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Risk Factors Associated with Necrotizing Enterocolitis in Preterm Infants

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Abstract

Objective: Necrotizing enterocolitis (NEC) is one of the most severe gastrointestinal disorders in preterm infants and is characterized by high rates of morbidity and mortality. Early identification of clinical and demographic differences in infants who develop NEC may improve risk stratification, timely diagnosis, and targeted prevention strategies.

Methods: This retrospective cohort study was conducted to compare the demographic, maternal, and clinical characteristics of preterm infants with and without NEC in a tertiary-level neonatal intensive care unit. A total of 40 preterm infants were included and categorized into two groups: the NEC group (*n = 18*) and the control group (*n = 22*). Data on perinatal risk factors, demographic variables, and clinical outcomes were obtained from hospital records. Comparative analyses were performed using appropriate parametric and non-parametric statistical tests, with significance defined as $p<0.05$.

Results: No statistically significant differences were observed between the two groups in terms of gestational age, birth weight, mode of delivery, or Apgar scores. Small for gestational age (SGA) status was more frequent in the NEC group. The mean hematocrit levels were significantly elevated in infants with NEC (52.44 ± 7.38%) compared to controls (46.11 ± 5.97%; *p = 0.006*). Other clinical variables, such as the need for mechanical ventilation and the presence of umbilical venous catheters, showed no significant differences between the groups.

Conclusions: Elevated hematocrit levels and being SGA were more commonly observed in infants who developed NEC, supporting the multifactorial nature of the disease and highlighting the value of close hematologic and nutritional monitoring. These findings highlight the importance of close monitoring of hematological parameters and individualized nutritional strategies in high-risk preterm infants. Further prospective, large-scale studies are needed to validate these associations and inform evidence-based preventive and therapeutic interventions.

Keywords Necrotizing enterocolitis, Preterm infants, Risk factors

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INTRODUCTION

In recent years, advancements in neonatal intensive care have significantly increased the survival rates of preterm infants. However, this improvement was accompanied by a parallel rise in neonatal morbidities. One of the most serious early-onset complications in preterm infants is necrotizing enterocolitis (NEC), which is a condition with a wide clinical spectrum ranging from mild abdominal distension to fulminant disease and death (1–3). The reported incidence of NEC varies between 3% and 15%, with a multicenter study from Türkiye indicating a prevalence of 9.1% among very low birth weight (VLBW) infants (4).

The etiology of NEC is multifactorial, but the three most widely recognized major risk factors include intestinal immaturity associated with prematurity, abnormal bacterial colonization, and feeding with formula (1–3). The overall mortality rate of NEC is reported to be 10-30%, although it may exceed 50% in infants who required surgical intervention (1–3, 5, 6). Histopathological findings typically include mucosal inflammation, hemorrhage, and coagulative necrosis of the intestinal wall (1–3).

Diagnosis is based on a combination of clinical examination, radiologic imaging, and both invasive and non-invasive laboratory tests, which are used to evaluate the disease stage and severity (7–12). The management of NEC depends on the clinical disease stage, with most cases being treated medically; however, surgical intervention is necessary in severe or refractory cases.

Therefore, identifying early predictors and associated risk factors are essential for the prevention, timely diagnosis, and effective management of NEC. This study aims to compare the demographic, maternal, and clinical characteristics of preterm infants with and without NEC to better elucidate the factors contributing to the development of NEC.

MATERIALS AND METHODS

This retrospective cohort study was conducted on preterm infants admitted to a tertiary-level neonatal intensive care unit between August 2017 and August 2018. Of the 1600 neonates followed during the study period, 40 who met the inclusion criteria were enrolled in the study. Eligible infants had a gestational age of less than 34 weeks and a birth weight below 1250 g. Infants with complex congenital heart disease, major congenital anomalies, use of inotrope, grade ≥3 intraventricular hemorrhage, hydrops fetalis, or chromosomal abnormalities were excluded.

