IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Predictive Role of the Systemic Immune-Inflammation Index in Catheter-Related Thrombosis among Neonates: A Retrospective Study

Tugba Barsan Kaya[1*], Zeynep Canan Ozdemir[2], Ozge Aydemir[1], Hulya Ozen[3], Simay Armagan[4], Ozge Surmeli Onay[1], Ener Cagrı Dinleyici[4], Ayse Neslihan Tekin[1]

1. Division of Neonatology, Department of Pediatrics, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkiye
2. Division of Pediatric Hematology and Oncology, Department of Pediatrics, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkiye
3. Department of Biostatistics, Faculty of Medicine, Gulhane Faculty of Medicine, University of Health Sciences, Ankara, Turkıye
4. Department of Pediatrics, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkiye

ABSTRACT

Background: This study aimed to evaluate changes in hematological parameters and the systemic immune-inflammation index (SII) to determine their utility in predicting and monitoring catheter-related thrombosis (CRT) in neonatal intensive care unit (NICU). We expect that this study will provide novel insights into the potential role of inflammation-based indices in the management of neonatal thrombosis.

Methods: A retrospective case-control study was conducted in a tertiary NICU over five years. Infants were divided into three groups: those with CRT, those with central venous catheters but without thrombosis (non-CRT), and healthy controls. Serial complete blood counts (CBCs) were analyzed, including inflammatory indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and SII.

Results: Compared to the other groups, CRT infants had significantly lower baseline hemoglobin levels and higher levels of white blood cells (WBC), absolute neutrophil count (ANC), NLR, C-reactive protein (CRP), and SII over time ($p < 0.05$ for all). No significant changes were found in monocyte count, MLR, or mean platelet volume. While SII decreased over time in the control group, it showed a rising trend in CRT infants, indicating ongoing inflammation.

Conclusion: Serial measurements of WBC, ANC, NLR, and SII may serve as useful indicators of thrombotic risk in catheterized neonates. These indices may provide better predictive value than standard CBC parameters. Larger multicenter studies are warranted to validate these findings. Larger multicenter studies are needed to confirm these findings.

Keywords: Inflammation, Neonatal intensive care, Systemic immune-inflammation index (SII), Thrombosis

Introduction

Venous thrombosis is a significant cause of morbidity and mortality in neonates, particularly those requiring intensive care. Due to their critical condition and frequent exposure to invasive procedures, infants in NICUs are highly vulnerable to complications, among which catheter-related thrombosis (CRT) is particularly common. Central venous catheters (CVCs) provide essential vascular access for prolonged administration of parenteral nutrition and medications. They account for over 80% of venous thrombotic events in neonates (1), as catheter insertion may trigger a

* *Corresponding author*: Tuğba Barsan Kaya, Division of Neonatology, Department of Pediatrics, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkiye. Email: tugbarsankaya@gmail.com

Please cite this paper as:
Kaya TB, Ozdemir ZC, Aydemir O, Ozen H, Armagan S, Onay OS, Dinleyici EC, Tekin AN. Predictive Role of the Systemic Immune-Inflammation Index in Catheter-Related Thrombosis among Neonates: A Retrospective Study. Iranian Journal of Neonatology. 2025 Jul: 16(3). DOI: 10.22038/ijn.2025.84800.2628

pro-inflammatory response that promotes thrombus formation.

Although traditional biomarkers such as D-dimer and fibrinogen are commonly used, their predictive value in neonates remains limited due to high false-positive rates and inconsistent baseline levels (2-3). These limitations highlight the need for more reliable and dynamic biomarkers to assess thrombotic risk in this population.

Recent studies have emphasized the pivotal role of inflammation in thrombosis pathophysiology, linking immune dysregulation to coagulation cascades—a process known as immunothrombosis (4). In this context, neutrophils, monocytes, and platelets contribute to thrombus formation through complex cellular interactions (5). The systemic immune-inflammation index (SII), which incorporates neutrophil, lymphocyte, and platelet counts, has emerged as a composite biomarker reflecting the overall immune-inflammatory status (6,7). It has demonstrated prognostic value in various thrombotic conditions, including deep vein thrombosis (8), pulmonary embolism (PE) (9), and stroke (10); however, its use in neonates remains largely unexplored.

