RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2025.2025-50
Cyprus J Med Sci 2025;10(6):363-368

Necrotizing Enterocolitis (NEC) in Premature Infants: A 4-Year Review of Our Cases

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Abstract

BACKGROUND/AIMS: This study aims to evaluate the outcomes of necrotizing enterocolitis (NEC) in premature infants, focusing on identifying potential biomarkers and risk factors that may guide early diagnosis and management strategies, while also addressing the limitations of current diagnostic criteria.

MATERIALS AND METHODS: A retrospective observational cohort study was conducted on 56 premature infants initially diagnosed with NEC at a single tertiary neonatal intensive care unit (NICU). Of these, 32 infants fulfilled the Modified Bell Criteria and were included in the analysis. Statistical tests were used to determine significant differences between infants with complications and those without.

RESULTS: The incidence of NEC in our NICU was 1.58%, lower than the 2-7% range typically reported in the literature. The mean gestational age was 29.25±2.99 weeks. Variability was observed in platelet and white blood cell counts, with thrombocytopenia suggested as a potential marker for more severe cases. Electrolyte disturbances, particularly changes in chloride (Cl) and sodium (Na) levels, were significantly associated with more severe NEC. Mortality was observed in 12.5% of cases, all of which were classified as stage IIIb NEC. Eight cases were excluded by the Modified Bell Criteria despite clinical diagnosis, highlighting the limitations of the current framework.

CONCLUSION: This study highlights the importance of early diagnosis and prompt intervention in NEC management. The findings suggest that electrolyte disturbances, particularly fluctuations in Na and Cl levels, may serve as predictive biomarkers of NEC severity. Furthermore, the results emphasise the need for updated diagnostic criteria to improve the accuracy and comprehensiveness of NEC detection in neonates.

Keywords: Necrotizing enterocolitis, diagnosis, electrolyte disturbances, platelet count, mortality rate

INTRODUCTION

Necrotizing enterocolitis (NEC) is a severe neonatal disease characterized by inflammation and tissue damage in the intestines.[1] The primary pathophysiological feature of the disease involves disruption of the intestinal flora and reduced resistance of the intestinal system to pathogenic microorganisms.[2] Consequently, NEC occurs more frequently in premature infants, although it can also develop-albeit less frequently in infants born at or beyond 32 weeks of gestation.[1]

Accurate diagnosis and staging of NEC are among the most critical steps in the treatment process. The most widely used classification system for this purpose is the Bell staging criteria criterion, developed by Bell et al.[3] in 1978. However, the Bell Criteria do not incorporate more

To cite this article: Deniz Y, Ekmen S, Demircioğlu B, Şakul Babaev G. Necrotizing enterocolitis (NEC) in premature infants: a 4-year review of our cases. Cyprus J Med Sci. 2025;10(6):363-368

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Received: 23.05.2025
Accepted: 16.10.2025
Publication Date: 16.12.2025

sensitive biochemical markers or advanced imaging modalities.[3] This shortcoming limits the early and accurate identification of NEC, leading to subsequent modifications of the Bell system over time.

In recent years, numerous studies have sought to address these diagnostic gaps by investigating potential biomarkers. In particular, inflammatory protein markers have been proposed as tools for determining both the diagnosis and severity of NEC. For example, some studies have reported that interleukin-8, interleukin-24, and C-C motif chemokine ligand 20 can differentiate between stage II and stage III NEC and may also assist in distinguishing NEC from sepsis.[4] However, the routine clinical use of these biomarkers remains limited, and they are currently considered supportive but insufficient diagnostic tools on their own.

