

Evaluation of the pan-immune-inflammation value (PIV) as a prognostic and surgical decision-making marker in necrotising enterocolitis

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ABSTRACT

Aims: Necrotizing enterocolitis (NEC) is a complex gastrointestinal disorder characterized by intestinal wall necrosis and a high mortality rate. The pan-immune-inflammation value (PIV) is a novel biomarker that reflects systemic inflammation and immune response, calculated from blood counts of neutrophils, platelets, monocytes, and lymphocytes. The present study evaluates the utility of PIV, an accessible and cost-effective parameter, in patients with NEC and investigates its potential to differentiate between those who recover with medical management and those who require surgical intervention.

Methods: Data from 793 patients admitted to the neonatal intensive care unit (NICU) between May 2018 and November 2022 were analyzed in a retrospective single-centre cohort study. The study included 40 NEC patients (stages 1, 2, and 3) and 753 control subjects (218 preterm, 535 term). The PIV [(neutrophils×platelets×monocytes)/lymphocytes] was calculated using complete blood count results obtained on postnatal days 0 and 1, at the NEC diagnosis time point (with postnatal-age-aligned control measurements) and, for NEC cases, at discharge/death. Because PIV values were markedly right-skewed and the Shapiro–Wilk test rejected normality in every group at every time point (all $p<0.001$), unadjusted between-group comparisons were performed with Kruskal–Wallis tests and Dunn–Bonferroni post-hoc tests; repeated measurements were analysed with a linear mixed model on log-transformed PIV for the time × group interaction. Receiver operating characteristic (ROC) analysis and multivariable logistic regression adjusted for gestational age and birth weight were performed to assess whether PIV predicts the need for surgery.

Results: PIV values showed significant differences between the study groups on postnatal day 0 ($p=0.001$) and day 1 ($p<0.001$). In contrast, PIV values were comparable between the groups at the time of NEC diagnosis ($p=0.358$) and did not differ significantly according to NEC stage at discharge or death ($p=0.875$). Contrary to the pattern suggested by group means, median PIV in the surgical NEC group was not the highest at any time point, and Dunn–Bonferroni post-hoc testing identified only one significant pair (Bell I vs term controls on day 1, $p=0.005$). ROC analysis showed no evidence of discriminative ability of PIV for the need for surgery at any evaluated time point (AUC 0.42–0.58; all 95% CIs included 0.50). PIV was not an independent predictor of surgery in multivariable logistic regression (day 1: OR 1.0004, 95% CI 0.9998–1.0009, $p=0.164$). The unadjusted NEC–control differences disappeared after adjustment for gestational age and birth weight (day 0: $p=0.858$; day 1: $p=0.339$), and the time × group interaction was not significant ($p=0.656$).

Conclusion: In this retrospective single-centre cohort, PIV did not discriminate NEC cases requiring surgery from those managed medically, and the apparent NEC–control differences were largely explained by gestational age and birth weight. These findings do not support the use of PIV as a stand-alone marker for surgical decision-making in NEC. Given the small surgical subgroup ($n=13$), the study is hypothesis-generating and the results require confirmation in larger, prospective, multicentre cohorts.

Keywords: Enterocolitis, necrotizing, pan-immune-inflammation value, surgical NEC, prematurity, biomarker

INTRODUCTION

Necrotising enterocolitis (NEC) is an acute characterised by necrosis of the intestinal wall.^{1,2} It is a necroinflammatory disease of the gastrointestinal tract, predominantly affects preterm infants with low birth



weight and is associated with high mortality and morbidity rates.^{1,2} Despite improvements in neonatal intensive care, NEC incidence and associated morbidity and mortality have remained substantial and may increase in some settings as survival of the smallest infants improves.¹ The pathogenesis of NEC is multifactorial and remains incompletely understood.^{2,3} An immature mucosal barrier, enteral feeding-related exposures, intestinal ischaemia, and intestinal dysbiosis are among the major factors implicated in disease development.^{2,4} Exaggerated Toll-like receptor 4 (TLR4)-mediated inflammatory signalling and intestinal barrier injury are central mechanisms in current models of NEC pathogenesis.^{3,5} Endothelial TLR4 activation may additionally impair intestinal microcirculatory perfusion and contribute to tissue injury.⁶