Given the strong association between immune activation and thrombosis, we hypothesize that the SII may serve as a valuable predictor of CRT in NICU newborns. This study aims to address a critical gap in the literature by evaluating the utility of SII in predicting and monitoring thrombotic events in neonates with CRT compared to those without CRT. We expect that serial measurements of SII will provide timely and clinically meaningful insights into thrombotic risk, potentially outperforming conventional hematologic markers and improving early detection and management strategies in this vulnerable population.

Methods

Study Design

This was a single-center, retrospective, case-control study conducted in the NICU of a tertiary university hospital between 2018 and 2023. The study was approved by the Local Ethical Committee of Eskisehir Osmangazi University Faculty of Medicine (26.09.2023/32). All procedures were carried out in accordance with institutional guidelines and the ethical standards of the 1964 Helsinki Declaration and its later amendments. As this study involved retrospective data analysis, informed consent was not required.

Study Population

The study included preterm infants born at the study institution and admitted to the NICU between 2018 and 2023. Eligible participants met the following criteria: (1) presence of an indication for CVC placement, and (2) availability of baseline complete blood count (CBC) measurements obtained both before and after catheterization. Two types of CVCs were included: umbilical venous catheters (UVCs) and peripherally inserted central catheters (PICCs) inserted via superficial veins.

Infants were categorized into three groups based on clinical characteristics:

- CRT group: Infants with CVCs who developed venous thrombosis during their NICU stay.
- Non-CRT group: Infants with CVCs but without thrombosis.
- Control group: Infants without CVCs, who had no signs of thrombosis or infection and received routine NICU care.

Exclusion criteria included the following: thrombosis diagnosed at external centers without pre-catheter CBC data; long-term comorbidities such as congenital heart disease, chronic lung disease, or neurological disorders; requirement for surgical intervention; thrombosis diagnosed beyond 28 days of life; and CVCs inserted through the jugular, subclavian, or femoral veins; and the presence of active infection at the time of CBC evaluation, including infants diagnosed with catheter related infection or suspected systemic infection.

We also evaluated maternal characteristics, including chorioamnionitis, diabetes mellitus, and hypertension. Neonatal demographic and clinical features assessed were sex, birth weight, gestational age, culture-proven sepsis, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), necrotising enterocolitis (NEC, Stage≥2), and intraventricular hemorrhage (IVH). The Score for Neonatal Acute Physiology–Perinatal Extension II (SNAPPE-II), routinely calculated within the first 12 hours of admission, was also recorded.

Catheter Insertion Procedure

In our NICU, preterm infants born before 32 weeks of gestation are routinely provided with a UVC upon admission. For this purpose, 5 Fr polyurethane catheters are typically used. If ongoing vascular access is required beyond the early neonatal period, the UVC is generally removed by day 10 of life and replaced with either

a PICC or a CVC, based on the infant's clinical condition. PICC lines are inserted under sterile conditions, without ultrasound guidance, via superficial veins of the forearm and advanced to the distal third of the superior vena cava. Catheter tip location is confirmed via chest radiography. Polyurethane catheters sized 1–2 French are commonly used for this procedure. In infants undergoing high-risk surgical procedures—such as those for necrotizing enterocolitis (NEC) or congenital heart disease—or in cases with limited peripheral venous access or the need for multiple drug infusions, centrally inserted CVCs are placed by cannulating deep veins in the supraclavicular or infraclavicular regions. To maintain catheter patency, a continuous low-dose heparin infusion (0.5 U/mL/h) is administered (11).

Thrombosis Assessment and Treatment Protocol

The presence of thrombosis was evaluated by a pediatric radiologist or cardiologist using Doppler ultrasonography (US) or echocardiography. Thrombosis was defined as a persistent echodense intravascular structure confirmed on two-dimensional imaging. Final treatment decisions were made by the pediatric hematology team, based on clinical and imaging findings. All infants diagnosed with CRT received low-molecular-weight heparin (enoxaparin), with dosage titrated to achieve target anti-factor Xa levels between 0.5 and 1 IU/mL. Infants were monitored weekly until complete thrombus resolution. In cases of thrombosis threatening limb, organ, or life, thrombolytic therapy with tissue plasminogen activators was administered. Catheters were promptly removed upon confirmation of thrombosis.