Imaging methods also hold potential in aiding NEC diagnosis. A meta-analysis that reviewed key studies reported that abdominal ultrasonography could provide sensitive information for the early detection of NEC.[5] Nevertheless, heterogeneity in methods, poor reporting quality, and the presence of uncertain bias have limited its practical use in clinical decision-making.[5]

In addition, artificial intelligence (AI) and machine learning-based models represent new and promising approaches, as they analyse multivariable clinical, and laboratory data to predict NEC risk.[6] Recent studies[6-8] have suggested that such models may facilitate both earlier and more accurate NEC diagnosis, while also reducing subjectivity in interpretation. However, these technologies still face limitations regarding data variability, model transparency, and clinical validity.[6-8]

In this context, the adequacy of the Bell Criteria-still regarded as the "gold standard" for NEC diagnosis remains controversial when considered against current technological advancements and clinical requirements.[7-10] The aim of the present study is therefore to evaluate NEC through the framework of the Bell Criteria and to question its current validity, as repeatedly emphasised in the literature.

MATERIALS AND METHODS

Study Location and Duration

This study was conducted at a single tertiary-care neonatal intensive care unit (NICU) in Türkiye. The study period spanned from January 1, 2020, to October 24, 2023, covering a total duration of nearly four years. During this period, cases of neonates diagnosed with NEC were retrospectively analyzed.

The study was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki. This study was approved by the Karabük University Non-Interventional Clinical Research Ethics Committee (approval number: 2023/1495, date: 08.11.2023). Informed consent forms were obtained from all participants in the study.

Inclusion and Exclusion Criteria

Inclusion criteria:

- **Diagnosis of NEC:** All patients included in the study must have been diagnosed with NEC according to the international classification of diseases (ICD) code P77.
- **Gestational age:** Only premature infants born between 24 and 32 weeks of gestation were included in the study. Infants born at 32 weeks + 0 days (32w + 0d), were included, while those born at 32w + 1d or later were excluded from the study.
- **Clinical stage according to the Modified Bell Criteria:** Only infants diagnosed with NEC according to the Modified Bell Criteria were included. These criteria assess the severity of the disease from stage I (suspected) to stage III (severe), including conditions such as intestinal perforation.
- **Laboratory and radiological findings:** Infants showing laboratory signs such as elevated leukocyte count, increased C-reactive protein (CRP), and radiological findings consistent with NEC (e.g., bowel dilation, free air in the abdominal cavity) were included in the study.

Exclusion criteria:

- **Failure to meet NEC criteria:** Infants who did not meet the Modified Bell Criteria for NEC were excluded. This includes cases with severe gastrointestinal disorders but without a diagnosis of NEC.
- **Severe genetic or congenital anomalies:** Infants with severe genetic syndromes or significant congenital anomalies, such as major cardiac defects, were excluded from the study.
- Infants born at or after 32 weeks and 1 day of gestation who were diagnosed with NEC were excluded.
- **Missing data:** Infants with incomplete clinical or laboratory data necessary for staging NEC and assessing its progression were excluded from the study. These data are essential for accurately staging the disease and monitoring its course.
- **Other gastrointestinal disorders:** Infants with other gastrointestinal conditions that may mimic NEC (e.g., Hirschsprung disease or intestinal atresia) were excluded from the study.

Identification of Study Participants

Initially, 56 patient records were selected based on the neonatal NEC diagnosis, identified through the hospital's P77 automation system, according to the ICD classification through the hospital's P77 automation system, according to the ICD classification. Each patient record was then reviewed and re-assessed based on the Modified Bell Criteria. Of the 56 records, only 32 patients met the criteria for NEC diagnosis, while the remaining 24 patients did not. However, it is important to note that these 24 patients were all clinically diagnosed with NEC by the attending physicians. Among them, 14 patients were excluded because their gestational age was over 32 weeks of gestation as the study was restricted to patients born at or before 32 weeks. Furthermore, 2 patients with known genetic conditions were excluded accordingly, according to the study protocol's exclusion criteria for genetic disorders. Additionally, three patient records were excluded due to insufficient data, which led to their removal from the study. As a result, the remaining five patients, despite not meeting the Modified Bell Criteria, had been diagnosed with NEC by the attending physicians and were recorded as such in the hospital's P77 automation system.

