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Research Article

Comparative Study Between Medically Managed and Surgically Managed Necrotising Enterocolitis in Preterm Infants: A Retrospective Cohort Study

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Abstract

Introduction: Necrotising enterocolitis (NEC) is a severe gastrointestinal disease predominantly affecting premature neonates. Earlier identification of infants who are likely to require surgical intervention remains challenging. This study compared medically and surgically managed NEC in preterm infants to identify clinical, biochemical, microbiological, and radiological markers associated with surgical management, disease severity, and mortality.

Methods: This retrospective cohort study was conducted at St Mary's Hospital, Manchester, using electronic patient records of infants diagnosed with NEC between January 2023 and December 2024. Infants were classified as having medically or surgically managed NEC. Demographic, biochemical, microbiological, radiological, and outcome variables were analysed. Statistical analyses included the Mann-Whitney U test, chi-square or Fisher's exact tests, Spearman's correlation, and logistic regression. A sensitivity analysis restricted to infants with Bell Stage II/III NEC was also performed.

Results: A total of 87 infants were included, comprising 42 with medically managed NEC and 45 with surgically managed NEC. Surgically managed infants had significantly higher lactate levels (p = 0.028), lower base excess (p = 0.025), and a greater frequency of pneumoperitoneum (p less than 0.001). Positive blood cultures were significantly associated with surgical management (p = 0.007; OR = 3.42). In a sensitivity analysis restricted to infants with Bell Stage II/III NEC, base excess was significantly lower in surgically managed infants (p = 0.013). Lower platelet counts were significantly associated with mortality (p = 0.019). An exploratory multivariable mortality model incorporating lactate, platelet count, and the type of NEC management demonstrated an area under the curve of 0.737.

Conclusions: Higher lactate levels, positive blood cultures, and pneumoperitoneum were associated with surgical management of NEC, while lower platelet counts were associated with mortality. Lower base excess was also associated with surgical management among infants with Bell Stage II/III disease. These routinely available clinical parameters may help identify infants with NEC who follow a more severe disease trajectory and could contribute to earlier risk stratification. Prospective multi-centre studies are required to determine their temporal and predictive value and validate their incorporation into clinical risk models.

Keywords: *Necrotising enterocolitis; Preterm infants; Surgical management; Lactate; Blood culture; Pneumoperitoneum; Platelet count; Base excess; Bell Stage II/III; Mortality; Risk stratification.*

1. Introduction

Necrotising enterocolitis (NEC), a condition predominantly affecting neonates, is known to be associated with alarmingly high morbidity and mortality rates [1]. It is a complex and multifactorial process resulting in the ischaemic necrosis of small and large bowels in its most threatening form, leading to sepsis and death [2]. It is known to occur primarily due to gut immaturity in premature infants. An immature gut is characterised by an underdeveloped intestinal structure, impaired mucosal protection, poorly regulated gut motility, and an overreactive inflammatory response to triggers such as hypoxia, enteral feeding, and disruptions in the microbial environment. Preterm neonates also have an underdeveloped intestinal vasculature, significantly before 32 weeks of gestation. This can result in inflammatory processes that further disrupt vascular development, intensifying the risk of ischaemic injury and NEC development [3].

NEC is managed with two main approaches: medical and surgical management. Around 50-70% of NEC cases are managed medically [4]. Treatment involves stopping feeding to allow the bowels to rest, intravenous fluid boluses, nasogastric decompression and broad-spectrum antibiotics [5]. Conservative measures yield more favourable results in early or less severe NEC, particularly in the absence of intestinal perforation [6]. Surgical management includes resection of necrotic tissue, ileostomy or anastomosis and peritoneal drainage in the event of a perforation [4,6]. Surgery is performed in infants with severe necrosis, which often results in an intestinal perforation, a sign of which is pneumoperitoneum, which is visible on chest radiograph [4,7].

Regardless of advancements in NEC research and the recognition of definitive surgical indications such as pneumoperitoneum, significant uncertainty remains in predicting which infants will deteriorate and require surgical treatment, particularly in the earlier stages of NEC. This study aimed to compare the clinical, laboratory and radiological characteristics of infants with medically and surgically managed NEC and to identify factors associated with disease severity, surgical intervention and the risk of mortality.

2. Methods

2.1 Study Design

This retrospective study included neonates diagnosed with NEC between January 2023 and December 2024 at St Mary's Hospital (a tertiary neonatal centre in Manchester, England). Neonates were classified according to whether NEC was surgically managed or medically managed, and evaluated according to mortality status. The focus was on observing patterns in clinical presentation, biochemical markers, and the outcomes between the two groups. No patients or members of the public were involved in the design, conduct, reporting, or dissemination of the research.