Transfontanel US was performed before initiating thrombolytic therapy and repeated weekly during treatment to monitor for IVH. In our unit, all premature infants routinely undergo transfontanel US within the first 72 hours of life. If no IVH is detected, follow-up scans are performed on days 7, 14, and at 1 month of age. In infants diagnosed with IVH, weekly follow-up US is continued until stabilization or resolutionis confirmed by two consecutive scans. The severity of germinal matrix hemorrhage was classified using the Volpe grading system (12).

Complete Blood Count Analysis and Calculation of Inflammatory Indices

The initial CBC, obtained within the first four hours of life, was designated as T0 and used as the baseline value. For infants in the CRT group, additional CBCs were recorded at the time of thrombosis diagnosis (T1) and approximately one week after diagnosis (T2). In the non-CRT and control groups, CBCs were recorded at two time points—designated as T1 and T2—within the first three postnatal weeks.

Inflammatory indices were calculated for each time point across all groups. The SII was calculated as follows:

SII = Platelet count × (Neutrophil count / Lymphocyte count) (9).

In addition, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) were also determined at each timepoint (T0, T1, and T2).

Outcomes

The primary outcome of this study was to evaluate the changes in hematological parameters and SII to determine their utility in predicting and monitoring CRT in neonates admitted to the NICU. The secondary outcome was to assess the temporal dynamics of inflammatory markers and their potential role in identifying infants at increased risk of developing CRT.

Statistical Analysis

All statistical analyses were performed using the SPSS Statistical Package for the Social Sciences (Illinois, CA, United States). Quantitative variables were presented as mean ± standard deviation (SD) or median (Q1–Q3), while qualitative variables were expressed as frequency and percentage. The Shapiro–Wilk test was used to assess the normality of continuous variables. For normally distributed data, one-way analysis of variance (ANOVA) was applied, whereas the Kruskal–Wallis test was used for non-normally distributed data. Post hoc pairwise comparisons were conducted using Dunn's test. Relationships between categorical variables were evaluated using Pearson's chi-square test.

Blood count parameters and inflammatory indices were analyzed using a two-way mixed ANOVA with group (CRT, non-CRT, control), time (T0, T1, T2), and their interaction as factors. For significant interactions, post hoc tests with Bonferroni corrections were performed. A p-value <0.05 was considered statistically significant.

In addition, a multivariable logistic regression analysis was conducted to identify independent predictors of CRT. The model included inflammatory indices at T1 (NLR and SII), gestational age, and birth weight as covariates.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, and a p-value <0.05 was considered statistically significant.

Ethical Approval

The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 32, Date: 26.09.2023).

Results

Descriptive Characteristics of the Study Population

During the study period, there were 4071 admissions to the NICU, of which 62 infants were diagnosed with thrombosis. Forty-seven of these infants were excluded for various reasons: metabolic disease (n = 2), congenital heart disease (n = 9), referred from an external center (n = 4), non-CRT (n = 12), asphyxia (n = 4), sepsis (n = 8), and thrombosis diagnosed after 28 days of life (n = 8). (Figue 1).

Fifteen newborns (six boys and nine girls; mean gestational age of 28.9 ± 5.0 weeks and birth weight of 1322.3 ± 856.9 g) who were diagnosed with CRT within their first 28 days postnatally were included in the CRT group. The non-CRT group included 24 infants with catheters but no thrombosis, while the control group included 25 infants. Both gestational age and birth weight were significantly lower in the CRT and non-CRT groups compared to the control group (p<0.001, both). Maternal characteristics, receipt of antenatal corticosteroids, maternal chorioamnionitis, maternal diabetes mellitus, types of delivery, and the rate of multiple births were similar (p>0.05). Preeclampsia was infrequent across all groups, with no statistically significant difference observed (p>0.05).