Biomarkers and Analytical Parameters

In this study, various laboratory parameters and biomarkers were assessed to evaluate the clinical progression and severity of NEC. These included common laboratory values such as white blood cell (WBC) count, platelet (PLT) count, CRP, sodium (Na), potassium (K), chloride (Cl), urea, creatinine (Cr), and liver enzymes [alanine

aminotransferase (ALT) and aspartate aminotransferase (AST)]. These parameters were collected and analyzed to monitor the patient's condition and to help identify any deviations indicative of NEC progression or complications.

Additionally, clinical data was recorded, including:

1. **Average gestational age:** The mean gestational age at birth for the study participants.
2. **Average length of hospitalization:** The average duration of hospital stay for patients diagnosed with NEC.
3. **Mortality rate**: The percentage of patients who experienced mortality during the study period.
4. **Recovery rate:** The percentage of patients who showed complete recovery from NEC.
5. **NEC incidence:** The frequency of NEC diagnoses within the study population, helping to evaluate the incidence rate during the specified study period.

These biomarkers and clinical parameters were used to assess the disease's clinical course, predict potential outcomes, and guide therapeutic decisions.

Data Collection and Validation

Data for this study were retrieved from the hospital's electronic health record system, which provided past patient records. Neonates diagnosed with NEC, according to the ICD classification, specifically those with the diagnosis of "P77 - fetal and neonatal NEC," were identified. Neonates with the diagnosis of "P77 - fetal and neonatal NEC," according to the ICD classification, specifically those diagnosed with NEC, were identified.

Statistical Analysis

The data were analyzed using Intellectus Statistics (online software). The normality of the distribution was assessed using the Shapiro-Wilk test, which indicated that the data were not normally distributed. Descriptive statistics for continuous variables are reported as mean, minimum, and maximum values, while categorical variables are presented as frequencies and percentages. For blood parameters, mean and standard deviation values are reported, with p-values <0.05 considered statistically significant.

RESULTS

During the study period, a total of 2015 patients were admitted to our NICU. Among these, 32 cases fulfilled the Modified Bell Criteria for NEC diagnosis, yielding an NEC incidence of 1.58% among NICU admissions. Notably, this incidence does not represent the incidence among all births but rather within the admitted NICU population. Additionally, due to the retrospective nature of the study, some clinically diagnosed NEC cases may not have been recorded, which could lead to underestimation. This limitation is inherent to retrospective studies and should be considered when interpreting the incidence data.

The mean gestational age was 29.25±2.99 weeks. The minimum gestational age was 23 weeks, and the maximum gestational age was 32 weeks. The median gestational age was 30.5 weeks, indicating that 50% of the infants were born before 30.5 weeks and 50% after. Additionally, the median gestational age of 30.5 weeks suggests that the majority of infants were born between 28 and 32 weeks (Table 1).

Table 1. Descriptive characteristics of the neonates

Characteristics	Mean ± SD	Min.-Max.
Gestational age	29.25±2.99	(23-32)
Hospitalization duration (days)	35.62±17.05	(6-65)
Mortality	**n**	**%**
- No mortality	28	87.50
- Mortality present	4	12.50
Recovery		
- Recovery present	28	87.50
- No recovery	4	12.50
Complication status		
- No complications	26	81.25
- Complications present	6	18.75
Risk factors		
- Prematurity, sepsis, antibiotic usage	10	31.25
- Prematurity, antibiotic usage	22	68.75
Complications		
- Perforation	6	18.75
- No perforation	26	81.25

SD: Standard deviation, Min.: Minimum, Max.: Maximum.

The average length of hospital stay for the patients was 35.62 days (±17.05 days), with a range between 6 and 65 days. Out of the 32 patients, 4 died, resulting in a mortality rate of 12.5% and a recovery rate of 87.5%.