2.2 Data Collection

Data in this study were recorded manually from HIVE Electronic Patient Records. Inclusion criteria comprised all cases of necrotising enterocolitis (NEC), both confirmed and suspected, based on clinical documentation within the electronic patient record. Cases were subsequently classified according to modified Bell's staging criteria by a single reviewer to standardise the severity of the disease. All cases were managed at St Mary's Hospital within the defined study period. This included both inpatients and referred patients. Analyses were conducted using available cases for each variable; therefore, any missing data were excluded only from analyses involving that variable, and the extent of missing data was noted where appropriate; no cases were excluded other than those with inadequate data. Due to the retrospective nature of this study, in which all eligible cases during the study period were included, no formal sample size calculation was undertaken. Infants were classified as medical or surgical NEC based on the treatment they ultimately received. Those who had surgical intervention at any point during their admission were classified as surgical NEC, while those only managed conservatively were classified as medical NEC. This meant infants who did not undergo surgery due to clinical instability were classified as medical NEC, regardless of the presence of complications such as pneumoperitoneum.

Where Bell's stage was documented in the medical record, this was recorded and verified against clinical features, laboratory results, and radiological findings. Where staging was not explicitly documented, Bell's stage was assigned retrospectively by a single reviewer using the same predefined criteria. Both individual Bell stages (IA, IB, IIA, IIB, IIIA, and IIIB) and grouped stages (I, II, and III) were recorded for analysis. Cases were subsequently classified by a single reviewer according to the modified Bell staging criteria, based on the original staging system described by Bell et al. and its subsequent modification by Walsh and Kliegman, to standardise assessment of disease severity [8,9].

Table 1. Modified Bell staging criteria used for classification of necrotising enterocolitis [8,9].

Modified Bell stage	Classification	Key criteria used for classification
IA	Suspected NEC	• Temperature instability, apnoea or bradycardia • Mild gastrointestinal features • Normal radiograph or mild intestinal dilatation/ileus
IB	Suspected NEC	• Features of Stage IA • Gross rectal bleeding
IIA	Definite NEC, mildly ill	• Absent bowel sounds • Abdominal tenderness may be present • Pneumatosis intestinalis
IIB	Definite NEC, moderately ill	• Features of Stage IIA • Metabolic acidosis • Thrombocytopenia • Portal venous gas ± ascites
IIIA	Advanced NEC, severely ill, bowel intact	• Hypotension and/or severe apnoea • Metabolic and/or respiratory acidosis • Neutropenia and/or DIC • Signs of peritonitis • No pneumoperitoneum
IIIB	Advanced NEC, severely ill, perforated bowel	• Features of Stage IIIA • Intestinal perforation/pneumoperitoneum

Notes: Author created table summary based on the original Bell staging criteria and subsequent modification by Walsh and Kliegman [8,9]. NEC: necrotising enterocolitis; GI: gastrointestinal; DIC: disseminated intravascular coagulation.

The variables collected included demographic and birth characteristics (gestational age, birth weight, sex, small for gestational age status, inborn status, and five-minute Apgar score); NEC presentation and onset (age at onset, presenting symptoms, pneumatosis, portal venous gas, pneumoperitoneum, NEC management, and Bell stage); clinical and laboratory parameters (C-reactive protein [CRP], white cell count [WCC], neutrophil count, platelet count, haemoglobin, sodium, lactate, blood pH, base excess, and blood culture results); management and treatment variables (feeding method, antibiotics, surgical procedures, timing of surgery, bowel resection, stoma formation and reversal, inotropic support, postoperative CRP, and time to CRP normalisation); and outcomes (length of hospital stay, mortality, complications including intestinal failure, discharge status, and weight at discharge).

When recording laboratory markers, the results noted were from the day of diagnosis or, if the infant was treated based on suspicion, from the day of suspicion (or the nearest available sample). For outborn infants where blood results from the birth hospital were unavailable, the earliest results obtained after admission were used. pH and base excess results were taken from blood gas measurements done during NEC diagnosis. Laboratory markers were recorded on the day of NEC diagnosis or suspicion; if unavailable, the nearest available results were used, with arterial gases preferred to capillary.

Not all babies had reported Apgar scores. Nonetheless, for those who had recorded Apgar scores, only 5-minute Apgar scores were recorded; hence, the use of 5-minute Apgar in this study. For laboratory markers that fell below detection thresholds, standardised values were used.

The feeding method was noted based on the infant's primary enteral nutrition source during the early postnatal period. Though some infants may have only had this type of feeding for a short period of time before being nil by mouth for NEC treatment, it was still documented. Infants exclusively fed breast milk or expressed breast milk were classified as breastfed, while those receiving only formula were classified as formula fed. Infants with documentation of both breast milk and formula at any point were classified as mixed fed. Infants receiving only intravenous fluids or total parenteral nutrition (TPN) since birth were classified as non-enteral feeding.

