



Can the systemic immune-inflammation index and the systemic inflammatory response score along with clinical findings predict the need for surgical intervention in necrotizing enterocolitis?

Asya Eylem Boztaş¹, Ayşe Demet Payza¹, Suedagül Yıldırım Erkan¹, Arzu Şencan²

Necrotizing enterocolitis (NEC) is a gastrointestinal emergency most commonly encountered in premature neonates and is associated with severe morbidity and mortality, affecting approximately 7% of premature and very low birth weight infants.^[1] A recent meta-analysis reported a mortality rate of 23.5% among infants with confirmed NEC and even higher in extremely low birth weight infants and those requiring surgical intervention, reaching 50.9% and 40.5%, respectively.^[2]

The pathogenesis of NEC remains incompletely understood, with multiple factors contributing to the susceptibility of the premature intestine to injury. Several mechanisms are reported to play a

Abstract

Objectives: The aim of this study was to assess the predictiveness of current biomarkers and identify parameters that could aid in decision-making regarding surgical intervention in necrotizing enterocolitis (NEC).

Patients and methods: Eighty-one neonates (44 females, 37 males; mean age at NEC diagnosis: 19.37 ± 13.54 days; range, 5 to 90 days) diagnosed with NEC in a tertiary-level pediatric referral hospital between January 2014 and December 2024 were retrospectively examined. Patients' demographic data, laboratory tests, including inflammation scores [SII and SIRI, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR)], ultrasonography findings, abdominal radiograph findings, and physical examination findings, were compared between medical and surgical NEC groups. The data were analyzed to assess the predictive importance of inflammation markers for the identification of patients needing surgical intervention.

Results: Overall, 47 (58%) patients required surgical intervention, and the mortality rate was 12.3%. There was no significant difference between groups in terms of gestational age, sex, age at diagnosis. The SII, NLR, C-reactive protein, and absolute neutrophil count were significantly higher in the surgical intervention group than in the medical treatment group ($p < 0.05$). However, the absolute lymphocyte count was lower in the surgical NEC group ($p = 0.034$). The SIRI score, white blood cell count, PLR, and MLR were not statistically significant predictive factors ($p > 0.05$). Length of hospital stay was longer in the medical NEC group ($p < 0.05$).

Conclusion: High values of SII, NLR, ANC, and low lymphocyte count can be considered adjunctive criteria alongside Bell's staging system to facilitate the triage of premature neonates with NEC, thereby optimizing surgical decision-making and improving clinical outcomes. Prospective studies are needed to confirm their predictive value and refine surgical decision-making.

Keywords: Inflammation marker, necrotizing enterocolitis, newborn.

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Correspondence: Asya Eylem Boztaş, MD.

E-mail: asyaeylem@gmail.com

¹Department of Pediatric Surgery, Health Sciences University, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, İzmir, Türkiye

²Department of Pediatric Surgery, Health Sciences University, İzmir Faculty of Medicine, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, İzmir, Türkiye

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and immature regulation of intestinal vascular tone; (2) a compromised intestinal barrier; (3) an exaggerated inflammatory response triggered by dysregulated bacterial colonization; and (4) an immature immune system leading to ineffective microbial clearance and subsequent translocation across the epithelium.^[3] In NEC, the inflammatory response also extends beyond the intestine, with evidence suggesting that the liver may play a critical role in amplifying systemic inflammation.^[4]

Considering the complex interactions among various immune cell lines in atherogenesis, two-line inflammatory indices, such as the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR) have been shown to correlate with cardiovascular disease and mortality risk.^[5] More recently, novel inflammatory biomarkers incorporating three cell lines, including the systemic inflammatory response index (SIRI) and the systemic immune-inflammation index (SII), have been evaluated for their prognostic value in neoplastic diseases and ischemic heart disease.^[5,6] The SII and SIRI incorporate multiple hematological components of neutrophils, lymphocytes, monocytes, and platelets into a single score. These indices provide a broader representation of the interplay between innate and adaptive immunity, as well as the balance between proinflammatory and regulatory pathways.^[5]

In the Bell classification first presented in 1978 and revised in 1986, NEC is divided into three stages. Stage I is mild or suspected NEC which requires medical monitoring.^[2] Stage II is moderate or definitive NEC with radiological findings and moderate systemic signs, and Stage III necessitates surgical intervention.^[2,7] Therefore, the treatment and monitoring processes are relatively well defined. Patients are managed based on physical examination findings, routine complete blood count and biochemical parameters obtained when clinical suspicion arises, and results from abdominal radiographs and ultrasound examinations. During this process, however, cases in Stage II remain in a gray area.

