INTRODUCTION

Necrotising enterocolitis (NEC) represents one of the most common and challenging neonatal surgical emergencies. NEC occurs in 1 to 3 per 1000 live births, and with 1 in 4 of these babies requiring emergency surgical intervention, significant morbidity and mortality are associated with the disease. While low birthweight and prematurity are well recognised NEC risk factors, NEC is also encountered in...
term infants and in these cases may co-exist with other co-morbidities reportedly with a more fulminant onset.5,6

Operative survival rates for NEC vary widely in the literature. Battersby et al’s 7 systematic review study initially identifies 1888 papers reporting NEC outcomes in high-income countries, in those chosen for review mortality rates ranged from 21.9% to 38%. Notable amongst those cited is a report from Youn et al (Korea) who analysed survival outcomes for surgically managed VLBW (<1500 gm) NEC newborns (n = 77) recording a 29% mortality in this subgroup.8 A study from Finland has further shown a 27% overall mortality rate for pre-term NEC infants having operation.9

Alder Hey Children’s NHS Foundation Trust is a UK tertiary specialist centre serving a catchment population of over 4.5 million where our regional service operates and manages an integrated neonatal network to triage all newborns requiring neonatal surgery. Within the network, decision to transfer a neonate for surgical review and operation is made between neonatologists and paediatricians in referring hospitals in consultation with the ‘on-call’ attending paediatric surgeon. Criteria defining indication(s) for operative intervention at our paediatric surgery centre include (a) cases of intestinal perforation and pneumoperitoneum, (b) bowel obstruction, (c) persistent inflammatory mass (d) and/or failure of maximum medical NEC conservative therapy(s). Operative strategy is determined by the duty surgeon and includes central venous catheter insertion (Bard® Broviac) or a secure peripheral venous access long line to facilitate resuscitation (antibiotics, blood products, inotropes, etc), laparotomy, bowel resection and/or stoma formation, or the use of the ‘clip and drop’ back technique when babies are very unstable. Post-operatively, we practise a care pathway where infants are re-located after immediate post-operative stabilisation back to tertiary-level NICUs within the regional network. A system is successfully undertaken and reported by other centres worldwide.10-14

This study herein examines trends in survival and outcomes in a 15-year period for all babies having emergency laparotomy for NEC at Alder Hey Children’s NHS Foundation Trust. We survey the influence of common variables such as year of birthweight, gestational age, congenital cardiac anomaly(s) requiring intervention, presence of pneumoperitoneum at presentation and area of diseased bowel segment affected on mortality (30 days and 1 year) in an effort to develop a mortality predictor. We have chosen these defined timescales as mortality at 30 days post-operatively is a well-established standard surgical metric for ‘operative complication(s)’. Large UK-wide cohort studies likewise utilise 1-year mortality as a long-term indicator of co-morbid outcome(s).15 This study also explored the effect of gestational age on the timing (postbirth) of emergent operation for NEC and its relationship (if any) to infant survival.

2 | METHODS

A retrospective search of all medical case records ICD coded as ‘NEC’ OR “Necrotising Enterocolitis” over the 15-year period was performed. Case records were then reviewed to obtain the total number of patients (N = 243) having operative management of NEC defined as ‘those undergoing laparotomy, with stated operative findings consistent with necrotising enterocolitis AND pathology reports confirming necrotising enterocolitis’. Other varied intestinal pathologies such as meconium inspissation syndrome(s) leading to gut perforation or spontaneous isolated intestinal perforations (SIPs) were excluded if they could not fit the above strict inclusion criteria.

Data were collected from electronic patient record systems (EPRs), scanned ‘hard copy’ medical records, operation logs and pathology departments. Where available we made effort to collect comprehensive data on gestation, birthweight, pneumoperitoneum on clinical presentation/referral, bowel sector region involved—small bowel (focal), large bowel (focal), small and large bowel (multifocal), pan-intestinal NEC, cardiac anomaly requiring surgical intervention, and age postbirth at surgery.

Data were analysed using SPSS. Descriptive statistics of the cohort were produced, and univariate logistic regression was then deployed to further analyse whether the recorded variables of gestation, birthweight, free air (at presentation), and type of bowel region involvement (focal, multifocal, pan-intestinal NEC) and/ or need for cardiac surgery had any significance on 30 days and 1-year mortality rate(s).

Base on the results from the univariate analysis, variables were chosen to perform a multivariate multiple regression model which was then used to produce a graphical post-operative NEC predictive mortality score.