The percentage of infants with a 5-minute Apgar score below 7 was highest in the CRT group compared to the non-CRT and control groups, but this difference did not reach statistical significance. The CRT group had significantly more infants with cord pH<7.2. Additionally, this group showed lower bicarbonate (HCO_3^-) and more negative base excess (BE) values, along with higher cord lactate levels, indicating greater perinatal acidosis (p<0.05 for all).

A total of 39 infants in the CRT and non-CRT groups underwent 50 catheter insertions, comprising 29 UVCs, 4 UACs, and 17 PICCs. Some infants received multiple catheter insertions (e.g., both UVC and PICC or UVC and UAC), explaining the total catheter count exceeding the number of patients. The mean age at CRT diagnosis was 16.7 days (SD=19.94). Table 1 summarizes the characteristics of the 64 infants. Detailed descriptive characteristics are summarized in Table 1.

Clinical Outcomes of the Patients

Infants in the CRT group had a higher need for inotropic support and were more likely to present with conditions such as PDA, invasive mechanical ventilation, and grades III and IV IVH (Table 1). SNAPPE II scores, hospitalization duration, and mortality rates were also significantly higher among CRT infants compared to the other groups (p<0.05 for all.) (Table 1).

While the insidence of early-onset sepsis did not differ significantly among groups, late-onset sepsis was significantly more frequent in both the CRT and non-CRT groups compared to the control group (p=0.001), with no difference observed between CRT and non-CRT groups. Although the incidence of RDS was higher in the CRT and non-CRT groups compared to controls, no statistically significant difference was observed between those two groups. Similarly, the rate of NEC (Stage ≥2) did not differ significantly among the groups (p>0.05). (Table 1).

Serial Changes in Blood Count Parameters

Hemoglobin (Hb) levels decreased over time in all the groups, as expected. However, the baseline Hb value in the CRT group was significantly lower compared to both the non-CRT and control groups (p<0.05) (Table 1).

Significant group differences were observed in white blood cell (WBC) count, absolute neutrophil count (ANC), and platelet levels. In the CRT group, WBC counts increased notably over time, particularly at T1, while no significant change was observed in the non-CRT or control groups. At T1, WBC counts in the CRT group were significantly higher than those in the other two groups. ANC showed a similar pattern, with significant increases in the CRT group at both T1 and T2, whereas ANC remained stable in the non-CRT group and decreased in controls.

Platelet counts increased over time in all groups (p = 0.01); however, values remained significantly lower in the CRT group compared to the non-CRT and control groups throughout the study period (p < 0.001). No significant time–group interaction was found for platelet trends (p > 0.05).

Mean platelet volume (MPV) also increased in all groups over time (p < 0.001), although this

Table 1. Demographic and clinical characteristics and clinical outcomes of the study groups