The study cohort was divided into two groups based on the presence or absence of NEC: Group 1 (control group, n = 22) included infants without NEC or with only feeding intolerance; Group 2 (NEC group, n = 18) included infants with clinical suspicion of NEC (Stage I) or with a confirmed diagnosis of NEC (Stage II or higher). The diagnosis and staging of NEC were determined according to the modified Bell's criteria, which incorporate clinical, radiological, and laboratory findings for comprehensive assessment. For analytical purposes, Stage I was defined by nonspecific systemic and gastrointestinal signs such as feeding intolerance, gastric residuals, abdominal distension, or bloody stools without definitive radiologic evidence, while Stage II or higher was defined by characteristic radiological findings (pneumatosis intestinalis, portal venous gas, or pneumoperitoneum) accompanied by progressive systemic deterioration (e.g., metabolic acidosis, thrombocytopenia, and shock) and more severe gastrointestinal manifestations such as abdominal tenderness, erythema, or palpable mass (2, 13). Feeding intolerance was defined as the presence of vomiting and abdominal distension in the absence of other systemic or radiological findings. Infants with no gastrointestinal symptoms or only feeding intolerance were assigned to the control group.

Data were retrospectively collected from the hospital records and included demographical characteristics (birth weight, gestational age, gender, mode of delivery, multiple gestation), maternal antenatal history (e.g., preeclampsia, premature rupture of membranes, chorioamnionitis), Apgar scores, initial hematocrit and lactate levels at birth, surfactant administration, type and duration of mechanical ventilation, presence and duration of umbilical venous catheters, time of first meconium passage, presence of hemodynamically significant patent ductus arteriosus (PDA), sepsis, intraventricular hemorrhage, erythrocyte transfusion within the first 14 days, time to achieve full enteral feeding, discharge or mortality status, and relevant biochemical (renal and liver function, serum electrolytes) and hematological parameters. These variables were compared between the two groups to evaluate potential differences in the clinical outcomes and risk factors associated with NEC.

Statistical Analysis

Statistical analysis was performed using SPSS v26.0. Continuous variables were analyzed using the Mann–Whitney U test and expressed as mean ± standard deviation or median (min–max). Categorical variables were analyzed using Pearson's chi-square or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

A comparison of the demographic, maternal, and antenatal characteristics between Group 1 (n = 22) and the NEC group (Group 2, n = 18) revealed no statistically significant differences in gestational age (29.27±1.64 vs. 29.50±2.18 weeks; $p = 0.923$) or birth weight (1378.18±275.55 g vs. 1226.67±271.27 g; $p = 0.187$). Male infants were more common in the NEC group (44.4%) than in the control group (27.3%; $p = 0.257$). Cesarean section was the predominant delivery method in both groups (81.8% vs. 83.3%; $p = 1.000$).

Table 1. Demographical, maternal and clinical characteristics

Variable	Group 1 (Control, n=22)	Group 2 (NEC, n=18)	*p* value
Gestational age (weeks)			
Min–Max (Median)	27-32 (30)	27-35 (29.5)	0.923[a]
Mean ± SD	29.27±1.64	29.50±2.18	
Gender			
Female, n (%)	16 (72.7)	10 (55.6)	0.257[b]
Male, n (%)	6 (27.3)	8 (44.4)	
Mode of delivery			
Vaginal delivery, n (%)	4 (18.2)	3 (16.7)	1.000[c]
Cesarean section, n (%)	18 (81.8)	15 (83.3)	
Birth weight (g)			
Min–Max (Median)	980-2000 (1345)	640-1550 (1310)	0.187[a]
Mean ± SD	1378.18±275.55	1226.67±271.27	
Multiple gestation			
No, n (%)	12 (54.5)	13 (72.2)	0.251[b]
Yes, n (%)	10 (45.5)	5 (27.8)	
Small for gestational age (SGA)			
No, n (%)	22 (100)	15 (83.3)	0.083[c]
Yes, n (%)	0 (0)	3 (16.7)	
Apgar score 1 min			
Min–Max (Median)	3-7 (5)	0-8 (5)	0.534[a]
Mean ± SD	5.23±1.07	4.89±1.64	
Apgar score 5 min			
Min–Max (Median)	6-8 (6.5)	5-9 (7)	0.839[a]
Mean ± SD	6.64±0.73	6.67±1.08	
Preeclampsia			
No, n (%)	19 (86.4)	14 (77.8)	0.680[c]
Yes, n (%)	3 (13.6)	4 (22.2)	
PPROM			
No, n (%)	16 (72.7)	18 (100)	0.024[c] *
Yes, n (%)	6 (27.3)	0 (0)	
Chorioamnionitis			
No, n (%)	16 (72.7)	17 (94.4)	0.105[c]
Yes, n (%)	6 (27.3)	1 (5.6)	

[a]*Mann-Whitney U Test* [b]*Pearson chi-square test* [c]*Fisher's exact test*

*$p < 0.05$ considered statistically significant.