Given the subjective nature of current surgical decision criteria, recent research has focused on identifying early predictive biomarkers. Complete blood count parameters have been investigated for

this purpose, particularly in adults.^[8] Epidemiological data indicate that approximately 30% of neonates diagnosed with NEC require surgical intervention.^[9] Finding an early prediction marker with both high sensitivity and specificity to assess the need for surgery can indicate potential risk of mortality. Additionally, prediction of surgical NEC may help to tailor the treatment process and management of future severe morbidities.^[10]

To date, only limited studies have assessed the role of SII and SIRI in neonatal conditions, and evidence specific to NEC is scarce. The aim of this study was to assess the predictiveness of current biomarkers and identify parameters that could aid in making decision regarding surgical intervention and mortality in NEC patients.

PATIENTS AND METHODS

A retrospective cohort of neonates diagnosed with NEC and managed by the Department of Pediatric Surgery and Neonatal Intensive Care Unit at the İzmir Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital between January 2014 and December 2024 were included in the study. The inclusion criteria for the study were as follows: cases with a confirmed diagnosis of NEC, patients with complete and accessible data, and individuals who were exclusively followed up at our institution. Neonates with spontaneous intestinal perforation, those who had cardiac surgery, those with missing data, or those who had received prior management for NEC at another hospital were excluded from the study. A total of 81 patients (44 females, 37 males; mean age at NEC diagnosis: 19.37 ± 13.54 days; range, 5 to 90 days) were included in the study (Figure 1). Written informed consent was obtained from the parents and/or legal guardians of the patients. The study protocol was approved by the İzmir Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital Non-Interventional Ethics Committee (Date: 27.06.2024, No: 62). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The first day of diagnosis was accepted as the first day of NEC. Patients' general demographic information were evaluated in terms of sex, gestational age, birth weight, mode of delivery

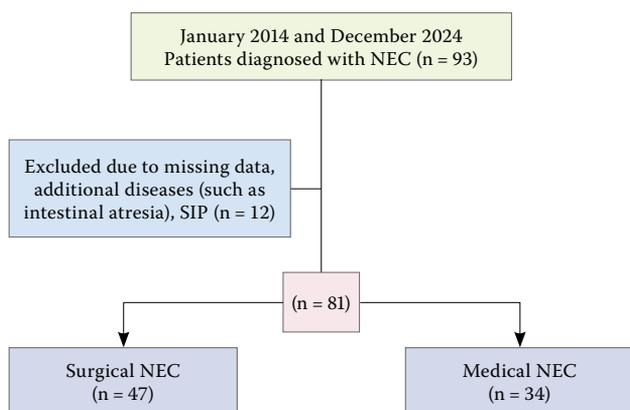


Figure 1. Flow diagram of the study design.

NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation.

(cesarean section or vaginal delivery), Bell's stage and age at the time of NEC diagnosis, and length of hospital stay and mortality. Laboratory inflammation scores, such as SII, SIRI, NLR, PLR, MLR, absolute lymphocyte count (ALC), platelet count (PLT), absolute neutrophil count (ANC), monocyte count (MO), and C-reactive protein (CRP) were obtained at the time of NEC diagnosis or within the first 12 h following diagnosis. At this stage, none of the patients had yet undergone surgical intervention. Surgical decisions were made subsequently, based on the progression of clinical and radiological findings, including evidence of intestinal perforation, progressive abdominal distension, erythema or discoloration of the abdominal wall, bilious drainage, or persistent rectal bleeding despite maximal conservative treatment. Thus, biomarker values were collected prior to or at the early stage of clinical deterioration and were not influenced by intraoperative or postoperative changes. This design allowed us to evaluate the association of early biomarker levels with the eventual need for surgical intervention.

For clinical assessment, ultrasonography findings, abdominal radiograph findings, and physical examination findings were evaluated. Patients were divided into two groups according to treatment strategies: the surgical NEC group (n = 47) and the medical NEC group (n = 34). All collected data were compared between medical and surgical NEC groups.