2.3 Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics (version 30). Categorical variables were analysed using χ^2 or Fisher's exact tests. Continuous variables were summarised using medians and interquartile ranges (IQRs) and compared between medically and surgically managed NEC groups using the Mann-Whitney U test, with effect sizes reported as r where applicable. Categorical variables were compared using Pearson's chi-square (χ^2) test or Fisher's exact test where expected cell-count assumptions were not met. The Kruskal-Wallis test was used for the exploratory comparison of 5-minute Apgar scores across Bell stages. Spearman's rank correlation was used to assess associations between continuous/ordinal variables and outcomes where appropriate. Univariable binary logistic regression was used to assess individual factors associated with mortality, with odds ratios (ORs) and 95% confidence intervals (CIs) reported. An exploratory multivariable binary logistic regression model was used to assess factors independently associated with mortality, and overall model significance was assessed using the likelihood-ratio chi-square test. Model discrimination was evaluated using receiver operating characteristic (ROC) analysis, with the area under the curve (AUC), 95% CI and p-value reported. Sensitivity analyses were performed by excluding the clinically unstable infant with pneumoperitoneum who did not undergo surgery and, separately, by restricting the cohort to infants with Bell Stage II/III NEC. All tests were two-sided, and a p-value <0.05 was considered statistically significant.

2.4 Ethical Consideration

This project did not require formal approval from the NHS Research Ethics Committee. Nonetheless, all data were handled in accordance with NHS data governance protocols. Only anonymised data were used for this study, and no identifiable patient information was included in the report.

3. Results

3.1 Cohort Characteristics

A total of 87 NEC patients were included: 42 managed medically and 45 surgically. For data analysis, the number of infants included is documented in the corresponding tables. In cases where fewer than 87 infants are shown, this reflects missing data for that variable.

For all NEC infants, the median gestational age was 27 weeks, and the median birth weight was 795g. Surgically managed NEC infants had lower gestational age and birth weight; these differences were not statistically significant ($p>0.05$). No significant association was found between being small for gestational age and NEC type (Table 2).

Bell stage was significantly associated with NEC management (Pearson $\chi^2 = 18.04$, $df = 2$, $p < 0.001$). Stage I disease was more common among medically managed infants (66.7% vs 42.2%), whereas Stage III disease was substantially more common among surgically managed infants (40.0% vs 2.4%) (Table 2).

Table 2. Cohort Characteristics: median (IQR) or n(%).

Variable Median(IQR) OR n(%)	Medically managed NEC (n=42)	Surgically managed NEC (n=45)	Test statistic	p-value
Gestational age (weeks)	27 (24-32)	26 (24-28)	U = 759.5	0.113
Birth weight (g)	942.5 (637-1482)	710 (555-1000)	U = 736.0	0.076
SGA (<10th centile)	18 (42.9%)	16 (35.6%)	χ^2 = 0.486	0.486
Mortality	5 (11.9%)	12 (26.7%)	χ^2 = 3.011	0.083
Bell stage (overall)			χ^2 = 18.04	<0.001
Stage I	28 (66.7%)	19 (42.2%)		
Stage II	13 (31.0%)	8 (17.8%)		
Stage III	1 (2.4%)	18 (40.0%)		

3.2 Demographic and Perinatal Factors

When birth weight was grouped as 0-999 g, 1000-1499 g and ≥1500 g, a greater proportion of surgically managed infants were in the 0-999 g category. However, there was no statistically significant association between birth-weight category and NEC management ($\chi^2(2)=3.36$, p=0.187; Figure *1*).

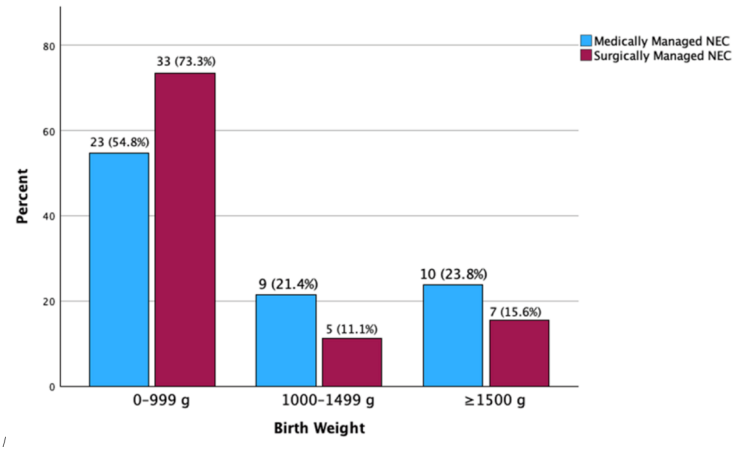


Figure 1. Birth-Weight Distribution by NEC Management Group (N=87).

Notes: Values above bars represent n (% within NEC group).

A Mann-Whitney U test was done to determine whether Apgar scores at 5 minutes differed between neonates with medically managed or surgically managed NEC. Only 41 infants had recorded Apgar scores; analysis was limited to these cases. There was no significant difference between the groups (median 8 vs 7, p = 0.199; Table *3*).

Table 3. Cohort Characteristics of Medical and Surgical NEC.

Variable Median (IQR) OR n(%)	Medical NEC (n=42)	Surgical NEC (n=45)	Test Statistic	p-value
5-minute Apgar score†	8 (6-9)	7 (6-8)	U = 137.0	0.199
Female Gender	18 (42.9%)	13 (28.9%)	χ^2 = 1.848	0.174
Age of NEC Onset (days)	9.0 (5.0-26.5)	7.0 (5.0-17.75)	U = 756.0	0.149
Length of Stay (days) ‡	27.0 (14.5-58.5)	79.5 (38.75-145.75)	U = 555.5	0.001

Notes: Continuous variables are presented as median (IQR) and were compared using the Mann–Whitney U test. Female sex is presented as n (%) and was compared using Pearson's chi-square test. NEC, necrotising enterocolitis; IQR, interquartile range.