SGA: Small for gestational age, PPROM: Preterm prelabor rupture of membranes

Being small for gestational age (SGA) was observed only in the NEC group (16.7%), although the difference was not statistically significant (*p = 0.083*). The incidence of preterm prelabor rupture of membranes (PPROM) was significantly higher in the control group (27.3%) than in the NEC group (*p = 0.024*). Other maternal conditions such as preeclampsia and chorioamnionitis were not significantly different between the groups.

Regarding postnatal clinical features, the two groups showed similar rates of surfactant use, invasive ventilation, and umbilical venous catheterization. Sepsis was present in all infants with NEC and in 81.8% of the control group (*p = 0.114*). Initial hematocrit levels at birth were significantly higher in the NEC group (52.44 ± 7.38% vs. 46.11 ± 5.97%; *p = 0.006*). Although not statistically significant, a history of packed red blood cell transfusion within the first 14 days was more frequent in the NEC group (27.8% vs. 4.5%; *p = 0.073*).

Table 2. Evaluation of Clinical and Laboratory Characteristics by Group

Variable	Control group (n=22)	NEC group (n=18)	*p* value
Surfactant therapy			
No, n (%)	2 (9.1)	2 (11.1)	1.000[c]
Yes, n (%)	20 (90.9)	16 (88.9)	
Invasive ventilation			
No, n (%)	11 (50.0)	5 (27.8)	0.154[b]
Yes, n (%)	11 (50.0)	13 (72.2)	
Invasive ventilation duration (days)			
Min–Max (Median)	1-18 (4)	2-13 (3)	0.768[a]
Mean ± SD	6.00±5.93	5.00±3.70	
Non-invasive ventilation			
No, n (%)	1 (4.5)	1 (5.6)	1.000[c]
Yes, n (%)	21 (95.5)	17 (94.4)	
Non-invasive ventilation Duration (days)			
Min–Max (Median)	1-83 (8.5)	1-39 (16)	0.428[a]
Mean ± SD	15.22±20.24	14.47±10.79	
Hemodynamically significant PDA			
No, n (%)	14 (63.6)	8 (44.4)	0.225[b]
Yes, n (%)	8 (36.4)	10 (55.6)	
Intraventricular hemorrhage (IVH)			
No, n (%)	15 (68.2)	13 (72.2)	0.781[b]
Yes, n (%)	7 (31.8)	5 (27.8)	
Sepsis			
No, n (%)	4 (18.2)	0 (0)	0.114[c]
Yes, n (%)	18 (81.8)	18 (100)	
Umbilical venous catheter			
No, n (%)	3 (13.6)	2 (11.1)	1.000[c]
Yes, n (%)	19 (86.4)	16 (88.9)	
Umbilical venous catheter Duration (days)			
Min–Max (Median)	3-18 (9.5)	3-19 (13)	0.312[a]
Mean ± SD	9.44±4.76	11.27±5.11	
Hematocrit at birth (%)			
Min–Max (Median)	37-58.1 (45.5)	40.4-67.5 (53.5)	0.006[a] **
Mean ± SD	46.11±5.97	52.44±7.38	
RBC transfusion within the first 14 days			
No, n (%)	21 (95.5)	13 (72.2)	0.073[c]
Yes, n (%)	1 (4.5)	5 (27.8)	
Passage of meconium			
Within 24 h, n (%)	11 (50.0)	10 (55.6)	0.726[b]
After 24 h, n (%)	11 (50.0)	8 (44.4)	
Day of initiation of minimal feeding			
[Min–Max (Median)]	1-6 (2)	1-5 (2)	0.063[a]
Mean ± SD	2.79±1.47	2.00±1.03	
Day of achieving full enteral feeding (150 mL/kg/day)			
Min–Max (Median)	10-36 (18.5)	18-50 (30.5)	0.001[a] **
Mean ± SD	19.67±7.04	32.25±9.29	
Length of hospital stay (days)			
Min–Max (Median)	10-111 (47)	10-206 (57.5)	0.248[a]
Mean ± SD	50.63±23.55	64.44±43.52	
Outcome			
Survived, n (%)	21 (95.5)	16 (88.9)	0.579[c]
Died, n (%)	1 (4.5)	2 (11.1)	