Surgical interventions included exploratory laparotomy with stoma creation or resection

and anastomosis and placement of a peritoneal drain followed by second-look exploration. These decisions were guided by the clinical judgment of the pediatric surgeon in collaboration with the neonatologist.

Inflammatory indices were calculated as follows: SIRI = $NE (10^9/L) \times MO(10^9/L) / ALC(10^9/L)$; SII = $PLT (10^9/L) \times NE (10^9/L) / ALC (10^9/L)$; PLR = $PLT (10^9/L) / ALC (10^9/L)$; NLR = $NE (10^9/L) / ALC (10^9/L)$; MLR = $MO (10^9/L) / ALC (10^9/L)$.^[11,12]

Statistical analysis

Data were evaluated using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as the number of units (n), percentage (%), and mean \pm standard deviation (SD) values. For numerical features, normality of the data was first assessed using the Shapiro-Wilk test. If the data were normally distributed ($p > 0.05$), an independent two-sample t-test was used to compare the means between the medical and surgical NEC groups. If the data were nonnormally distributed ($p \leq 0.05$), the Mann-Whitney U test was applied to compare the distributions of the two groups. For categorical features, the chi-square test was used to determine whether there were significant associations between each categorical variable and the outcome (medical-surgical). A p -value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) analysis was used to assess optimal cutoff values for inflammatory biomarkers with sensitivity and specificity. The area under the ROC curve was calculated with a 95% confidence interval (CI).

RESULTS

Among the patients included in the study, 47 (58%) underwent surgical intervention during the follow-up period, while 34 (42%) received only medical treatment. The overall mortality rate was 12.3%, with 10 reported deaths. Among conservatively treated patients, mortality rate was 2.9% (n = 1); in the surgical NEC group, mortality rate was higher, with 19.1% (n = 9). Although mortality was numerically higher in the surgically treated group, the difference did not reach statistical significance ($p = 0.174$).

Among these, 32 (68.1%) underwent staged surgery, consisting of an initial exploratory

laparotomy with stoma creation followed by stoma closure. Additionally, 29 (61.7%) patients received bedside drain placement, and some of them required a second-look laparotomy after clinical stabilization, while eight (17%) patients underwent primary resection and anastomosis (Table 1).

There was no statistically significant difference between treatment groups in terms of gestational age and age at diagnosis ($p > 0.05$). Length of hospital stay was higher in the medical NEC group ($p < 0.05$).

Results of the laboratory test performed at the time of NEC diagnosis were compared between groups. Higher CRP (median 3.26 vs. 0.18, $p < 0.005$), ANC (median 7.71 vs. 4.13, $p < 0.05$), NLR (median 2.53 vs. 1.21, $p < 0.05$), SII score (median 425.81 vs. 216.2, $p < 0.05$), and lower ALC (median 2.36 vs. 3.64, $p < 0.05$) were found significantly associated

with surgical intervention. However, despite higher values of SIRS score, MLR, and PLR in the surgical group, these parameters were not statistically significant for surgical prediction. White blood cell count, MO, and PLT were not significantly associated with prediction of surgical intervention need ($p > 0.05$; Table 2).

Optimal cutoff values for significant inflammation markers (CRP, ANC, ALC, SII score, and NLR) were determined by ROC analysis. These statistically significant cutoff values predicting the need for surgical intervention were: CRP, > 1.9 mg/L; ANC, $> 6.96 \times 10^9/L$; SII score, < 333.01 ; NLR, > 1.74 ; ALC, $\leq 2.72 \times 10^9/L$ (Table 3).

In the ROC analysis conducted to evaluate the surgical predictive power of CRP, ANC, ALC, SII score, and NLR values, the corresponding area under the curve values were found to be statistically significant ($p < 0.05$; Figure 2).

TABLE 1
Patient demographics (n=81)

	n	%	Mean \pm SD	Median	Min-Max
Gestational age (weeks)			30.17 \pm 3.91	30	21-39
Age at diagnosis (days)			19.37 \pm 13.54	11	5-90
Sex					
Female	44	54.3			
Male	37	45.7			
Birth weight (g)					
< 1000	29	35.8			
< 1500	26	32			
< 2500	22	27.1			
≥ 2500	4	4.9			
Treatment					
Medical	34	42			
Surgical	47	58			
Operation					
Stoma	32	68			
Drain placement + second look laparotomy	10	21.3			
Primary resection + anastomosis	5	10.7			
Exitus					
Mode of delivery					
C/S	67				
Vaginal delivery	14				

SD, standard deviation; C/S, cesarean section.