† Five-minute Apgar scores were available for 41 of 87 infants (28 medically managed and 13 surgically managed).

‡ One infant had not been discharged at the time of data collection; therefore, length of stay could not be determined.

In an exploratory comparison across Bell stages, median 5-minute Apgar scores were 6.5 (IQR 3; n=24) for Stage I, 8.0 (IQR 3; n=13) for Stage II and 7.5 (IQR 7; n=4) for Stage III. The overall difference across Bell stages was statistically significant (Kruskal-Wallis H=6.836, df=2, p=0.033), although this analysis was based on only 41 infants and was not explored further.

3.3 Clinical Presentation and Disease Onset

For both medically managed NEC and surgically managed NEC patients, statistical significance between the age of onset was not seen (p=0.149; Table *3*). The median time from diagnosis to surgery among infants with surgically managed NEC was 2.5 days (IQR 1-13.5). Timing of surgery was available for 44 of 45 surgically managed infants; data were unavailable for one infant.

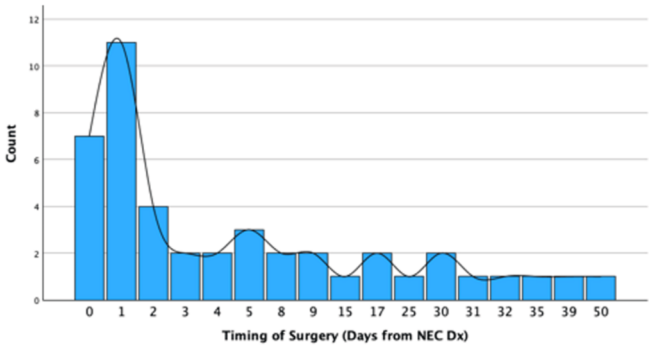


Figure 2. Distribution of Time From NEC Diagnosis to Surgery Among Surgically Managed Infants (n=44)

Notes: Distribution of time from NEC diagnosis to surgical intervention among the 44 surgically managed infants for whom timing data were available. Timing data were unavailable for one of the 45 surgically managed infants.

Most surgical interventions occurred relatively soon after NEC diagnosis, although the distribution was right-skewed, with a small number of infants undergoing surgery substantially later (Figure *3*).

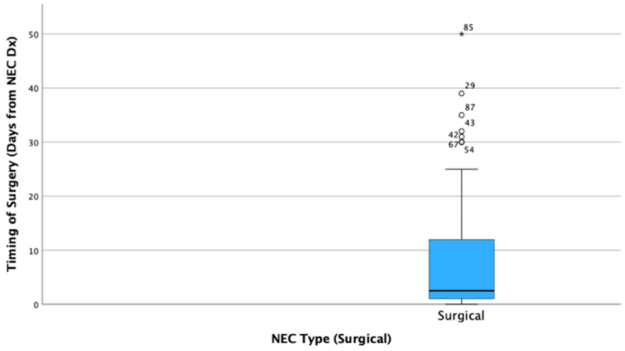


Figure 3. Time From NEC Diagnosis to Surgery Among Surgically Managed Infants (n=44)

Notes: Boxplot showing the distribution of time from NEC diagnosis to surgical intervention among surgically managed infants with available timing data (n=44). Numbers adjacent to individual data points identify the corresponding cases in the dataset; they are SPSS case identifiers and do not indicate the number of days to surgery.

Length of hospital stay was significantly longer in the surgically managed group than in the medically managed group (median 79.5 versus 27.0 days, respectively; p = 0.001; Table 3). This difference is illustrated in Figure 4.

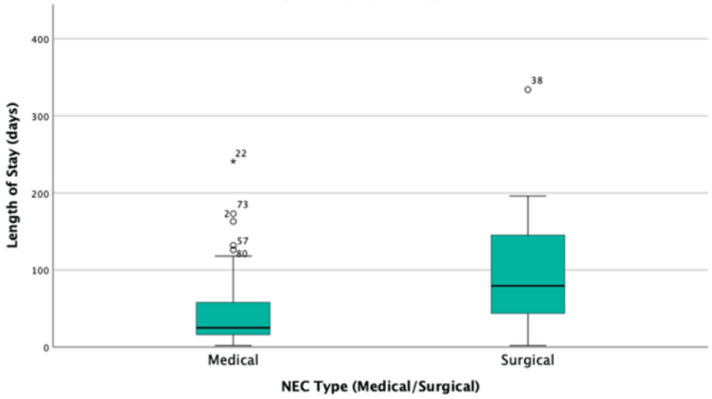


Figure 4. Length of Hospital Stay by NEC Management Type (n=86)

Notes: Boxplot comparing length of hospital stay between medically and surgically managed NEC infants with available data (n=86). Numbers displayed adjacent to individual data points (e.g. 22 and 38) represent SPSS case identifiers and do not represent length of stay in days. Length of stay was unavailable for one infant who had not been discharged at the time of data collection.