[a]*Mann-Whitney U Test* [b]*Pearson chi-square test* [c]*Fisher's exact test*

****p < 0.01** was considered statistically significant.

PDA: Patent ductus arteriosus; IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis; RBC: Red blood cell.

While the day of initiation of minimal enteral feeding did not differ significantly (median: 2 days in both groups; *p = 0.063*), the time to reach full enteral feeding (150 cc/kg/day) was significantly longer in the NEC group (median: 30.5 vs. 18.5 days; *p = 0.001*). The length of hospital stay tended to be longer in the NEC group (median: 57.5 vs. 47 days), although the difference was not statistically significant (*p = 0.2438*). Mortality was slightly higher in the NEC group (11.1% vs. 4.5%; *p = 0.579*). The clinical characteristics of the infants are summarized in Table 2.

DISCUSSION

In this retrospective study, we described the demographic, maternal, and clinical characteristics of preterm infants with and without NEC. Within the NEC group, the initial hematocrit levels at birth were significantly higher, and the time to achieve full enteral feeding was significantly longer. Although not statistically significant, being small-for-gestational-age (SGA) and a history of packed red blood cell transfusion within the first 14 days were also more frequent among infants with NEC. Notably, SGA status was observed exclusively in the NEC group, which agrees with large-scale cohort studies reporting that impaired fetal growth is associated with an increased risk of NEC in preterm infants. It is likely that the limited sample size of our single-center cohort reduced the statistical power to detect a statistically significant difference for SGA, despite a clinically meaningful trend. Numerous antenatal, perinatal, and postnatal risk factors for NEC have been well documented in previous studies (3, 5, 7–9, 12, 16, 18–21, 23, 24). Careful evaluation of these risk factors and close monitoring of all preterm infants through clinical, laboratory, and radiological assessments are essential for early detection and prevention. In recent years, non-invasive imaging modalities have emerged as valuable diagnostic tools with high accuracy. However, in centers where such modalities are not available, conventional clinical, radiographic, and laboratory evaluations remain of critical importance.

Inadequate nutrition during the fetal period and early postnatal life has been associated with long-term adverse outcomes, including an increased risk of cardiovascular disease, metabolic syndrome, and neurodevelopmental impairments (14). Timely and adequate provision of both parenteral and enteral nutrition is therefore critical for reducing these complications and improving the overall prognosis. Furthermore, the early initiation of enteral feeding has been shown to decrease catheter-related complications, reduce the risk of infection, and shorten the duration of hospitalization (14, 15).

An unexpected finding in our cohort was the significantly higher rate of preterm prelabor rupture of membranes (PPROM) in the control group compared with the NEC group. This observation is not consistent with most previous reports, in which PPROM was associated with an increased risk of adverse neonatal outcomes, including NEC. One possible explanation is the small sample size of our single-center study, which may have led to random imbalances between the groups. In addition, closer antenatal surveillance and earlier delivery of fetuses at risk after PPROM in our unit might have contributed to better postnatal stabilization and more cautious feeding advancement, thereby mitigating the risk of NEC in this subgroup. Given these limitations, the obvious protective association of PPROM in our cohort should be interpreted with caution and warrants confirmation in larger multicenter studies.

Our findings agree with previous literature identifying NEC as a multifactorial disease resulting from complex interactions among intestinal immaturity, feeding practices, infection, and vascular compromise. The significantly elevated hematocrit levels observed in infants with NEC support the hypothesis that altered blood viscosity may contribute to mesenteric ischemia and impaired intestinal perfusion, mechanisms well recognized in NEC pathophysiology (3, 16, 19). In line with these observations, hematocrit levels were significantly higher in the NEC group in our cohort.