TABLE 2
Distribution of inflammation markers between medical and surgical groups

	Medical NEC		Surgical NEC		Z	p
	Median	Min-Max	Median	Min-Max		
Gestational age (weeks)	29	24-38	30	21-39	-0.849	0.396
Age at diagnosis (days)	12	1-75	10	1-62	-0.536	0.592
WBC ($\times 10^9/L$)	10.46	3.73-22.05	10.86	0.94-39.9	-0.550	0.582
CRP (mg/L)	0.18	0.02-17.03	3.26	0.02-23.61	-4.085	0.000
ANC ($10^9/L$)	4.13	1.43-15.86	7.71	0.16-76.9	-2.325	0.020
ALC ($10^9/L$)	3.64	0.18-7.84	2.36	0.46-9.93	-2.125	0.034
Monocyte count ($10^9/L$)	0.96	0-4.93	0.59	0-19.1	-1.330	0.183
Platelet count ($10^9/L$)	220	36-522	196	8-551	-0.971	0.331
Platelet/lymphocyte ratio	60.65	12.53-1083.33	69.49	3.77-584.78	-0.172	0.863
SII score	216.2	63.36-10833.33	425.81	2.15-22720.45	-2.268	0.023
SIRI score	0.92	0-273.89	1.99	0-47.17	-1.273	0.203
Neutrophile/lymphocyte ratio	1.21	0.42-55.56	2.53	0.24-58.26	-3.435	0.001
Monocyte/lymphocyte ratio	0.32	0-27.39	0.41	0-12.82	-0.239	0.811
Length of hospital stay (days)	48	11-156	36	12-140	-2.010	0.044

NEC, necrotizing enterocolitis; WBC, white blood cell count; CRP, C-reactive protein; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index.

TABLE 3
The results of the ROC analysis conducted to evaluate the predictive power of CRP, ANC, ALC, SII score, and NLR values for surgical outcomes

	CRP	ANC	ALC	SII score	NLR
Criterion	>1.9	>6.96	≤ 2.72	>333.01	>1.74
Sensitivity	59.57	51.06	61.70	61.70	70.21
95% CI	44.3-73.6	36.1-65.9	46.4-75.5	46.4-75.5	55.1-82.7
Sensitivity	88.24	82.35	76.47	79.41	76.47
95% CI	72.5-96.7	65.5-93.2	58.8-89.3	62.1-91.3	58.8-89.3
+LR	5.06	2.89	2.62	3.00	2.98
95% CI	2.0-13.1	1.3-6.3	1.4-5.0	1.5-6.0	1.6-5.6
-LR	0.46	0.59	0.50	0.48	0.39
95% CI	0.3-0.7	0.4-0.8	0.3-0.8	0.3-0.7	0.2-0.6
+PV	87.5	80.0	78.4	80.6	80.5
95% CI	71.0-96.5	61.4-92.3	61.8-90.2	64.0-91.8	65.1-91.2
-PV	61.2	54.9	59.1	60.0	65.0
95% CI	46.2-74.8	40.3-68.9	43.2-73.7	44.3-74.3	48.3-79.4
AUC	0.767	0.652	0.639	0.648	0.725
95% CI	0.659-0.853	0.538-0.755	0.525-0.743	0.534-0.751	0.614-0.818
p	<0.0001	0.013	0.032	0.021	0.000

ROC, receiver operating characteristic; CRP, C-reactive protein; ANC, neutrophil count; ALC, absolute lymphocyte count; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; CI, confidence interval; LR, likelihood ratio; PV, predictive value; AUC, area under the curve.