Variables	CRT group (n = 15)	Non-CRT group (n = 24)	Control group (n = 25)	p value
Gestational age (weeks)	28.9 ± 5.0	30.7 ± 2.8	34.6 ± 1.7	<0.001*
Gender (Boys/Girls)	6/9	20/4	17/8	0.06
Birth-weight (gram)	1322.3 ± 856.9	1619.7 ± 530.5	2440.2 ± 483.8	<0.001*
Antenatal steroid n(%)	11 (44%)	18 (75%)	6 (50%)	0.17
Preeclampsia n(%)	2 (15.4%)	1 (4.2%)	1 (4%)	0.52
Chorioamnionitis, n(%)	1 (8.3%)	3 (12.5%)	0 (0%)	0.18
Gestational diabetes n(%)	4 (26.6%)	2 (8.3%)	1 (3.8%)	0.18
Cesarean delivery n(%)	11 (84.6%)	23 (95.8%)	23 (92%)	0.62
Multiple birth, n(%)	3 (23.1%)	8 (33.3%)	6 (24%)	0.70
Fifth Apgar score (<7), n(%)	5 (33.3%)	3 (12.5%)	1 (3.8%)	p < 0.05
Cord pH (<7.2), n(%)	5 (33.3%)	3 (12.5%)	1 (3.8%)	p < 0.05
Cord HCO_3 (mmol/L)	18.77 ± 3.56	20.13 ± 2.63	20.8 ± 2.18	0.12
Cord lactate (mmol/L)	4.7 ± 2.51	3 ± 1.41	2.98 ± 0.83	p < 0.05**
Cord BE (mmol/L)	7.25±4.48	4.7±3.96	3.47 ± 1.94	p < 0.05**
Venous catheter, days	14.9 ± 11.09	14.92 ± 1.44	0	0.96
SNAPPEII	41.08 ± 2.4	25.04 ± 10.82	9.84 ± 11.39	p < 0.001
Invasive mechanical ventilation, days	13.08 ± 5.7	2.63 ± 4.69b	0.4 ± 0.91	p < 0.001
Early onset sepsis, n (%)	5 (38.5%)	4 (16.7%)	2 (8%)	0.06
Late onset sepsis, n (%)	7 (53.8%)	7 (29.2%)	0 (0%)	p < 0.001*
RDS, n(%)	9 (69.2%)	14 (58.3%)	4 (16%)	p < 0.001*
PDA, n(%)	6 (46.2%)	4 (16.7%)	0 (0%)	p < 0.001
NEC stage ≥2, n(%)	2 (15.4%)	1 (4.2%)	0 (0%)	0.17
IVH (grade≥3), n(%)	3 (23.1%)	0 (0%)	1 (4%)	p < 0.01
Inotropic support, n(%)	4 (33.3%)	0 (0%)	1 (4%)	p < 0.01**
Hospitalization (days)*	85.8 ± 58	44.75 ± 22.96	17.6 ± 12	p < 0.001
Mortality, n(%)	3 (23.1%)	0 (0%)	0 (0%)	p < 0.01**
Mortality, n(%)	3 (23.1%)	0 (0%)	0 (0%)	p < 0.01**

Data were expressed as mean ± SD or n(%).

*p indicates a statistically significant difference between the control group and both the CRT and non-CRT groups (p < 0.05). However, no significant difference was found between the CRT and non-CRT groups. **p indicates a statistically significant difference between the CRT group and both the non-CRT and control groups (p < 0.05). However, no significant difference was found between the non-CRT and control groups CRT: catheter-related thrombosis, BE: base excess, HCO3-: bicarbonate, mmol/L: millimoles per liter, pH: potential of hydrogen, mean values followed by different letters in the rows are RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; MV, mechanical ventilation.

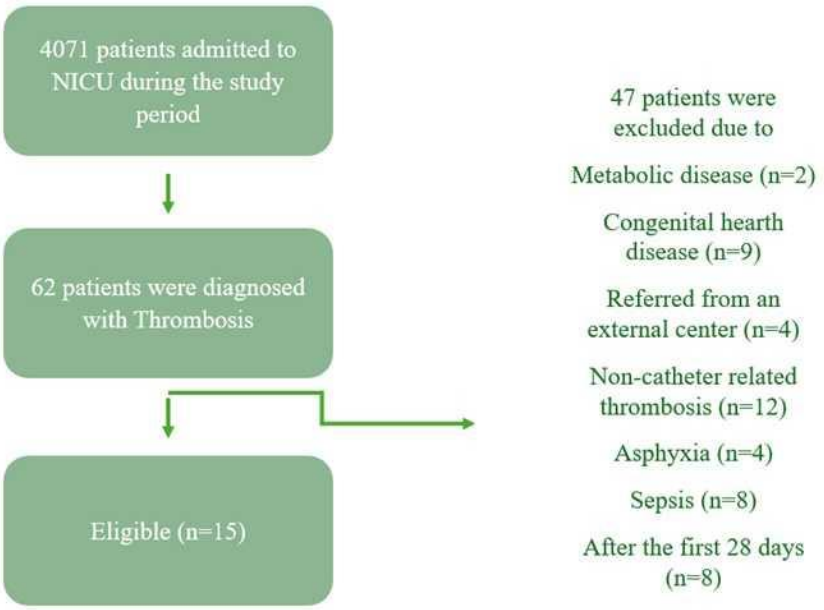

Figure 1. Flow chart of patients with thrombosis in our neonatal intensive care unit during the study period