A major challenge in the clinical management of NEC is determining when medical treatment becomes insufficient and surgical intervention, such as primary peritoneal drainage or laparotomy, is required. Pneumoperitoneum due to intestinal perforation is an established indication for surgery, whereas identifying severe disease before perforation remains more difficult.^{7,8} Beyond perforation, decisions regarding surgical intervention rely on the evolution of clinical, laboratory, and radiological findings, and no single biomarker currently defines the optimal timing of surgery.^{9,10}

The pan-immune-inflammation value (PIV) is a composite index derived from neutrophil, platelet, monocyte, and lymphocyte counts obtained from a routine complete blood count. It is calculated as (neutrophil count $\times$ platelet count $\times$ monocyte count) divided by lymphocyte count.¹¹ PIV has gained attention as a systemic immune-inflammatory prognostic marker in several oncological settings.^{11,12} Neutrophils and platelets participate in pro-inflammatory and thrombo-inflammatory processes, monocytes contribute to innate immune and macrophage responses, and lymphocytes reflect adaptive immune function; these cell populations are also developmentally regulated in preterm infants and altered during NEC.^{13,14} Despite its use in other clinical contexts, the role of PIV in NEC has not been established. The objective of this study is to evaluate whether PIV can serve as an effective biomarker for the early detection and management of severe NEC in preterm infants.

This study aims to evaluate the prognostic value of PIV, a simple, cost-effective, reproducible parameter routinely assessed, in patients with NEC. Additionally, the study investigates whether PIV could serve as a novel biomarker to differentiate NEC cases responsive to medical treatment (stages 1 and 2) from those requiring surgical intervention (stage 3).

METHODS

This retrospective single-centre cohort study reviewed medical records of newborn patients admitted to the Neonatal Intensive Care Unit at Gülhane Training and Research Hospital between May 2018 and November 2022. The study protocol was approved by the Ethics Committee for Non-interventional Clinical Researches at Gülhane Training and Research Hospital, University of Health Sciences (Date:

17.05.2023, Decision No: 2023/119), and the research adhered to the principles of the Declaration of Helsinki. Data were collected retrospectively using the hospital information management system (FONET HBYS). As no additional diagnostic or therapeutic interventions were performed, the ethics committee waived the requirement for informed consent.

A total of 793 newborn medical records were reviewed. The study group consisted of 40 patients diagnosed with necrotising enterocolitis (NEC) according to Bell staging criteria, based on clinical and radiological findings.¹⁵ These patients were further categorized by disease severity: Bell stage 1 (n=15), stage 2 (n=12), and stage 3 (surgical NEC) (n=13). The control group included 753 newborns without an NEC diagnosis. Control cases were classified by gestational age as preterm (born before 37 weeks' gestation; n=218) or term (born at 37 weeks' gestation or later; n=535). Exclusion criteria included major congenital anomalies, incomplete clinical records, or missing complete blood count data.

For each patient, data collected included birth weight, gestational age, mode of delivery, maternal age, length of hospital stay, surgical intervention, and mortality status. The PIV was calculated as (neutrophil $\times$ platelet $\times$ monocyte)/lymphocyte, using values from the complete blood count.¹¹

To evaluate temporal changes in the inflammatory response, haematological parameters were analyzed at four time points: the initial complete blood count at birth (postnatal day 0), the count within the first 24 hours (postnatal day 1), the count at diagnosis, and the final assessment. In the NEC group, the time of diagnosis corresponded to the day clinical suspicion arose and treatment began. For the control group, routine complete blood count results from postnatal days 5 to 12 were standardized to align with the mean diagnosis time in NEC cases (8.32 postnatal days). For NEC cases, the final assessment used the most recent laboratory results prior to discharge or, for deceased patients, prior to death.