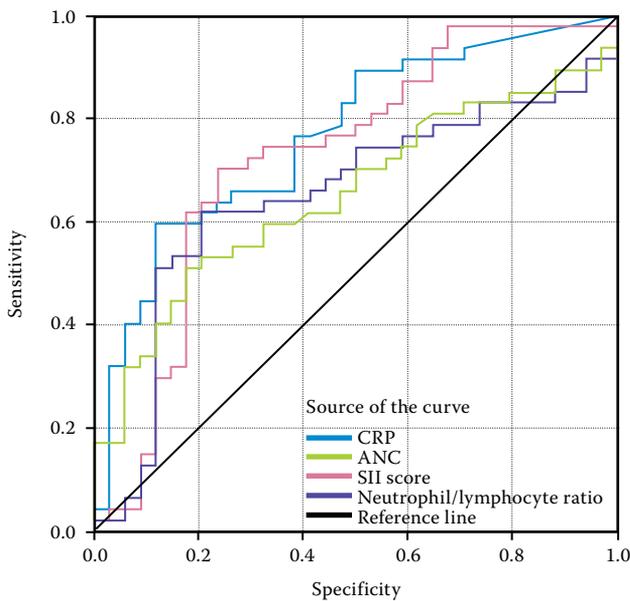


Figure 2. Receiver operating characteristic curves plotted to assess the predictive power of CRP, ANC, ALC, SII score, and NLR values for surgical outcomes.

CRP, C-reactive protein; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio.

DISCUSSION

Although NEC is a frequently encountered pathology in neonatal intensive care units and a classification system exists to categorize the disease, specific parameters predicting the need for surgical intervention and mortality in affected patients have yet to be clearly established. The relative surgical indications for NEC remain a topic of debate.

Clinical follow-up plans for patients are determined based on physical examination findings, routine complete blood count and biochemical parameters obtained when clinical suspicion arises, as well as abdominal radiographs and ultrasonographic evaluations.^[13] The lack of a “gold standard” diagnostic method and subjective parameters for surgical decision lead to inconsistencies in the literature.^[14]

Previous studies have shown that early surgical intervention has the potential to improve outcomes. Therefore, recent research focuses not only on preventing NEC but also on predicting it earlier to guide treatment strategies toward surgery.^[15] This study presented objective biomarkers as additional criteria alongside Bell’s staging system to facilitate

proper triage of premature neonates with NEC and to ensure optimal surgical treatment.

Recent developments of neonatal intensive care led the rise of survival of premature infants, which also increased the incidence of NEC in neonates. Recent studies showed that almost 30% of neonates with NEC require surgical intervention, either laparotomy or drain placement.^[16] In the literature, overall mortality rate in patients with confirmed NEC is 15%, and this rate is at 34.5% in patients requiring surgical intervention^[13,17] In our study population, the overall mortality rate was 12.3%, and the in surgical group, the rate was higher with 19.1%.

The pathogenesis of NEC remains poorly understood, with multiple factors potentially contributing to the susceptibility of the premature intestine to injury. Excessive production of inflammatory mediators further exacerbates the condition by recruiting neutrophils, ultimately causing tissue damage and necrosis.^[3]

Since inflammatory mediators play a crucial role in the development of NEC, recent studies have focused on predictive markers for early evaluation of these critical patient group. Previous experimental studies have emphasized the role of immunomodulatory mechanisms in the pathogenesis of NEC, demonstrating that modulation of intestinal immune responses may influence the severity of inflammation and tissue injury.^[18,19]

Some of the studies offer to calculate the CRP/albumin ratio and examine albumin, interleukin (IL)-6, IL-8, IL-10, CRP, and lactate levels to predict early diagnosis of NEC.^[10,20,21]

While a low ALC indicates cellular immunity in response to a systemic inflammation, thrombocytosis and neutrophilia are observed during inflammation status. High platelet activity results releasing bolus of chemokines and promotes neutrophils, which are the primary inflammatory cells in the bloodstream.^[22] Several studies show that increased SII scores are related with more severe inflammatory responses, and in our study, SII scores were higher in surgical intervention group, consistent with the literature.^[23,24] The SII score is calculated by using ANC, ALC, and PLT. In patients who underwent surgical treatment,

high values of ANC and low values of ALC were observed. There was no significant difference in terms of PLT between groups. In a pediatric appendicitis cohort, high SII scores were correlated with complicated appendicitis.^[23] Elevated SII scores have been broadly linked to unfavorable outcomes across various malignancies. Additionally, it has been associated with adverse prognoses in multiple clinical conditions, such as cardiovascular diseases and autoimmune disorders.^[25,26]

The SIRI score is also a widely used inflammation scoring in many diseases. Several studies showed its effectiveness in gastric cancer, ischemic heart disease, complicated appendicitis, and parapneumonic effusions.^[5,12,27] Higher SIRI scores are associated with acute coronary artery syndrome. Higher values of both SII and SIRI were associated with complicated coronary artery diseases.^[5] Its compounds are ANC, MO, and ALC counts. In our study population, SIRI scores were not statistically different between groups.

