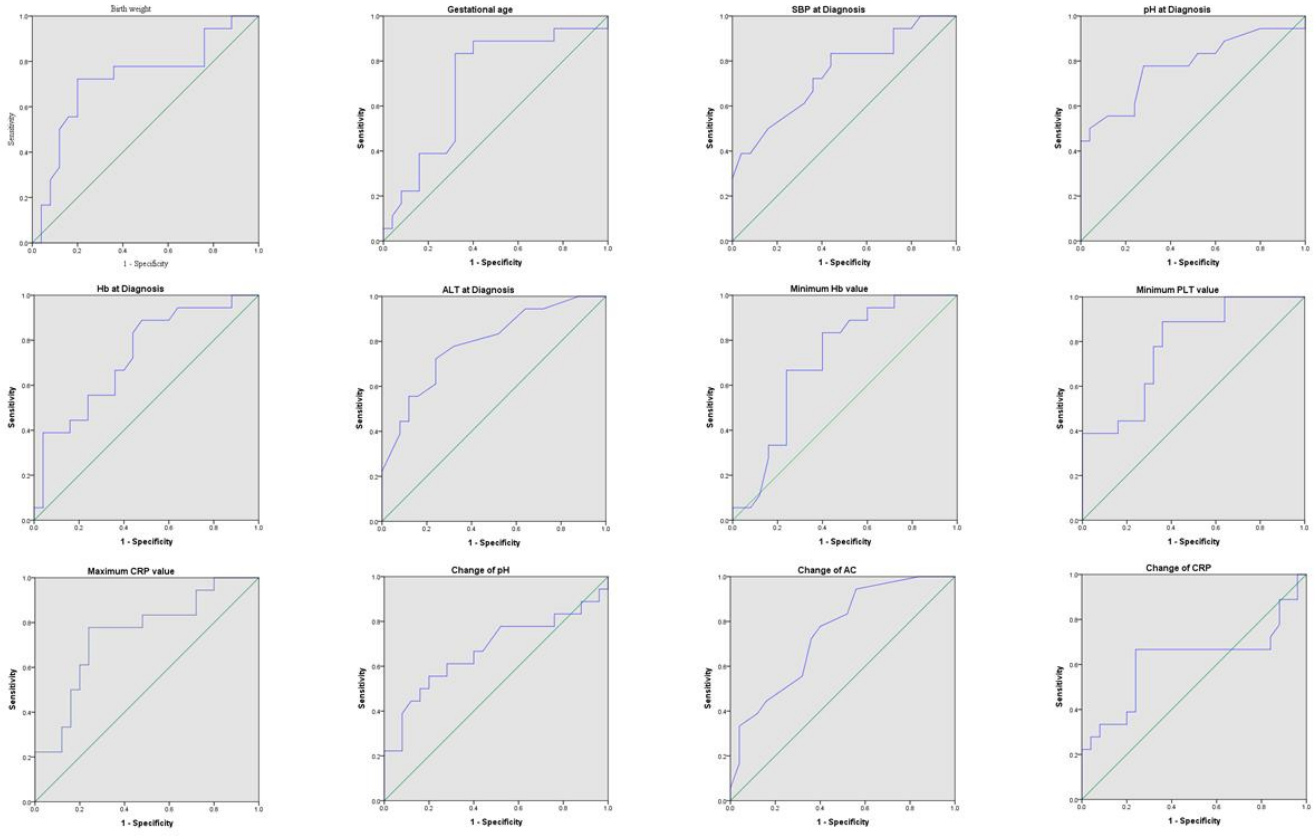
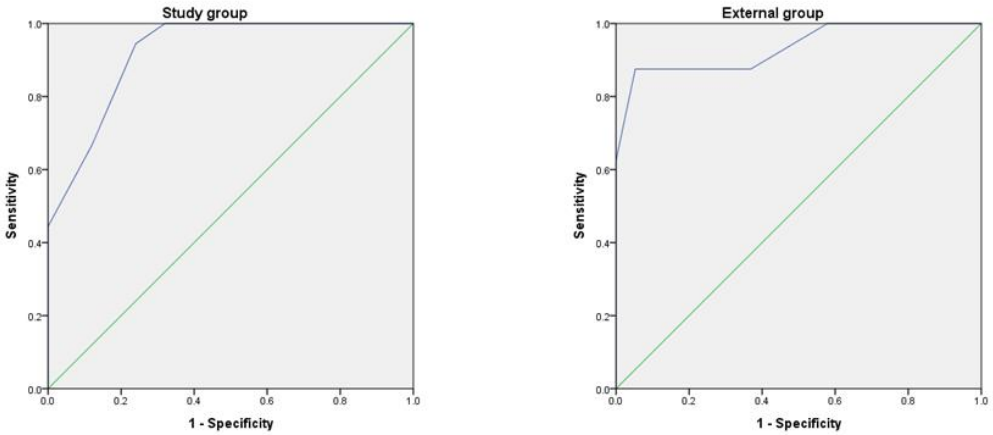