An initial sample-size calculation was conducted using G*Power (Version 3.1.9.7) based on a one-way analysis of variance (ANOVA) model. With an assumed effect size of 0.65, a type I error probability (α) of 0.05, and 80 percent power, the minimum required sample size was 32 patients; under that original planning scenario, 40 NEC cases corresponded to 83.15 percent power. This calculation does not quantify power for the revised primary surgical-versus-medical ROC and multivariable analyses; given the small surgical subgroup (n=13), those analyses are considered exploratory.

Statistical Analysis

The data analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.1 (packages pROC, lme4 and logistf). The distribution of all continuous variables was examined before analysis. Normality was assessed within each study group using the Shapiro–Wilk test together with visual inspection of histograms and Q–Q plots and evaluation of skewness. PIV was markedly right-skewed and the Shapiro–Wilk test rejected normality in every group at every time point



($W=0.48-0.84$, all $p<0.001$); Levene's test also indicated heterogeneity of variances on postnatal day 1 ($p=0.026$) and at diagnosis ($p<0.001$). For unadjusted group comparisons of PIV, parametric tests were therefore considered inappropriate and non-parametric methods were used. Continuous variables are presented as median (interquartile range, Q1–Q3); means with standard deviations are additionally reported for comparability with earlier literature. Two groups were compared with the Mann–Whitney U test and three or more groups with the Kruskal–Wallis H test, with epsilon-squared (ϵ^2) as the effect size. Where the Kruskal–Wallis test was significant, pairwise comparisons were performed with Dunn's test and Bonferroni adjustment for multiple comparisons. Because the four PIV measurements were obtained from the same infants at unequal and partly missing time points, repeated measurements were analysed with a linear mixed-effects model on log-transformed PIV with a random intercept per patient; the $\text{time} \times \text{group}$ interaction was tested by likelihood-ratio comparison against a main-effects model, and the Friedman test was used as a sensitivity analysis in patients with complete data. The ability of PIV to predict the need for surgery within the NEC cohort was evaluated by receiver operating characteristic (ROC) analysis; the area under the curve (AUC) is reported with bootstrap 95% confidence intervals (2,000 resamples), and optimal cut-off values were derived from the Youden index. Univariable and multivariable binary logistic regression models were fitted to assess whether PIV predicts surgery independently of gestational age and birth weight. To address the potential confounding effect of gestational age and birth weight on the NEC–control comparison, linear models on log-transformed PIV were fitted with and without adjustment for these two variables. A two-tailed p-value of <0.05 was considered statistically significant in all analyses.

RESULTS

A total of 40 neonates diagnosed with NEC based on the Bell criteria, along with 753 control subjects without NEC, were incorporated into the study.

Within the NEC cohort, 52.5 percent ($n=21$) of cases were female, and 47.5 percent ($n=19$) were male. Conversely, in the control cohort, females comprised 45.3 percent, and males 54.7 percent. The rate of cesarean section was 90.0 percent ($n=36$) within the NEC group, compared to 60.4 percent in the control group.

The mean birth weight was 1800.00 ± 750.75 grams in the NEC group and 2991.07 ± 627.47 grams in the control group. The mean gestational age was 31.35 weeks in the NEC group and 37.29 weeks in the control group. The average duration of hospital stay was 43.75 ± 31.55 days for the NEC group and 8.86 ± 8.28 days for the control group. There was no statistically significant difference in maternal age between the groups (NEC: 29.20 ± 5.70 years; control: 28.45 ± 5.83 years).

Among all patients monitored in the neonatal intensive care unit (NICU) during the study period, the overall incidence of NEC was 5.04 percent. Among preterm neonates, the incidence was 14.5 percent. Surgical intervention was necessitated in 32.5 percent of NEC cases ($n=13$). The overall mortality rate was 12.5 percent, with mortality in the surgical NEC subgroup reaching 23.07 percent. The mean duration until the resumption of enteral feeding in NEC cases was 8.1 days.

Table 1 provides a comparison of PIV levels, calculated at various time points, between the groups.