White blood cell count is a routine biomarker of inflammation nonspecific to any disease. C-reactive protein is a relatively late responder to systemic inflammation, which rises after 12 h and peaks at 48 h.^[28]

In our study, while high CRP values were significantly more common in the surgical NEC group, white blood cell counts remained nonsignificant. This finding suggests that CRP may better reflect the severity and progression of inflammatory injury requiring surgical intervention, while white blood cell count alone may be insufficient to discriminate disease severity in neonatal NEC. Similar observations have been reported in previous neonatal studies, in which CRP demonstrated greater prognostic value than leukocyte counts in advanced or complicated NEC.^[29]

In interpreting our ROC analysis, it is important to note that some of the cutoff values identified, such as CRP > 1.9 mg/L, fell within ranges generally considered normal in routine clinical practice (reference value < 3 mg/L). This does not imply that values below the traditional upper limit of normal are pathologic; rather, it reflects the statistical optimization of sensitivity and specificity for surgical NEC within our study population. Thus, even modest increases in CRP, although

technically within the normal laboratory range, may still provide discriminatory value in neonates with NEC. Importantly, these biomarker thresholds should not be viewed as absolute criteria for surgical decision-making. Instead, they should be considered as adjunctive markers that may support established clinical and radiological findings in guiding surgical intervention. Further prospective studies with larger cohorts are warranted to validate whether such population-specific thresholds hold generalizable predictive value.

While several conventional hematological ratios, including NLR, PLR, and LMR, also demonstrated statistical significance in predicting surgical NEC, their discriminative ability was comparatively limited. In contrast, SII and SIRI integrate neutrophils, lymphocytes, monocytes, and platelets into composite indices that may better capture the complex interplay of inflammatory and immune pathways in NEC. Thus, although traditional markers retain potential adjunctive value, our findings suggest that SII and SIRI provide a more comprehensive and clinically actionable assessment of disease severity. To the best of our knowledge, this is the first study to assess multiple recent investigated biomarkers to predict surgical NEC in neonates.

This study had some limitations. This study was conducted retrospectively with a limited number of patients in a single tertiary center, which may restrict the generalizability of the findings. Multiple pediatric surgeons were involved in the follow-up and surgical management of NEC patients, and individual variation in clinical judgment may have influenced treatment decisions. Furthermore, the timing of surgery in NEC is inherently subjective and dependent on evolving clinical and radiological parameters, which could have affected the postoperative course and outcomes. Another important limitation concerns the temporal relationship between biomarker measurement and surgical decision-making. Biomarkers were obtained at the time of diagnosis or within 12 h; however, surgical decisions were typically made later, based on progression of clinical signs such as intestinal perforation, abdominal distension, erythema, or discoloration. Thus, while our findings demonstrate an association between biomarker levels and surgical NEC, they cannot be interpreted as definitive evidence of predictive value.

Additionally, the cutoff values identified in our ROC analysis (e.g., CRP > 1.9 mg/L) reflect statistical optimization of sensitivity and specificity within our study cohort and, in some instances, fall within ranges considered normal in standard laboratory practice. These thresholds should, therefore, be viewed as population-specific indicators rather than universal diagnostic criteria.

In conclusion, parameters derived from the laboratory values at the time of diagnosis, in conjunction with clinical presentation and radiological findings, can serve as reliable predictors of the need for surgery in patients with NEC. Cutoff values of > 333.01 for the SII, > 1.74 for the NLR, > $6.96 \times 10^9/L$ for the ANC, and $\leq 2.72 \times 10^9/L$ for the ALC may be effective in identifying NEC patients who require prompt surgical intervention. We propose that these parameters be considered as adjunctive criteria to facilitate the triage of premature neonates with NEC, thereby optimizing surgical decision-making and improving clinical outcomes.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: A.E.B.: Idea/concept, design, writing the article; A.Ş.: Control/supervision, critical review; S.Y.E., A.E.B., A.D.P.: Data collection; A.E.B., A.D.P.: Processing analysis and/or interpretation, literature review.

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