Table 2. Hematological parameters (Hgb, WBC, ANC, ALC, AMC, PLT, MPV) of CRT, non-CRT, and control groups at different time points (T0, T1, and T2)

Variables	Time	Groups			p1	p2
		Control[a] n = 25	non-CRT[b] n = 24	CRT[c] n = 15		
Hb (g/dl)	T0	18.58 ± 0.36	18.39 ± 0.44	16.25 ± 1.04	1[a-b] 0.019[a-c] 0.043[b-c]	0.001
	T1	16.96 ± 0.45	14.66 ± 0.48	12.88 ± 0.69	0.003[a-b] <0.001[a-c] 0.094[b-c]	
	T2	13.85 ± 0.63	11.33 ± 0.31	11.5 ± 0.75	0.003[a-b] 0.024[a-c] 1[b-c]	
WBC $10^3/\mu L$	T0	12.42 ± 0.75	10.43 ± 0.82	10.78 ± 1.2	0.293[a-b] 0.751[a-2] 1[b-c]	0.081
	T1	10.34 ± 0.49	9.10 ± 0.79	14.67 ± 2.4	1.000[a-b] 0.047[a-c] 0.005[b-c]	
	T2	10.25 ± 0.49	11.44 ± 0.72	12.66 ± 1.32	0.715[a-b] 0.144[a-c] 0.936[b-c]	
ANC $10^3/\mu L$	T0	4.59 ± 0.63	3.67 ± 0.49	4.49 ± 0.78	0.725[a-b] 1[a-c] 1[b-c]	<0.001
	T1	3.55 ± 0.16	3.39 ± 0.41	7.69 ± 1.74	1.000[a-b] 0.001[a-c] 0.001[b-c]	
	T2	2.66 ± 0.25	3.55 ± 0.46	5.98 ± 0.95	0.527[a-b] <0.001[a-c] 0.008[b-c]	
ALC $10^3/\mu L$	T0	5.96 ± 0.35	5.32 ± 0.41	4.94 ± 0.56	0.62	0.134
	T1	4.62 ± 0.25	4.02 ± 0.25	4.3 ± 0.67	0.06	
	T2	5.62 ± 0.22	5.65 ± 0.31	4.47 ± 0.73	0.08	
AMC $10^3/\mu L$	T0	1.32 ± 0.08	1.12 ± 0.12	1.15 ± 0.15	0.52	0.791
	T1	1.64 ± 0.13	1.72 ± 0.16	1.90 ± 0.35	0.25	
	T2	1.35 ± 0.09	1.53 ± 0.16	1.71 ± 0.39	0.06	
PLT $10^3/\mu L$	T0	245.36 ± 13.11	220.54 ± 11.67	197.46 ± 31.28	0.04	0.011
	T1	279.08 ± 23.69	288.20 ± 20.18	200 ± 32.51	0.03	
	T2	368.95 ± 19.14	394.83 ± 24.91	279.38 ± 41.79	0.03	
MPV (fL)	T0	9.84 ± 0.14	9.89 ± 0.13	9.69 ± 0.44	0.33	0.339
	T1	10.44 ± 0.17	11.4 ± 0.15	11.27 ± 0.4	0.06	
	T2	11.3 ± 0.23	11.35 ± 0.17	11.12 ± 0.45	0.79	

Hb: hemoglobin, WBC: white blood cell count, ANC: absolute neutrophil count, ALC: absolute lymphocyte count, AMC: absolute monocyte count, PLT: platelet count, MPV: mean platelet volume, NS: not significant
Data were expressed as mean ± SD
p^2: p value representing the comparison of the data of the CRT, non-CRT, and control groups.
p^{a-b}: p value representing the comparison of the data of the control and non-CRT groups.
p^{a-c}: p value representing the comparison of the data of the control and CRT groups.
p^{b-c}: p value representing the comparison of the data of the non-CRT and CRT groups.

change did not appear to be associated with thrombosis risk ($p > 0.05$).