3.4 Biochemical Markers

Table 4 summarises the biochemical markers in medically managed and surgically managed NEC. Lactate was significantly higher in surgically managed NEC than in medically managed NEC ($p = 0.028$). CRP was higher in the surgical group, although this difference was not statistically significant ($p = 0.100$). Base excess was significantly lower in surgically managed NEC than in medically managed NEC ($p = 0.025$). No significant differences were observed for WCC, haemoglobin, sodium, neutrophils, platelets or pH (all $p > 0.05$).

Table 4. Biochemical Markers of Medically managed and surgically managed NEC

Marker	Reference range	n†	Medically managed NEC, Median (IQR)	Surgically managed NEC, Median (IQR)	Mann–Whitney U	p-value	Effect size (r)
WCC (×10⁹/L)	6–21 ×10⁹/L	87	10.95 (8.05–17.78)	11.45 (5.13–20.95)	889.5	0.637	0.05
Hb (g/L)	110–180 g/L	83	110.5 (95.0–119.8)	113.0 (98.0–135.0)	874.0	0.546	0.07
Na (mmol/L)	132–142 mmol/L	87	137.0 (133.0–141.0)	139.0 (135.0–142.75)	779.0	0.158	0.15
Lactate (mmol/L)	0.6–2.5 mmol/L	87	1.60 (1.10–3.20)	2.40 (1.50–4.40)	668.0	0.028	0.24
Neutrophils (×10⁹/L)	1.5–10 ×10⁹/L	86	5.15 (3.47–10.00)	5.10 (1.84–12.13)	878.5	0.704	0.04
Platelets (×10⁹/L)	150–500 ×10⁹/L	86	176.5 (87.75–266.0)	167.0 (86.0–216.0)	794.0	0.261	0.12
CRP (mg/L)	<1 mg/L	87	4.50 (1.00–40.75)	29.00 (2.25–73.50)	752.5	0.100	0.18
pH	7.35–7.45	87	7.29 (7.23–7.34)	7.27 (7.19–7.33)	829.0	0.324	0.11
Base excess (mmol/L)	-2.0 to +2.0	87	−2.1 (−4.45 to 1.18)	−5.7 (−8.15 to −0.70)	681.0	0.025	0.24

Notes: Values are presented as median (IQR). Comparisons between medically and surgically managed NEC infants were performed using the Mann–Whitney U test. NEC, necrotising enterocolitis; IQR, interquartile range; WCC, white cell count; Hb, haemoglobin; Na, sodium; CRP, C-reactive protein. Sample size differs where laboratory values were unavailable.

† Sample size differs because of missing laboratory values.

3.5 Radiological findings

Pneumoperitoneum was a characteristic radiological finding, present in 19.5% of infants. A large number of these were seen in surgically managed NEC infants (16/45; 35.6%) compared to medically managed NEC (1/42; 2.4%). This difference was statistically significant (p<0.001; Table *5*).

Table 5. Comparison of Radiological Findings and p value in Medically managed and Surgically managed NEC.

Radiological finding	Medical NEC (n=42), n (%)	Surgical NEC (n=45), n (%)	Test statistic (χ^2)	p-value	Statistical test
Portal venous gas	1 (2.4%)	0 (0.0%)	—	0.483	Fisher's exact
Pneumoperitoneum	1 (2.4%)	16 (35.6%)	15.207	<0.001	Pearson χ^2
Pneumatosis	12 (28.6%)	10 (22.2%)	0.464	0.496	Pearson χ^2

Notes: Data are presented as n (%). Comparisons were performed using Pearson's χ^2 test where expected cell-count assumptions were satisfied and Fisher's exact test where these assumptions were not met. NEC, necrotising enterocolitis. — indicates that no χ^2 statistic is reported for Fisher's exact test.

Pneumatosis was observed in 12 medically managed and 10 surgically managed NEC cases, with no significant difference between groups (p=0.496; Table *5*).

Portal venous gas was documented in one infant with medically managed NEC; this finding was not associated with NEC type (p=0.483; Table *5*).

3.6 Microbiology and Feeding

57.8% of surgically managed NEC infants had positive blood cultures, compared with 28.6% in the medically managed group. Further analysis using logistic regression supported this finding, with positive blood cultures being associated with increased odds of surgically managed NEC (OR 3.42, 95% CI 1.40-8.36, p=0.007).

Breast milk use was similar between the two groups. Mixed feeding was more common in medically managed NEC, while parenteral nutrition was more common in surgically managed NEC. However, these differences were not statistically significant (Chi-square; $\chi^2(3) = 2.227$, p = 0.527).

Feeding methods are shown in Table *6*.

Table 6. Comparison of Feeding Types Between Medically and Surgically Managed NEC.