When examining the complication status, it was found that 81.25% of the infants did not experience any complications, while 18.75% developed complications. Among the complications, perforation was the most frequently encountered condition, identified in 18.75% of the cases. In terms of risk factors, 31.25% of the infants had a combination of prematurity, sepsis, and antibiotic use, while 68.75% had both prematurity and antibiotic use. These findings indicate that prematurity and antibiotic use are prevalent risk factors in this patient group.

Clinical Staging and Outcomes

According to the Modified Bell Criteria, the patients were distributed as follows:

- **Stage I (suspicious NEC):** 14 patients (43.8%)
- **Stage II (localized NEC):** 10 patients (31.2%)
- **Stage III (advanced NEC):** 4 patients (12.5%)
- **Stage IIIb (IV) (perforation):** 4 patients (12.5%)

Laboratory Findings

Several laboratory parameters were evaluated to assess the progression and severity of NEC. Table 2 compares the laboratory findings of infants with and without complications.

The average gestational age of infants with complications was 26.67±4.23 weeks, while the average gestational age of those without complications was 29.85±2.36 weeks. This difference was not statistically significant (p=0.107). However, the length of hospital stay for infants with complications (11.67±8.02 days,) was significantly longer compared to those without complications (41.15±13.34 days, p=0.000).

No significant difference was found between infants with and without complications in terms of WBC count (p=0.480). Similarly, PLT count did not show a significant difference between the two groups (p=0.225).

Although this difference is borderline statistically significant (p=0.069), Na levels tend to be lower in infants with complications (135±2.68) compared to those without complications (138.23±4.16), although this difference is borderline statistically significant (p=0.069). Cl levels were significantly higher in infants with complications (112.33±1.03) than in those without complications (106.38±6.28) (p=0.014). This finding indicates that electrolyte imbalances occur more often in infants with complications. As for K levels, no significant difference was found between the two groups (p=0.308).

Urea levels tend to be higher in infants with complications (73.67±80.85) compared to those without complications (32.46±57.45), although this difference is only borderline statistically significant (p=0.069). No significant difference was found between the two groups in terms of Cr levels (p=0.189). AST levels did not show a significant difference between infants with and without complications (p=0.480). However, ALT levels were significantly lower in infants with complications (5.00±0.89) compared to those without complications (28.38±35.2) (p=0.000) (Table 2).

Given that the dataset did not follow a normal distribution and the sample size was relatively small, non-parametric statistical tests were used in this analysis. These tests were selected to provide reliable comparisons between groups and to appropriately account for potential skewness in the data.

DISCUSSION

In our study, the NEC incidence among NICU admissions was 1.58%, which is lower than the 2-7% range commonly reported in the literature.[9] This may reflect the effectiveness of treatment protocols or changes in NEC diagnostic criteria. McElroy and Lueschow.[8] highlighted adjustments in diagnostic approaches for premature infants that may explain this decrease. Although machine learning tools are not used in our unit, the low incidence likely reflects advances in neonatal care-such as improved feeding strategies, immune support, and antibiotic use-which facilitate the early NEC management and contribute to reduced mortality, supporting the success of our protocols.

According to our findings, the mean gestational age of premature infants was 29.25±2.99 weeks, with a median gestational age of 30.5 weeks. Our findings align with the literature, which indicates that NEC is more commonly observed in infants born between 28 and 32 weeks of gestation.[10-13] The clinical implication of these findings highlights the necessity for more vigilant monitoring for NEC in preterm infants and emphases the need for improved management strategies for this high-risk group.