When PIV was analysed with methods appropriate to its distribution, group differences were significant on postnatal day 0 ($H=18.311$, $p=0.001$, $\epsilon^2=0.038$) and postnatal day 1 ($H=19.876$, $p<0.001$, $\epsilon^2=0.034$), but not at the time of diagnosis ($H=4.372$, $p=0.358$); among the NEC stages, no difference was observed at discharge/death ($H=0.268$, $p=0.875$). Effect sizes were small at the three time points for which ϵ^2 was reported. It is important to note that the ranking of groups differed from that suggested by the arithmetic means: although the surgical NEC group had the highest mean PIV on postnatal day 1 (1418.09 ± 1218.45), its median (282.6) was lower than that of both control groups, indicating that the high mean was driven by a small number of extreme values rather than by a systematic elevation. Similarly, the difference at diagnosis that appeared significant under one-way ANOVA ($p=0.004$) was not confirmed by the Kruskal–Wallis test ($p=0.358$). Dunn's test with Bonferroni adjustment identified only one significant pairwise difference across all comparisons, namely Bell stage I versus term controls on postnatal day 1 ($p=0.005$); no post-hoc comparison involving the surgical NEC group reached significance.

Diagnostic Performance of PIV for the Need for Surgery

Within the NEC cohort ($n=40$; 13 surgical, 27 medical), ROC analysis was performed for each time point with sufficient surgical and medical data (postnatal day 0, postnatal day

Table 1. PIV levels by group and time point, median (Q1–Q3)

Measurement time	Bell stage I	Bell stage II	Bell stage III/ surgery	Term controls	Preterm controls	H	p*	ϵ^2
Postnatal day 0	151.0 (92.0–302.0) n=13	516.0 (163.5–1012.0) n=11	142.0 (61.5–446.8) n=12	761.8 (276.6–1606.6) n=271	786.6 (330.6–1452.0) n=75	18.311	0.001	0.038
Postnatal day 1	190.2 (47.2–303.3) n=13	399.1 (267.5–642.0) n=8	282.6 (114.7–1602.3) n=12	701.8 (368.7–1264.3) n=312	533.0 (298.5–1009.2) n=127	19.876	<0.001	0.034
At diagnosis	522.3 (80.4–773.7) n=15	596.5 (96.5–1522.0) n=11	215.8 (133.1–1090.1) n=11	349.7 (210.9–639.0) n=341	315.9 (156.5–529.5) n=154	4.372	0.358	0.001
Discharge/death	137.3 (92.0–470.2) n=15	145.3 (63.8–540.4) n=9	149.6 (51.3–375.3) n=10	–	–	0.268	0.875	–

* Kruskal–Wallis H test. ϵ^2 : epsilon-squared effect size (0.01 small, 0.06 medium, 0.14 large). Medians are reported because PIV was non-normally distributed in all groups (Shapiro–Wilk $p<0.001$). Bold p values are statistically significant. For controls, the 'at diagnosis' comparison uses routine complete blood counts from postnatal days 5–12 aligned to the mean NEC diagnosis time; discharge/death values were available only for NEC cases, so that comparison is among Bell stages only. PIV: Pan-immune-inflammation value, NEC: Necrotising enterocolitis



1, and diagnosis; **Table 2**). PIV showed no evidence of discriminative ability for the need for surgical intervention at any evaluated time point: AUC values ranged from 0.422 to 0.575 and all bootstrap 95% confidence intervals included 0.50. Corresponding Mann–Whitney U comparisons between surgical and medical NEC cases were also non-significant ($p=0.460$, 0.489 and 0.855 for day 0, day 1 and diagnosis, respectively). The cut-off values derived from the Youden index were unstable and clinically uninformative, with either very low sensitivity (8.3% on day 0) or very low specificity (23.8% on day 1).