No significant differences were observed in absolute monocyte count (AMC) or absolute lymphocyte count (ALC) across groups or time points that would suggest a clinical association with thrombosis ($p > 0.05$).

Detailed data are presented in Table 2.

Serial Changes in Inflammatory Indices

As shown in Figure 2A, At baseline (T0), NLR did not differ significantly among the groups ($p > 0.05$). However, a significant increase in NLR over time was observed only in the CRT group ($p < 0.05$), with no meaningful change in the non-CRT and control groups. No significant time-related changes or group differences were observed for

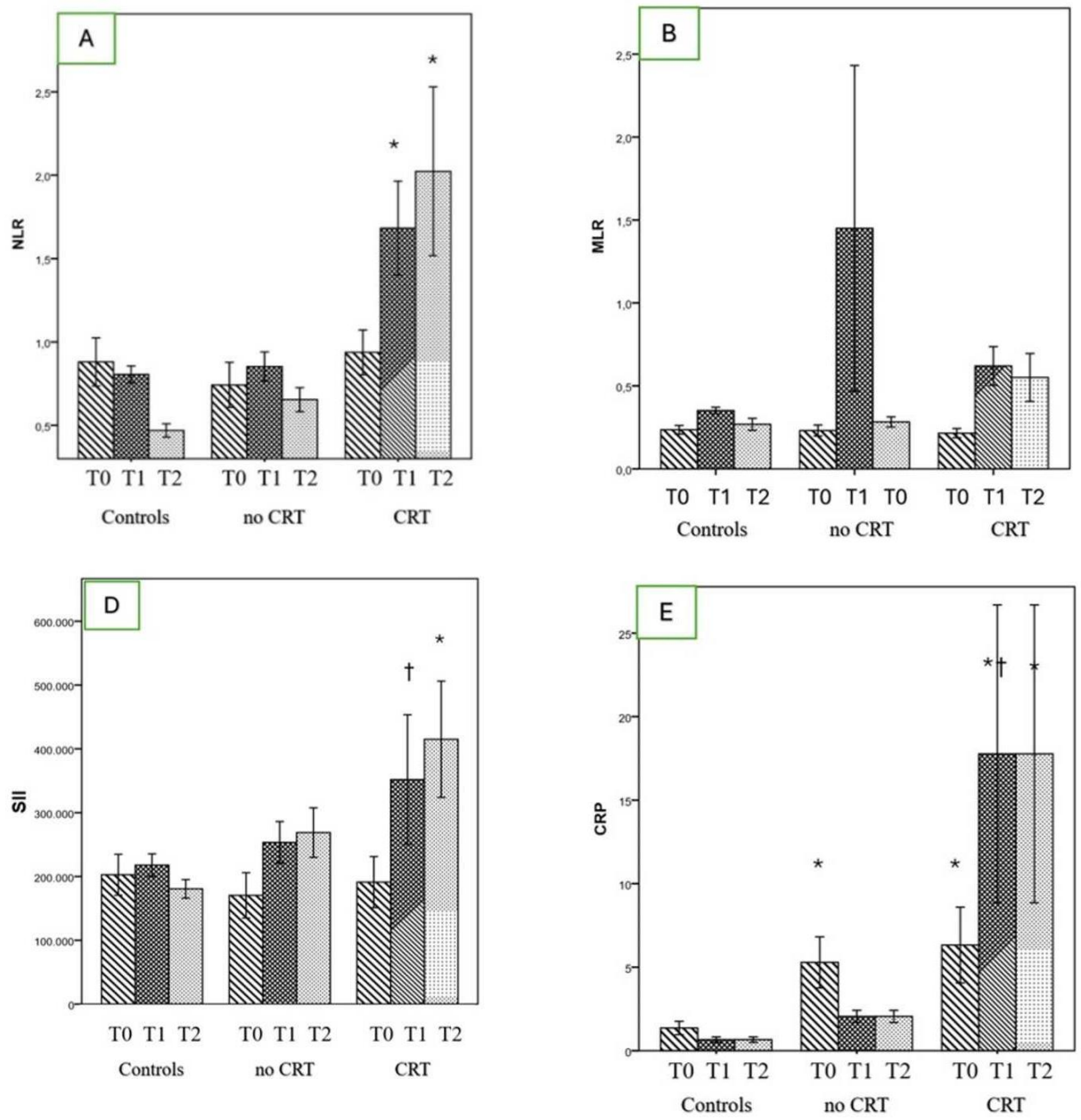

Figure 2. Comparison of neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), systemic inflammation index (SII), and C-reactive protein levels at T0, T1, and T2. (A): NLR; (B): MLR; (C): PLR; (D): SII; and (E): CRP.

MLR and PLR ($p > 0.05$, Figures 2B and 2C).

SII showed a significant upward trend in the CRT group, peaking at T2 ($p < 0.05$), while no statistically significant change was observed in the non-CRT group. At T2, SII levels were lowest in the control group (Figure 2D).

Initial CRP levels (CRP0) were significantly higher in both the CRT and non-CRT groups compared to the control group ($p < 0.05$), but did not differ significantly from each other. In the CRT group, CRP levels continued to rise at T1 (CRP1) and T2 (CRP2), remaining significantly higher than in the other groups throughout the study period ($p < 0.001$, Figure 2E). In contrast, CRP values decreased over time in both the non-CRT and control groups.

Multivariable Logistic Regression Analysis for Predicting CRT

To evaluate the independent predictive

Table 3. Multivariable logistic regression analysis for predicting catheter-related thrombosis (CRT) in neonates with central venous catheters

Variable	B	SE	Wald	P value	OR (exp(B))	95%Cl for OR
NLR (T1)	3.989	1.478	7.282	0.007	54.02	3.6-802.5
SII (T1)	0.000	0.000	3.536	0.060	1.000	1.000-1.001 (approx)
Gestational age	NS	-	-	>0.05	-	-
Birth Weight	NS	-	-	>0.05	-	-

capacity of inflammatory markers for catheter-related thrombosis (CRT), a multivariable logistic regression analysis was performed using NLR and SII values at T1, with gestational age and birth weight included as covariates.