The significantly delayed achievement of full enteral feeding in the NEC group likely reflects clinical caution in advancing feeds in these infants, but also underscores the risks associated with prolonged parenteral nutrition. This is consistent with the findings of Wondafrash et al., who identified NEC as an independent predictor of delayed feeding (17). Moreover, the presence of sepsis in all NEC cases in our cohort reinforces its role as both a risk factor and a potential trigger, as previously reported (18, 19). Sepsis and the associated systemic inflammatory response may contribute to intestinal barrier dysfunction, altered microcirculation, and microbial dysbiosis, all of which are considered to be key mechanisms in NEC pathogenesis. Simultaneously, sepsis was also frequent in the control group, indicating that sepsis alone is not sufficient to cause NEC but rather acts in combination with other vulnerabilities such as intestinal immaturity and suboptimal perfusion. Because detailed microbiological data (e.g., pathogen type and strain-level characteristics) were not systematically available in our retrospective dataset, we could not further explore the potential differences in the infectious agents between the groups. Larger prospective studies with comprehensive microbiological and inflammatory profiling are needed to clarify the complex interplay between sepsis and NEC. In line with the literature, the time to reach full enteral feeding (150 mL/kg/day) was significantly longer in the NEC group.

Although mechanical ventilation and umbilical catheter use did not differ significantly between the groups, previous studies have suggested that prolonged exposure to these invasive procedures may increase the risk of NEC through mechanisms such as systemic inflammation and microbial translocation (20). The presence of SGA infants exclusively in the NEC group, although not statistically significant, is consistent with the large-scale findings of Kim et al.,

indicating that impaired fetal growth may predispose infants to NEC (21).

The critical role of early nutrition is further highlighted by evidence demonstrating that delayed initiation of enteral feeding does not protect against NEC and may instead increase the risk of infection (22). Moreover, although not assessed in our study, human milk remains central to NEC prevention owing to its well-recognized immunological and anti-inflammatory properties (23).

This study has several limitations that should be acknowledged. First, its retrospective design inherently restricts the ability to establish causal relationships between risk factors and the development of NEC. Second, the relatively small sample size may have reduced the statistical power to detect subtle yet potentially meaningful differences, particularly for less frequent variables. Third, as the study was conducted at a single tertiary center, the generalizability of the findings to other institutions with different clinical practices and patient populations may be limited. In addition, detailed information on feeding types (e.g., exclusive breast milk vs. formula) and microbiological colonization patterns, both recognized as important factors influencing NEC risk, was not comprehensively available. Finally, although the modified Bell's criteria were applied for NEC diagnosis, interobserver variability in clinical and radiological interpretation could have introduced some diagnostic heterogeneity.

Another important limitation is that several established risk factors for NEC were not systematically recorded in our retrospective dataset. In particular, detailed information on antenatal corticosteroid exposure, timing and mode of cord clamping (including delayed cord clamping), type and proportion of enteral feeds (exclusive human milk versus formula or mixed feeding), and the use of feeding protocols or probiotics was not available for all infants. These unmeasured variables may have influenced both hematocrit levels at birth and the risk of NEC, and thus may partly account for the observed association between higher hematocrit and NEC in our cohort. The absence of these data should be considered when interpreting our results, as residual confounding cannot be excluded.

Future multicenter, prospective studies with larger cohorts and standardized data collection are needed to validate and extend these findings.

CONCLUSION

This study supports the multifactorial etiology of NEC in preterm infants, identifying elevated hematocrit levels, sepsis, delayed achievement of full enteral feeding, and being small-for-gestational-age as factors associated with the development of NEC. Although no significant differences were observed in other interventions such as mechanical ventilation or catheter use, these variables remain clinically relevant. A balanced, individualized feeding strategy that avoids both overly aggressive advancement and prolonged withholding appears essential for minimizing the risk of NEC. Future multicenter studies with larger cohorts are needed to validate these associations and to guide the development of standardized prevention protocols for NEC.

Competing Interests	The authors declare no conflicts of interest.
Ethics Committee Approval	Ethic Committee Approval was obtained from the Ethics Committee of Harran University School of Medicine (10/08/2018-31551).
Informed Consent	Informed consent was waived due to the retrospective design of the study.
Peer review	Externally peer reviewed.
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