Feeding Type	Medical NEC (n=42)	Surgical NEC (n=45)	Total (n=87)	Test statistic	p-value
Breast milk	17 (40.5%)	17 (37.8%)	34 (39.1%)		
Formula	3 (7.1%)	4 (8.9%)	7 (8.0%)		
Mixed	12 (28.6%)	8 (17.8%)	20 (23.0%)		
IV	10 (23.8%)	16 (35.6%)	26 (29.9%)	**$\chi^2 = 2.227$**	**0.527**
Total	42	45	87		

3.7 Antibiotic Regimens

The most commonly prescribed antibiotic combinations in both groups were cefotaxime, vancomycin and metronidazole, with no clear differences in prescribing patterns between medically and surgically managed NEC (Figure 5).

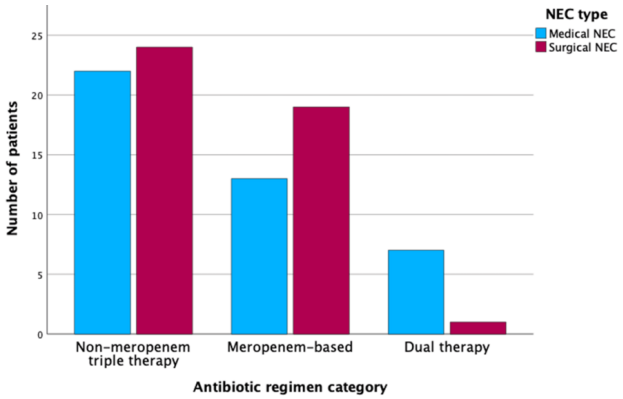


Figure 5. Distribution of Antibiotic Regimens in Medically (n=42) and Surgically Managed (n=45) NEC Infants.

Notes: Bar chart showing the number of medically and surgically managed NEC infants receiving each antibiotic regimen.

3.8 Surgical Procedures: Resection and Stoma Formation

Detailed operative data were available for 43 of the 45 surgically managed patients. Among these, bowel resection with stoma was the most frequently performed procedure, occurring in 26 infants (Table 7).

Table 7. Breakdown of Surgical Procedures Among Surgically Managed NEC Infants.

Feature	n (%)
Bowel resection only	7 (16%)
Stoma formation only	4 (9%)
Both	26 (61%)
Neither (e.g. exploratory laparotomy only)	6 (14%)

Notes: Specific surgical procedure data were unavailable for two infants; therefore, percentages are based on infants with available data (n = 43).

Seven infants (16%) underwent only resection, and four (9%) had only stoma formation. Six patients (14%) underwent exploratory laparotomy due to disease being too extensive for bowel resection or stoma formation.

Postoperative outcomes are summarised in Table *8*.

Table 8. Postoperative Outcomes in Surgically Managed NEC Infants (n=43)

Outcome	n (%)
Required inotropes	3 (7%)
Post-op CRP >150	9 (21%)
CRP normalised <7 days	3 (7%)
Stoma reversed	22 (51%)
Intestinal failure	1 (2%)

Inotropic support was required in three patients (7%). Nine patients (21%) exhibited a CRP above 150 mg/L after 24 hours, and CRP normalised within 7 days in three patients (7%). Twenty two infants (51% of surgical cohort) underwent stoma reversal during follow up. One patient developed intestinal failure following surgery.

3.9 Mortality

Overall mortality following NEC admission was 19.5% (17/87). Mortality was higher among surgically managed NEC infants (26.7%) than medically managed NEC (11.9%), although this difference was not statistically significant (p=0.083; Table *2*). Lactate was positively correlated with mortality (p=0.003), with a weak to moderate correlation coefficient (ρ = 0.314).

In a univariable logistic regression analysis, platelet count was the only significant variable associated with mortality (OR 0.990, 95% CI 0.982-0.998; p=0.019; Table *9*).

Table 9. Univariable Logistic Regression Analysis of Factors Associated With Mortality in NEC.

Variable	n	p-value	OR	95% CI
Lactate (mmol/L)	87	0.730	0.988	0.921–1.059
CRP (mg/L)	87	0.742	0.998	0.986–1.010
NEC type (surgical vs medical)	87	0.149	2.523	0.718–8.862
WCC (×10⁹/L)	87	0.957	1.003	0.892–1.128
Neutrophils (×10⁹/L)	86	0.483	1.057	0.906–1.233
Platelets (×10⁹/L)	86	0.019	0.990	0.982–0.998

Notes: Univariable binary logistic regression was performed with mortality as the outcome (survival=0; death=1). For NEC type, medically managed NEC (0) was the reference category, and surgically managed NEC was coded as 1. Odds ratios for continuous predictors are reported per 1-unit increase in the measured value of the variable. OR, odds ratio; CI, confidence interval; NEC, necrotising enterocolitis; CRP, C-reactive protein; WCC, white cell count. Sample size differs where laboratory values were unavailable.

An exploratory multivariable logistic regression model including lactate, platelet count, and NEC management remained statistically significant overall (χ^2=11.881, df=3, p=0.008), with platelet count remaining independently associated with mortality (OR 0.991, 95% CI 0.984-0.998; p=0.014; Table *10*).