Multivariable Analysis

Because gestational age, birth weight and prematurity may influence both PIV and the need for surgery, univariable and multivariable logistic regression models were fitted within the NEC cohort (**Table 3**). Neither PIV on postnatal day 1 nor PIV at diagnosis was associated with the need for surgery in univariable analysis, and PIV remained non-significant after adjustment for gestational age and birth weight (day 1: OR 1.0004, 95% CI 0.9998–1.0009, $p=0.164$). Gestational age and birth weight were likewise not independent predictors. It should be emphasised that with only 13 surgical events and three covariates the number of events per variable was approximately 4, well below the conventionally recommended minimum of 10; these models are therefore substantially underpowered and their estimates should be regarded as exploratory.

Effect of Gestational Age and Birth Weight on the NEC–Control Comparison

NEC cases were considerably more preterm and of lower birth weight than controls (median gestational age 31.0 versus 38.0 weeks and median birth weight 1795 versus 3030 g; both $p<0.001$), and PIV correlated positively with both gestational age ($\rho=0.186$, $p<0.001$) and birth weight ($\rho=0.195$, $p<0.001$) on postnatal day 1. In linear models on log-transformed PIV, the unadjusted NEC–control difference was significant on postnatal day 0 ($\beta=-0.989$, $p<0.001$) and day 1 ($\beta=-0.770$, $p<0.001$), but both associations disappeared after adjustment for gestational age and birth weight (day 0: $\beta=-0.050$, $p=0.858$; day 1: $\beta=-0.230$, $p=0.339$). After adjustment, the NEC–control differences were no longer

statistically significant, suggesting that gestational age and birth weight substantially confounded the unadjusted comparison.

Repeated Measurements and Time×Group Interaction

A linear mixed-effects model on log-transformed PIV with a random intercept per patient was fitted to the four time points within the NEC cohort (140 observations from 40 patients). Neither the main effect of time nor the main effect of surgical status reached significance, and the time×group interaction was not significant (likelihood-ratio test $\chi^2=1.616$, $df=3$, $p=0.656$). A Friedman test restricted to patients with complete data at all four time points ($n=24$) likewise showed no significant temporal change ($\chi^2=1.850$, $p=0.604$). Thus the temporal trajectory of PIV did not differ between surgical and medical NEC cases.

DISCUSSION

To the best of current knowledge, this study is the first to evaluate the relationship between the PIV, disease stage, and the need for surgery in newborns with NEC. The findings do not support PIV as a stand-alone marker of the need for surgery and indicate that unadjusted NEC–control differences are strongly influenced by gestational age and birth weight. The overall NEC incidence of 5.04 per cent in the NICU and the incidence of 14.5 per cent among preterm newborns fall within the broad range reported across neonatal populations, although published estimates vary substantially according to gestational age, birth-weight thresholds, and case definitions.^{16,17} The need for surgical treatment (32.5 per cent), overall mortality (12.5 per cent), and mortality in the surgical NEC subgroup (23.07 per cent) are broadly comparable with contemporary outcome data, although several systematic and multicentre reports have described higher mortality, particularly among surgical NEC cases.^{18,19} Such variation likely reflects differences in case mix, disease definitions, gestational-age distribution, and centre-level practice.

A central question of this study was whether PIV can identify NEC cases that will require surgery. Although the arithmetic mean PIV on postnatal day 1 was highest in the

Table 2. ROC analysis of PIV for predicting the need for surgery within the NEC cohort

Time point	n (surgical/medical)	AUC	95% CI (bootstrap)	Cut-off	Sensitivity	Specificity	p†
Postnatal day 0	36 (12/24)	0.422	0.204–0.647	>4012.0	8.3%	100.0%	0.460
Postnatal day 1	33 (12/21)	0.575	0.363–0.786	>48.5	100.0%	23.8%	0.489
At diagnosis	37 (11/26)	0.479	0.276–0.680	>130.7	81.8%	34.6%	0.855

† Mann–Whitney U test comparing surgical and medical NEC cases. ROC: Receiver operating characteristic, PIV: Pan-immune-inflammation value, NEC: Necrotising enterocolitis, AUC: Area under the receiver operating characteristic curve, CI: Confidence interval (2,000 bootstrap resamples). Cut-off values were derived from the Youden index. All confidence intervals include 0.50, indicating no discriminative ability.