3 | RESULTS

3.1 | Descriptive statistics and mortality figures

The data are non-normally distributed (median and interquartile ranges have been used where appropriate). The population range—the male:female ratio was 3:2, median (IQR) gestation was 28 weeks (25-31), and median (IQR) birthweight was 1030 grams (780-1537). The cohort study population was then analysed in 5-year consecutive time periods (2000-2004, 2005-2009, 2010-2014) to critically evaluate trends (if any) in survival that could be correlated with improving neonatal care of the pre-term infant particularly those born at the margins of gestational viability. As no statistical difference(s)
| Gestation (wk) | Birthweight (grams) | Age at surgery (d) | Free air (N = 161 imaged) | Area affected by NEC (N = 237 histology) | Cardiac defect requiring surgery (N = 243) | 30-d mortality | 1-y mortality |
|---------------|---------------------|-------------------|---------------------------|------------------------------------------|------------------------------------------|---------------|--------------|
| <28 wk        | 25 + 4 (25-26 + 5)  | 788, 684-920      | 22, 9-31                  | 1-96/126 (76%) 2-10/126 (8%) 3-10/126 (8%) 4-10/126 (8%) | 9/128 (7%) | 28% (36/128) | 45% (58/128) |
| 28-<32 wk     | 29 + 2 (28-30)     | 1200, 963-1400    | 24, 5-32                  | 1-48/66 (73%) 2-6/66 (9%) 3-9/66 (14%) 4-3/66 (5%) | 3/69 (4%) | 12% (8/69)  | 21% (15/69) |
| 32-<37 wk     | 33 + 5 (33-34)     | 1790, 1400-2225   | 20, 3-27                  | 1-14/27 (52%) 2-5/27 (19%) 3-6/27 (22%) 4-2/27 (7%) | 1/27 (4%) | 7% (2/27)   | 15% (4/27)  |
| >37 wk        | 38 + 3 (37-40)     | 3065, 2476-3576   | 9, 3-11                   | 1-8/18 (44%) 2-7/18 (39%) 3-2/18 (11%) 4-1/18 (6%) | 4/19 (21%) | 0% (0/19)   | 5% (1/19)   |
| Totals        | 28 + 4 (25-30 + 2) | 1250 (760-1400)   | 22, 6-30                  | 1-166 (70%) 2-28 (12%) 3-27 (11%) 4-16 (7%) | 17 | 18.9% | 32% |

Note: NEC disease is coded: 1 = small bowel, 2 = colon, 3 = illeo-colic and 4 = pan-intestinal disease.
Area affected by NEC key: 1—small bowel, 2—colon, 3—ileo-colic, 4—pan-intestinal
in mortality were found within the 5-year sub-sets, further data analysis was then undertaken for the whole patient cohort. When the total patient NEC population is considered, the 30-day mortality rate was 18.9% \((n = 46)\) and the 1-year mortality rate was 32\% \((n = 78)\). Since year 2000, the overall survival rate at the extremes of viability \(<28\) weeks\) was 72\% at 30 days with Table 1 showing mortality at 30 days and 1 year.

Factors impacting mortality on the total patient NEC cohort of 243 cases were further examined. Patients \(<27\) week\(s)\) represented over half of our total index case mix load, with a median gestation age of 25 + 4 weeks and birthweight 788 grams. Imaging available for full review in 50\% of these neonates demonstrated free air with 76\% cases having only small-bowel involvement. Mortality was highest here in this subgroup. Table 1 shows a decreasing younger age at operation, with a declining prevalence of small-bowel NEC disease involvement with increasing gestational age and a corresponding increased burden of colonic segment NEC (40\%) and associated cardiac defects (21\%) in the term cohort.

### 3.2 | Operative strategy

Of the 243 patients having operations for NEC, 3 cases underwent ‘clip and drop back’ procedures, 11 had resection with primary anastomoses and 229 babies resection and enterostomy formation ± a downstream anastomosis in defunctioned bowel. There were 6 planned ‘second look’ procedures, of which 4 patients all here with pan-intestinal NEC disease died. Twenty-five patients (10\%) required further abdominal surgery before reversal of stoma, 2 of these were cases operated at other UK centres and transferred to our unit for further management. Three babies had an initial primary anastomosis and associated complications requiring stoma formation. The remaining patients required operations for further recurrent NEC disease progression including management of strictures and/ or intestinal obstruction with adhesiolysis, or management of stoma complications. There were no statistical differences found in outcome\(s\) for the operative technique deployed. Mortality in this cohort group was 24\% \((6/25)\).