Table 10. Multivariable Logistic Regression Analysis of Factors Associated With Mortality in NEC (N=86)

Variable	OR (Exp(B))	95% CI	p-value
Lactate (mmol/L)	0.985	0.924–1.050	0.640
Platelets (×10⁹/L)†	**0.991**	**0.984–0.998**	**0.014**
NEC type (surgical vs medical)	2.690	0.799–9.061	0.110

Notes: Multivariable binary logistic regression was performed with mortality as the outcome (survival=0; death=1). The model included 86 infants. Medically managed NEC (0) was the reference category for NEC type, with surgically managed NEC coded as 1. Odds ratios for continuous predictors are reported per 1-unit increase in the measured value of the variable. Overall model significance was assessed using the likelihood ratio chi-square test ($\chi^2(3) = 11.881$, $p = 0.008$).

†Platelet data were missing for one infant.

The exploratory multivariable model demonstrated an AUC of 0.737 (Figure *6*).

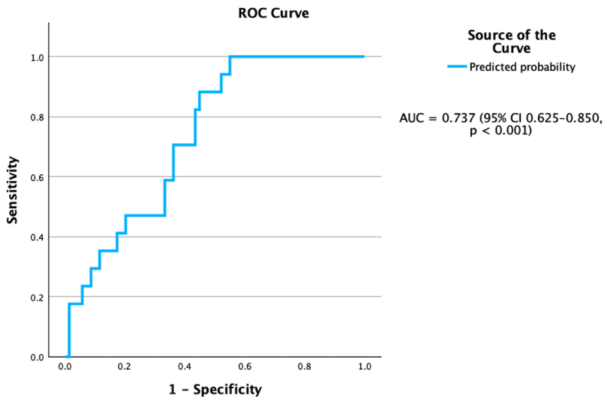


Figure 6. Receiver Operating Characteristic Curve for the Multivariable Mortality Model.

Notes: Receiver operating characteristic (ROC) curve for the exploratory multivariable logistic regression model assessing mortality (n=86). The model demonstrated an AUC of 0.737 (95% CI 0.625–0.850, p<0.001).

3.10 Sensitivity Analyses

A sensitivity analysis excluding the infant with pneumoperitoneum who did not undergo surgery because of clinical instability, yielded similar findings. Higher lactate levels (p=0.017), positive blood cultures (Fisher's exact p=0.010), and lower base excess (p=0.015) remained significantly associated with surgically managed NEC, while the other markers remained materially unchanged.

In a sensitivity analysis restricted to Bell Stage II/III NEC (n=40), only base excess remained significantly associated with surgically managed NEC (p=0.013). Within this restricted cohort, there were no significant differences between the medically managed and surgically managed groups in lactate, blood culture positivity, CRP, WCC, neutrophil count, platelet count, pH, or mortality (all $p > 0.05$).

4. Discussion

4.1 Principal Findings

This study identified clinical, biochemical, microbiological, and radiological markers in order to identify markers of disease severity and mortality in Necrotising Enterocolitis. Bell's staging remained strongly associated with disease severity and need for surgical management.

In the overall cohort, elevated lactate levels, lower base excess, positive blood cultures and pneumoperitoneum were associated with surgically managed NEC. Elevated lactate and lower base excess may reflect the greater physiological compromise and metabolic acidosis seen in infants requiring surgical intervention. Positive blood cultures were also substantially more frequent in surgically managed NEC, suggesting an association between those with bloodstream infection and infants who ultimately require surgical management. Pneumoperitoneum was strongly associated with surgically managed NEC. However, as pneumoperitoneum is an established indication for surgical intervention, this finding is closely related to the management decision itself and should not be interpreted as an independent early marker for surgery.

In the sensitivity analysis restricted to Bell Stage II/III NEC, only base excess remained significantly associated with surgically managed NEC. Lower base excess in surgically managed infants may reflect greater metabolic acidosis, however, this finding should be interpreted as a potential marker requiring further validation.

Platelet count was the only laboratory marker that was independently associated with mortality in the exploratory multivariable analysis, likely reflecting the haematological disturbance associated with systemic inflammation in severe NEC. Feeding practices did not differ significantly, indicating the prioritisation of breast milk in both surgically managed and medically managed NEC cases as soon as they are suspected. Although mortality was higher in surgically managed NEC than medically managed NEC, this difference was not statistically significant. An exploratory multivariable regression model including these markers demonstrated moderate discrimination in predicting mortality, although the limited number of mortality records limits conclusions about its predictive performance.

4.2 Comparison with Existing Literature

The finding that higher Bell's stages were concentrated in surgically managed NEC cases supports prior work. Yu et al. reported that no medically managed infants presented with stage IIA or IIB, while Song et al. developed a nomogram distinguishing between stage I and stages II/III with strong discrimination [10,11].

Lactate was significantly higher in surgically managed NEC and correlated with mortality in the present cohort. This agrees with the findings of Ahmed et al., who reported lactate 6.95 mmol/L or greater had 75% sensitivity and 100% specificity for surgical NEC [12]. Other studies also confirm rising lactate and CRP in surgical cases, and associations with mortality [13,14]. In the present analysis, lactate was associated with surgically managed NEC and should be interpreted in the wider clinical context rather than as a standalone marker.