Table 3. Univariable and multivariable logistic regression for the need for surgery within the NEC cohort

Variable	Univariable OR (95% CI)	p	Multivariable OR (95% CI)	p
PIV, postnatal day 1	1.0003 (0.9998–1.0009)	0.250	1.0004 (0.9998–1.0009)	0.164
PIV, at diagnosis	0.9998 (0.9992–1.0004)	0.591	–	–
Gestational age (weeks)	1.012 (0.849–1.206)	0.897	0.845 (0.580–1.229)	0.378
Birth weight (g)	1.0004 (0.9995–1.0014)	0.336	1.0017 (0.9996–1.0038)	0.109

NEC: Necrotising enterocolitis, OR: Odds ratio, CI: Confidence interval, PIV: Pan-immune-inflammation value. Multivariable model includes PIV on postnatal day 1, gestational age and birth weight ($n=33$, 12 events; events per variable =4). No variable reached statistical significance.



Bell stage III group, this pattern was not confirmed when methods appropriate to the highly skewed distribution of PIV were applied: the median value in the surgical group was lower than in either control group, no post-hoc comparison involving the surgical group was significant, and ROC analysis demonstrated no discriminative ability at any time point (AUC 0.42–0.58, all 95% CIs including 0.50). PIV also failed to predict the need for surgery in multivariable models adjusted for gestational age and birth weight. Taken together, these analyses indicate that the initial impression of an early inflammatory signal in surgical NEC was driven by a small number of extreme values rather than by a systematic difference. TLR4-mediated inflammatory signalling and intestinal barrier disruption are central to NEC pathogenesis.⁵ Experimental and human data also implicate TLR4-dependent intestinal lymphocyte influx in NEC.²⁰ Nevertheless, the present data do not support PIV as a quantitative marker of these processes in a form that is clinically useful for surgical decision-making.

Median PIV at the time of diagnosis was numerically lower in the Bell stage III group than in stage I and stage II cases, but this difference did not reach statistical significance (Kruskal–Wallis $p=0.358$), and the significant result obtained with one-way ANOVA ($p=0.004$) was not robust to the violation of normality. In the full-text analysis by Feng et al.,²¹ patients who underwent surgical intervention had significantly lower Systemic Immune-Inflammation Index (SII) values than those who received medical treatment (158.84 vs. 332.92, $p<0.001$). Although SII and PIV are distinct indices, both incorporate neutrophil, platelet, and lymphocyte counts, while PIV additionally incorporates monocytes; they therefore capture partly overlapping information from circulating inflammatory cell populations.^{11,21} The present study is therefore directionally consistent with that full-text analysis but does not reproduce its statistical significance, which may reflect the substantially smaller surgical subgroup available here.

Thrombocytopenia and abnormalities in neutrophil and monocyte counts are well described in NEC and may provide diagnostic or prognostic information, particularly in severe disease.²² Peripheral consumption, cellular redistribution, and inflammatory-cell trafficking are plausible contributors to these haematological changes.^{14,22} Because neutrophils, platelets, and monocytes are all in the numerator of the PIV formula, a reduction in any of these cell populations can mathematically lower PIV even in the presence of severe inflammation.¹¹ Therefore, the low PIV levels observed at diagnosis in the surgical NEC group may reflect consumption or redistribution of circulating immune and haematological cells rather than a reduction in the inflammatory response.^{14,22} However, because this mechanism was not directly investigated in the present study, this interpretation should be regarded as a pathophysiological hypothesis.

PIV values were higher in term than in preterm control infants on postnatal day 1, and PIV correlated positively with both gestational age and birth weight across the whole cohort. Immaturity of innate and adaptive immune responses in preterm newborns, together with gestational- and postnatal-age-related variation in neonatal blood-cell

counts, provides a biologically plausible explanation for this observation.^{13,23} Importantly, this maturity dependence has direct implications for the interpretation of the NEC–control comparison: because NEC cases were markedly more preterm and of lower birth weight than controls, the unadjusted differences in PIV were substantially confounded by maturity and were no longer statistically significant after adjustment for gestational age and birth weight. Future evaluations of PIV in this population should therefore account for gestational age and birth weight, for example through matching and/or multivariable adjustment.