### 3.3 | Mortality

Of a total of 78 deaths recorded at 1 year post-operatively, causes of mortality were fully available for 41 infants. This was linked to EPR hospital systems upgrades at the midpoint of study. Available data clearly showed that death within 30 days was equally due to (a) NEC disease severity, (b) overwhelming systemic sepsis and (c) physiological derangement\(s\) with NEC, OR a progressive unsurvivable concomitant pathology notably cardiac, respiratory or neurological sequelae. Late mortality was primarily linked to other system\(s\) pathology and the consequences of prematurity (eg BPD lung disease, neurological disorders, cardiac illness) with a smaller mortality case load related to post-NEC short-bowel syndrome or further abdominal surgery\(\)\(\).
Mean time to operation in the term neonate was 9 days and 22 days in those who were pre-term, applying a correlation analysis to 'time to surgery' we found here a 'decreasing time to definitive operative intervention' represented by the median (IQR) values shown in Table 1 which was statistically significant; negative Pearson correlation ($P$-value 0.027) (Figure 1).

### 3.5 Statistical analysis and mortality predictor

A univariate linear regression model was conducted using SPSS looking at all collected variables (including year of surgery) and their effect on 1-year mortality. Table 2 here details $P$-values and odds ratios (95% CI) for the regression calculations with mortality at 1 year as the dependent variable. Gender had no significant influence(s) on survival outcome. Birthweight and gestational age both demonstrated statistical significance with increasing gestational age and larger birthweight newborns being more likely to survive NEC. Risk categorisation analysis showed that the presence of free air and pan-intestinal NEC was associated with an increased 1-year mortality rate (odds ratio pneumoperitoneum $-1.85$ ($P$-value: 0.07), odds ratio pan-intestinal NEC $-5.56$ ($P$-value 0.006)).

Using significant variables of gestation and the area of bowel region involved a multivariate multiple regression model was then deployed to produce a predictive mortality score with presence here of pneumoperitoneum also included. Using these variables (gestation, involved bowel region and free air) in a forward build of the model, significance ($P$-value < 0.05) was maintained (model $P$-value $-0.049$)–Table 3. Applying information from the multivariate model, sigma plot allowed us to develop a graph permitting the operator to

| Variable | Incidence | $P$-value | Odds ratio (95% CI) |
|----------|-----------|-----------|-------------------|
| Gender (N = 243) | Male sex | 150 (62%) | 0.75 | 0.92 (0.52-1.60) |
| | Female sex | 93 (38%) |  |
| Birthweight (N = 227) | <1000 g | 113 (50%) |  |
| | 1000 g-21500 g | 95 (42%) | 0.0002 | 0.40 (0.22-0.74) |
| | >2500 g | 19 (8%) | 0.08 (0.01-0.60) |
| Gestation (categorical) (N = 243) | <28 wk | 128 (53%) |
| | 28-<32 wk | 69 (28%) |  |
| | 32-<37 wk | 27 (11%) | <0.0001 | 0.22 (0.07-0.66) |
| | >37 wk | 19 (8%) | 0.07 (0.01-0.53) |
| Gestation (continuous) | Gestation continuous (per wk) | <0.0001 | 0.81 (0.71-0.89) |
| Free air (N = 165) | no | 98 (59%) | 0.07 | 1.85 (0.95-3.62) |
| | yes | 67 (41%) |  |
| Bowel (N = 237) | 1&2 (focal) | 194 (82%) |  |
| | 3 (multifocal) | 27 (11%) | 1.10 (0.44-2.6) |
| | 4 (pan-intestinal) | 16 (7%) | 0.006 | 5.56 (1.85-16.74) |
| Underwent cardiac surgery (N = 243) | no | 226 (93%) | 0.86 | 0.91 (0.31-2.68) |
| | yes | 17 (7%) |  |

### Table 3 Multivariate multiple regression model

| Coefficients$^a$ | Unstandardised Coefficients | Standardised Coefficients |
|------------------|-----------------------------|---------------------------|
| Model | B | Std. Error | Beta | t | Sig. |
| 1 (Constant) | 1.011 | 0.277 | 3.649 | 0.000 |
| Gestation | -0.029 | 0.009 | -0.247 | -3.291 | 0.001 |
| bowel | 0.157 | 0.050 | 0.232 | 3.118 | 0.002 |
| free air | -0.140 | 0.071 | -0.150 | -1.984 | 0.049 |

$^a$Dependent variable: 1-y mortality.

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predict mortality for gestational age by incorporating the variables of free air and region of bowel involvement—see Figure 2.