Other laboratory markers, such as CRP, WCC, neutrophil count, and haemoglobin, trended higher in surgically managed NEC but did not reach statistical significance. This differs from Wang et al., who found significantly higher CRP in surgical infants, and Sokou et al., who reported CRP, platelet count, and neutrophils as valuable severity indicators [13,15]. Our lack of significance may be attributable to the limited sample size and the reliance on single measurements rather than serial measurements.

Platelet count was the only independent marker of mortality in our study, consistent with Sokou et al. and Zhang et al., who linked thrombocytopenia to increased risk of death and need for surgery [15,16]. This reinforces its prognostic value for identifying high-risk infants.

Microbiologically, positive blood cultures were significantly associated with approximately threefold greater odds of surgical management. Uauy et al. similarly found associations between bacteraemia and stage III NEC with mortality, while Garg et al. noted 25% of premature NEC infants had positive cultures [17,18]. This supports the role of systemic infection in driving severity and influencing treatment decisions.

Radiologically, pneumoperitoneum was strongly associated with surgically managed NEC in our cohort, showing its role as a recognised marker of bowel perforation and an indication for surgical intervention. However, literature shows that only 50% of confirmed perforations are radiologically visible [19]. Pneumatosis intestinalis and portal venous gas were not discriminatory here, echoing findings from Neu et al. and Tam et al. [20,21]. Portal venous gas, historically viewed as ominous, has also been shown by Sharma et al. and Ricketts & Jerles to be a poor predictor of surgical need [22,23].

Feeding practices showed no significant association with NEC type. This is at odds with Quigley et al.'s meta-analysis demonstrating a protective effect of human milk [24]. The lack of association may reflect current neonatal practice, where breast milk or donor milk is prioritised once NEC is suspected, thereby minimising exposure differences.

4.3 Limitations

This study had several limitations. The sample size (n = 87) may have limited statistical power to detect differences in some variables, such as CRP and neutrophil count, despite observed trends. Only 17 deaths occurred, limiting the reliability of multivariable mortality analysis. Additionally, a small proportion of infants (8.0%) presented with early isolated pneumoperitoneum, suggesting overlap between the diagnosis of necrotising enterocolitis (NEC) and spontaneous intestinal perforation (SIP) in retrospective datasets and may lead to a misclassification bias.

As Bell's staging was retrospectively assigned for a proportion of cases by a single reviewer, there is a possibility of misclassification and observer bias. Inclusion of Bell Stage I cases may have introduced diagnostic heterogeneity. Sensitivity analysis restricted to Bell Stage II/III NEC attenuated some associations, highlighting the importance of diagnostic certainty. Feeding classifications were based on the primary source documented in the early postnatal period; however, possible changes in feeding over time were not recorded. Blood marker timing was standardised to diagnosis or suspicion, but variability remained, and single measurements may not reflect peak values. Serial readings of these markers could improve prognostic value. The retrospective design prevented confirmation that laboratory measurements preceded the decision for surgery. The retrospective dataset did not allow consistent distinction between true bacteraemia and contamination, particularly coagulase-negative staphylococci. Additionally, although platelet count predicted mortality, more specific indices (such as MPV and PDW) were not routinely available and could not be analysed, limiting the depth of haematological assessment. Therefore, these limitations could have resulted in an underestimation of the strength of associations between clinical markers and the need for surgical intervention or mortality. The exploratory mortality model requires external validation. In addition, classification according to treatment received may not always reflect the underlying biological severity of NEC, as some infants with severe disease may not undergo surgery because of clinical instability. However, sensitivity analysis excluding this case produced similar results, suggesting the main findings were robust.

4.4 Future Research Directions

Future studies should involve larger, multicentre cohorts to improve generalisability and reduce centre-specific bias. Analysis of serial biochemical markers, rather than single measurements, may improve predictive accuracy. Alternative classification models could integrate markers of NEC severity and the need for surgery. Given the findings regarding platelet count, future studies should also assess platelet levels and function in relation to surgical intervention and coagulopathy. Although future multicentre studies would improve generalisability, the single-centre retrospective design of the present study may limit its usefulness for other neonatal populations. As this study was conducted in a tertiary surgical unit that manages a higher proportion of severe and surgically managed NEC cases, differences in referral patterns across neonatal centres may affect generalisability. Nevertheless, the consistency of findings based on existing literature supports relevance to similar high-acuity settings.

5. Conclusions

This retrospective cohort study identified several markers associated with disease severity and clinical outcomes in NEC. Higher lactate, lower base excess, positive blood cultures, and pneumoperitoneum were associated with surgically managed NEC in the overall cohort, although only lower base excess remained significantly associated with surgical management when the analysis was restricted to Bell Stage II/III disease. Platelet count was independently associated with mortality in the exploratory multivariable analysis.

These findings suggest that these routinely available biochemical, microbiological, and radiological markers analysed in this study may provide additional information when assessing disease severity in infants with NEC. Larger prospective multi-centre studies incorporating serial measurements are required to determine whether these markers, individually or in combination, can improve risk stratification and help identify infants at greatest risk of deterioration or adverse outcomes.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this article.

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