Figure 3. ROC curve of the scoring system (study group and external group)



References

1. Obladen, M., Necrotizing enterocolitis--150 years of fruitless search for the cause. Neonatology, 2009. 96(4): p. 203-10.

2. Eaton, S., C.M. Rees, and N.J. Hall, Current Research on the Epidemiology, Pathogenesis, and Management of Necrotizing Enterocolitis. Neonatology, 2017. 111(4): p. 423-430.

3. Neu, J. and W.A. Walker, Necrotizing enterocolitis. N Engl J Med, 2011. 364(3): p. 255-64.

4. Sho, S., et al., A novel scoring system to predict the development of necrotizing enterocolitis totalis in premature infants. J Pediatr Surg, 2014. 49(7): p. 1053-6.

5. Federici, S. and L. De Biagi, Long Term Outcome of Infants with NEC. Curr Pediatr Rev, 2019. 15(2): p. 111-114.

6. Allendorf, A., et al., Necrotizing enterocolitis as a prognostic factor for the neurodevelopmental outcome of preterm infants - match control study after 2 years. Journal of Pediatric Surgery, 2018. 53(8): p. 1573-1577.

7. Bizzarro, M.J., R.A. Ehrenkranz, and P.G. Gallagher, Concurrent bloodstream infections in infants with necrotizing enterocolitis. J Pediatr, 2014. 164(1): p. 61-6.

8. Young, C., et al., Biomarkers for infants at risk for necrotizing enterocolitis: clues to prevention? Pediatr Res, 2009. 65(5 Pt 2): p. 91R-97R.

9. Hackam, D.J., C.P. Sodhi, and M. Good, New insights into necrotizing enterocolitis: From laboratory observation to personalized prevention and treatment. J Pediatr Surg, 2019. 54(3): p. 398-404.

10. Nantais-Smith, L. and M. Kadrofske, Noninvasive biomarkers of necrotizing enterocolitis. J Perinat Neonatal Nurs, 2015. 29(1): p. 69-80.

11. Robinson, J.R., et al., Surgical necrotizing enterocolitis. Semin Perinatol, 2017. 41(1): p. 70-79.

12. Thuijls, G., et al., Non-Invasive Markers for Early Diagnosis and Determination of the Severity of Necrotizing Enterocolitis. Annals of Surgery, 2010. 251(6): p. 1174-1180.

13. Gomez-Chaparro Moreno, J.L., et al., The beta-glucosidase assay: a new diagnostic tool for necrotizing enterocolitis. Sensitivity,

specificity, and predictive values. Eur J Pediatr, 2016. 175(7): p. 931-41.

14. Frost, B.L., et al., New Medical and Surgical Insights Into Neonatal Necrotizing Enterocolitis: A Review. JAMA Pediatr, 2017. 171(1): p. 83-88.

15. Hull, M.A., et al., Mortality and management of surgical necrotizing enterocolitis in very low birth weight neonates: a prospective cohort study. J Am Coll Surg, 2014. 218(6): p. 1148-55.

16. Short, S.S., et al., Late onset of necrotizing enterocolitis in the full-term infant is associated with increased mortality: results from a two-center analysis. J Pediatr Surg, 2014. 49(6): p. 950-3.

17. Goldstein, S.D., et al., Early detection of necrotizing enterocolitis using broadband optical spectroscopy. J Pediatr Surg, 2018. 53(6): p. 1192-1196.