4 | DISCUSSION

This UK single-centre study shows good survival outcomes for NEC babies with low 30-day and 1-year mortality metrics consistent with large UK nationwide reports. These outcomes have been achieved with a clinical network utilising co-location to regional NICUs to facilitate post-operative recovery demonstrating the effectiveness of integrated service led pathways. This UK cohort study is therefore widely supportive of data published elsewhere from other centres of this safe practice.

We demonstrate a significant relationship with gestational age and birthweight to NEC 30-day and 1-year mortality rate(s). Our analysis showed that anatomically localised NEC disease yields improved survival outcomes compared to more regional intestinal involvement. Previous reports exist to suggest that pneumoperitoneum does not adversely affect infant survival though we have found in this current study an increased odds ratio for mortality in patients demonstrating ‘free air’. Death at 30 days is most often attributable to the disease consequence(s) of NEC. This direct link thereafter diminishes as late mortality at 1 year which we have shown is often due to other system co-morbidities and the consequences of prematurity.

In this study, particular note should be taken of the findings we report relating to term NEC. A statistically significant correlation was observed in this current study between increasing gestation age and a younger age at emergency laparotomy likely demonstrating a more rapid fulminant progress of NEC in the term newborn. These data findings thus support previously published work by Andrews et al and Ostlie et al. Our term NEC data set results (Table 1) also further confirm the previous recorded findings of an increased incidence of colon bowel sector involvement and the added burden of cardiac surgery in the mature infant. We speculate term NEC may well have a very different aetiology and pathogenesis to its pre-term disease counterpart.

This study also included babies undergoing cardiac surgery as this cohort clearly showed that significant cardiac pathology requiring intervention (PDA’s, Fallot’s Tetralogy, Hypoplastic Arch, etc) is not contraindications for operative management of NEC. Mortality in this special group of infants at 30 days was 6% (1/17) and at 1 year 24% (5/17).

Mortality at 1 year was deployed in our logistic regression modelling tool in an effort to generate a predictive patient outcome model. This model was built on NEC disease classification, that is focal, multifocal and pan-intestinal NEC to demonstrate significance with bowel sector involvement and pneumoperitoneum. This model represents ‘a first step’ in guiding post-operative counselling to parents with regard to mortality risk(s) associated with surgery in the management of advanced NEC. Here, we acknowledge that increasing patient case load numbers and larger data sets gathered prospectively may potentially add to the utility and accuracy of a ‘new’ NEC predictive model.

With ‘improving’ survival now achieved by surgery in the sickest NEC babies, key findings of the ORACLE study and Matei

**FIGURE 2** Demonstrates an NEC outcome predictive mortality score. Using sigma plot to build the multivariate analysis (gestation, bowel, free air: P-value 0.049). The graph plot defines %risk of mortality at 1 y according to anatomical site region of disease and the presence of free-air pre-op with gestational age (wk)
et al’s 23 recent publication are worthy of mention in closing. These reports clearly show the long-term consequences of NEC on gut function, motor, sensory, and neurodevelopmental/cognitive outcome(s) highlighting the significant morbidity on patient quality of life. Healthcare teams and paediatric surgeons should be wholly mindful therefore of their professional responsibilities when counselling parents. 22, 24, 25

5 | CONCLUSION

In summary, this study shows good survival outcomes for advanced NEC in babies managed in a single UK centre adopting a care pathway for emergency laparotomy in the setting of a collaborative neonatal network. 26 The increased mortality observed in infants during the first year of life (from 30 days to 1 year) at all gestational ages demonstrates the ongoing challenges these vulnerable infants sustain from the additional co-morbidities of prematurity and chronic illness. 3, 27

Gestational age and birthweight are once again confirmed as the largest contributing factor(s) to high mortality in NEC newborns. Extent of anatomical region of bowel sector involvement and presence of ‘free air’ are added variables that lend themselves to future predictive analysis.

In this study, we further uncovered the interesting observation notably a statistically significant link between gestational age of babies acquiring NEC and their time course to emergent operation, that is a rapid fulminant progress of disease with failure of conservative medical therapy(s). The study findings also demonstrate that NEC even in the term newborn additionally carries late mortality (5% at 1 year follow up). This late mortality in a term cohort group appeared linked to the consequence(s) of cardiac co-morbidities. We conclude that NEC survival metrics may be usefully predicted by exploring statistical modelling tools that may be of value in guiding future NEC collaborative multicentre studies.

CONFLICT OF INTEREST

There are no conflicts of Interest for any authors.

ETHICAL APPROVAL

Ethical approval was not required for this study.

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