The analysis revealed that the average length of hospital stay for patients was 35.62±17.05 days. This duration is comparable to the reported hospitalisation times for medical NEC cases in the study by Velazco et al.[14] However, in Velazco et al.[14] research, the average hospital stay for NEC patients who underwent surgical treatment was reported as 63±36.94 days (medical group: 34±22.61 days). This finding aligns with the general trend in the literature, which associates longer hospital stays with NEC cases requiring surgical intervention.[14,15] In our study, however, all patients were evaluated together, without separately analyzing the surgical and medical treatment groups, leading to an overall calculation of hospital stay. In this context, one might have expected longer hospitalisation times by focusing solely on medical NEC cases; nevertheless, similar results were obtained as those observed in Velazco et al.[14] study, with shorter hospitalisation durations. Several factors could play a role in these discrepancies in length of stay. However, the most likely explanation may stem from the

Table 2. Impact of complication status on laboratory findings

Features	Complication				Test used*	p-value
	Perforation		Absent			
	Mean ± SD	Median (Min.- Max.)	Mean ± SD	Median (Min.- Max.)		
Gestasyonal age	26.67±4.23	25 (23-32)	29.85±2.36	31 (25-32)	1.692	0.107
Hospitalization duration (days)	11.67±8.02	7 (6-22)	41.15±13.34	38 (22-65)	3.680	**0.000**
WBC	128.33±106.79	6.6 (5.3-26.6)	209.92±257.33	8.9 (3.7-22.9)	0.870	0.480
PLT	200.33±183.74	124 (44-433)	263±123.39	235 (47-541)	1.258	0.225
Na	135±2.68	135 (132-138)	138.23±4.16	137 (134-151)	1.857	0.069
K	53±8.530	5.8 (4.2-5.9)	48.46±7.71	4.8 (3.2-6.1)	-1.066	0.308
Cl	112.33±1.03	113 (111-113)	106.38±6.28	104 (96-120)	-2.428	**0.014**
Urea	73.67±80.85	24 (19-178)	32.46±57.45	9 (3- 220)	-1.840	0.069
Creatinine	9.67±8.78	0.4 (0.4-2.1)	18±46.2	0.3 (0.07-1.7)	-1.368	0.189
AST	44±41.91	20 (14-98)	40.46±21.59	37 (18-76)	0.870	0.480
ALT	5.00±0.89	5 (4-6)	28.38±35.2	14 (4-33)	3.295	**0.000**

*Shapiro-Wilk test.
WBC: White blood cell, PLT: Platelet, Na: Sodium, K: Potassium, Cl: Chloride, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SD: Standard deviation, Min.: Minimum, Max.: Maximum.

diversity in hospital treatment protocols, patient care processes, and clinical management strategies.

In our study, the mortality rate was determined to be 12.5% (4/32), and all mortality cases occurred in patients in stage IIIb (intestinal perforation). This finding is consistent with the high mortality rates observed in surgical NEC cases in the study by Flahive et al.[16] Flahive et al.[16] reported a mortality rate of 23.5% in stage II and higher NEC cases, with the rate rising to 50.9% in infants with low birth weight (<1000 g). Other studies in the literature have also indicated that mortality rates in surgical NEC cases can range from 30% to 50%.[16-18] The lower mortality rate observed in our study may be attributed to the fact that, in the majority of cases, early intervention led to recovery without the need for surgical intervention. Nevertheless, it was observed in our study that mortality rates in surgical NEC cases remain significantly higher, which is consistent with the current literature.

Our data highlight the importance of monitoring electrolyte disturbances, such as increased Cl and decreased Na levels, in the early identification of severe forms of NEC. These findings are in line with previous studies that have explored the biochemical alterations in NEC and their correlation with disease severity.[19,20] The significant relationship of Cl and Na fluctuations with the risk of complications suggests that these biomarkers could potentially offer predictive insight into the clinical course of NEC, particularly if monitored alongside other emerging markers such as inflammatory cytokines and gut-specific proteins. Understanding electrolyte imbalances in relation to other biomarkers could provide predictive insights and guide interventions. Another critical finding is the increase in urea levels, which monitors kidney function. Leading studies in the literature indicate that such increases are critical in advanced-stage NEC cases, particularly those requiring surgical intervention, and could elevate the mortality risk of patients.[21]