18. Zamora, I.J., et al., Low Abdominal NIRS Values and Elevated Plasma Intestinal Fatty Acid-Binding Protein in a Premature Piglet Model of Necrotizing Enterocolitis. PLoS One, 2015. 10(6): p. e0125437.

19. Luo, L., et al., Correlative Factors of the Deterioration of Necrotizing Enterocolitis in Small for Gestational Age Newborns. Sci Rep, 2018. 8(1): p. 13.

20. Elfvin, A., et al., Low birthweight, gestational age, need for surgical intervention and gram-negative bacteraemia predict intestinal failure following necrotising enterocolitis. Acta Paediatr, 2015. 104(8): p. 771-6.

21. Suply, E., et al., Spontaneous Intestinal Perforation and Necrotizing Enterocolitis: A 16-Year Retrospective Study from a Single Center. Eur J Pediatr Surg, 2015. 25(6): p. 520-5.

22. Bhatt, D., et al., Predicting Mortality or Intestinal Failure in Infants with Surgical Necrotizing Enterocolitis. J Pediatr, 2017. 191: p. 22-27 e3.

23. Gephart, S.M., et al., Changing the paradigm of defining, detecting, and diagnosing NEC: Perspectives on Bell's stages and biomarkers for NEC. Semin Pediatr Surg, 2018. 27(1): p. 3-10.

24. Khalak, R., et al., Physical examination score predicts need for surgery in neonates with necrotizing enterocolitis. J Perinatol, 2018. 38(12): p. 1644-1650.

25. Tepas, J.J., 3rd, et al., Timing of surgical intervention in necrotizing enterocolitis can be determined by trajectory of metabolic derangement. J Pediatr Surg, 2010. 45(2): p. 310-3; discussion 313-4.

26. Palatnik, A., et al., Predictors of early-onset neonatal sepsis or death among newborns born at <32 weeks of gestation. J Perinatol, 2019. 39(7): p. 949-955.

초 록

배경: 괴사성 장염은 신생아에게서의 위장관계 응급 중 가장 흔하고 위험한 질환 중 하나이며, 높은 사망률과 장기적인 합병증을 동반한다. 신생아 중증치료의 발전에도 불구하고, 괴사성 장염의 발생률이나 사망률, 합병증 발생률 등은 줄지 않은 상태이다. 이 연구의 목적은 괴사성 장염의 진행에 영향을 주는 위험인자를 분석하여 위험이 있는 환자를 예측하는 점수체계를 개발하는 것이다.

연구방법: 2003년 1월부터 2016년 11월까지 진단 시 수술받지 않은 괴사성 장염 환자 43명의 자료를 후향적으로 조사하였다. 환자들은 2개의 군으로 나누었다: 질병이 진행하지 않은 군과 질병이 진행한 군. 임상적 자료 및 검사결과 자료들을 비교 분석하였다. 다변량분석에서 유의미한 인자들을 이용하여 질병 진행을 예측하는 점수체계를 개발하였다. 또한, 이 점수체계를 28명의 외부환자군에서 검증하였다.

결과: 43명의 괴사성 장염 환자 중, 18명의 환자가 질병이 진행하여 수술적 치료를 받게 되었다. 질병이 진행한 군은 그렇지 않은 군에 비해 재태나이가 어렸고, 최소 혈소판 수치가 낮았으며, 최대 C-reactive protein (CRP) 수치가 높았다. 이 인자들을 이용하여 총점 10점의 점수체계를 개발하였고, 5점 이상에서 94.4%의 민감도와 76%의

특이도를 가졌다. 또한, 외부환자군에 시행한 검증에서도 87.5%의 민감도와 80%의 특이도를 확인하였다.

결론: 이 연구에서는 괴사성 장염의 진행을 예측하는 새로운 점수체계를 개발하였다. 이 점수체계는 질병 진행의 위험에 있는 환자를 조기에 발견하는 데 유용하며, 임상의가 적절한 시간에 수술적 치료를 결정하는 데에 도움을 줄 수 있다.

주요어 : 괴사성 장염, 재태나이, 혈소판, C-reactive protein, 점수체계

학 번 : 2018-28262