Longitudinal or dynamic PIV assessment has shown prognostic relevance in other disease settings, raising the possibility that PIV trajectory may be more informative than a single measurement.²⁴ This hypothesis was tested directly in the present study using a linear mixed-effects model, and the time×group interaction was not significant ($p=0.656$), nor was there evidence of significant temporal change in a Friedman sensitivity analysis ($p=0.604$). The available data therefore do not support the notion that serial PIV measurement adds discriminative information about the need for surgery, although the limited number of patients with complete serial data ($n=24$) leaves this question only partially answered.

Limitations

This study has several important limitations. First and most critically, only 13 infants required surgery. This small subgroup severely limits statistical power: with three covariates the multivariable model had approximately four events per variable, below the traditional 10-events-per-variable rule of thumb for logistic regression.²⁵ The bootstrap confidence intervals around the AUC estimates were correspondingly wide (spanning up to 0.44 AUC units). The study was therefore unable to detect any but very large effects, and the negative findings reported here should be interpreted as an absence of evidence rather than as definitive evidence of absence. Second, the NEC and control groups differed substantially in gestational age and birth weight; although we addressed this by adjusted analysis, residual confounding cannot be excluded, and a gestational-age-matched control design would be preferable. Third, the retrospective, single-centre design restricts generalisability and precludes standardisation of the timing of blood sampling. Fourth, to compare haematological parameters at the time of diagnosis with those of the control group, routine complete blood count results obtained between postnatal days 5 and 12 in the control group were used, based on the mean time of diagnosis in NEC cases (postnatal day 8.32). Because neonatal haematological reference ranges vary with both gestational and postnatal age, this approach may have introduced measurement bias.²³ Fifth, serial data were incomplete, with only 24 patients contributing measurements at all four time points, which further limited the repeated-measures analysis. Finally, PIV was evaluated in isolation; its potential incremental value when combined with clinical, radiological, and other laboratory findings was not assessed.

CONCLUSION

In this retrospective single-centre cohort, the PIV did not discriminate between NEC cases that required surgery and



those managed medically. ROC analysis did not demonstrate discriminative ability at any of the three evaluable time points (postnatal day 0, postnatal day 1, and diagnosis), PIV was not an independent predictor of surgery in multivariable models, and the temporal trajectory of PIV did not differ between surgical and medical cases. The unadjusted PIV differences between NEC cases and controls were no longer statistically significant after adjustment for gestational age and birth weight, indicating substantial confounding by maturity.

PIV remains an attractive candidate biomarker in principle because it can be calculated from a routine complete blood count without an additional laboratory assay. However, the present data do not support its use as a stand-alone marker for surgical decision-making in NEC, and no cut-off value could be identified with acceptable sensitivity and specificity. Given the small surgical subgroup, these findings are hypothesis-generating rather than definitive. Adequately powered, prospective, multicentre studies with gestational-age-matched controls, standardised sampling times, and prespecified analysis plans are required before any conclusion can be drawn about the clinical utility of PIV in this setting; such studies should also examine whether PIV contributes incremental information when combined with established clinical, radiological, and laboratory criteria.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Ethics Committee for Non-interventional Clinical Researches at Gülhane Training and Research Hospital, University of Health Sciences (Date: 17.05.2023, Decision No: 2023/119).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: IY, IS; Design: IY, IS; Control: IY, IS; Resources: IY, SEUB, GBB, IS; Materials: IY, SEUB, GBB, IS; Data Collection and/or Processing: IY, SEUB; Analysis and/or Interpretation: GBB, IS; Literature Review: GBB, IS; Critical Review: GBB, IS; Final Approval: IY, GBB, IS; Accountability: IY, IS.

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