In our study, the mean PLT count in the overall population showed a wide variabilityvaried widely. This finding suggests that some infants may have had thrombocytopenia. However, there was no significant difference in PLT counts between infants with and without complications. Although this variability was not statistically significant, the existing literature suggests that thrombocytopenia may reflect disease progression.[20,22]

Furthermore, although K and urea levels were not statistically significant, Na and Cl levels were found to be significant. In particular, the detection of pronounced hyperchloremia and hyponatremia in infants with complications indicates that these electrolyte disturbances may be associated with severe forms of NEC. This finding suggests that Cl and Na levels may serve not only as markers for disease monitoring but also as biomarkers for early diagnosis. The relationship between electrolyte imbalances and NEC severity is consistent with previous literature.[19] These parameters may provide clinicians with important clues in predicting NEC severity.

The relationship between risk factors, including prematurity and antibiotic usage, also emerged as a significant finding in this study. The combination of prematurity and antibiotic use accounted for the majority of medical cases, with 68.75% of infants exposed to antibiotics in conjunction with prematurity. This is consistent with findings in other studies suggesting that antibiotic therapy, particularly the use of broad-spectrum antibiotics in premature infants, may disrupt the normal gut flora and contribute to the pathogenesis of NEC.[23] This highlights the need to carefully manage antibiotic exposure in this vulnerable population and suggests that antimicrobial stewardship strategies should be a key component of NEC prevention.

In this study, 32 cases of NEC were confirmed using the Bell Criteria; however, the NEC diagnosis for the remaining 5 patients, although being clinically established by clinicians, could not be validated. As a result, while a total of 37 NEC diagnoses should have been made, only 32 patients received this diagnosis, leading to a diagnostic loss of approximately 13.5%. This situation caused an incomplete diagnosis in these patients. The inadequacy of the Bell Criteria in diagnosing NEC is not specific to this study. Therefore, the growing need for more sensitive and specific diagnostic methods is frequently emphasized in the literature.[7,8] This finding demonstrates that the Bell Criteria are insufficient in certain cases and emphasizes the necessity for new diagnostic methods to ensure accurate and timely diagnosis of NEC, particularly in its early stages.

Although our study included both medically and surgically managed NEC cases, the small number of surgical cases (n=4) precluded subgroup analysis. This represents a limitation, as stratification by treatment modality could provide further insights into outcome differences. Future multicentre studies with larger cohorts are needed to address this gap.

Study Limitations

This study had a retrospective design, which may have caused some clinically diagnosed but unrecorded NEC cases to be missed. The NEC incidence was calculated only among patients admitted to the NICU and therefore does not reflect the general birth population. The presence of outliers in some parameters, such as electrolyte values, may have limited the reliability of the statistical analyses. In addition, the relatively small sample size and the study being conducted in a center may restrict the generalisability of our findings.

CONCLUSION

Our findings highlight the need for multidimensional diagnostic approaches. In particular, the significant association of electrolyte disturbances such as hyponatremia and hyperchloremia with NEC suggests that these parameters may serve as potential biomarkers in diagnosis and prognosis. The integration of such laboratory data with AI algorithms may enable the development of more sensitive and earlier diagnostic models for NEC.

MAIN POINTS

- Changes in chloride and sodium levels were significantly associated with necrotizing enterocolitis (NEC) severity.
- All mortality cases occurred in infants with stage IIIb NEC, indicating high-risk at advanced stages.
- The Bell Criteria failed to capture some clinically diagnosed cases, highlighting diagnostic limitations.

ETHICS

Ethics Committee Approval: The study was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki. This study was approved by the Karabük University Non-Interventional Clinical Research Ethics Committee (approval number: 2023/1495, date: 08.11.2023).

Informed Consent: Informed consent forms were obtained from all participants in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.D., S.E., Concept: Y.D., B.D., Design: Y.D., Data Collection and/or Processing: B.D., G.Ş.B., Analysis and/or Interpretation: B.D., G.Ş.B., Literature Search: Y.D., S.E., Writing: Y.D.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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