In the final model, NLR emerged as a statistically significant independent predictor of CRT (OR: 54.0, 95% CI: 3.6–802.5, p = 0.007), even after adjustment for gestational age and birth weight. SII demonstrated a near-significant association with CRT (p = 0.060). Gestational age and birth weight were not independently associated with CRT in the adjusted model.

The final model demonstrated good discriminatory ability, correctly classifying 82.1% of cases (Table 3).

Discussion

This study is, to our knowledge, the first to evaluate the predictive role of SII in neonatal CRT. We found that CRT infants exhibited persistently elevated levels of ANC, NLR, CRP, and SII over time. These findings indicate a sustained inflammatory response not observed in the control group and less pronounced in the non-CRT group, suggesting that inflammation-based markers—particularly SII—may be valuable tools for early risk stratification in the NICU.

Understanding the role of neutrophils in thrombosis is essential, given their central function in the innate immune response and emerging evidence linking them to thromboinflammatory mechanisms. Neutrophils contribute to thrombus formation through both direct interactions with platelets and paracrine signaling pathways. Furthermore, neutrophil extracellular traps (NETs), composed of decondensed chromatin and granular proteins, have been identified in venous thrombi in experimental models, underscoring their mechanistic role in clot propagation (13,14). The NLR, reflecting the balance between neutrophil-dominant innate and lymphocyte-driven adaptive immunity, is increasingly recognized as a marker of systemic inflammation and thrombotic risk. Elevated NLR levels have been associated with poor outcomes in conditions such as acute coronary syndrome (15), pulmonary embolism (16), and vasculitic syndromes like Henoch–Schönlein purpura (17). In our study, CRT cases exhibited consistently higher ANC and NLR values than both control groups, reinforcing the contribution of neutrophil-driven inflammation to thrombotic processes in neonates and supporting their use as early warning indicators.

Among the evaluated indices, the SII is particularly noteworthy due to its ability to simultaneously capture neutrophilic inflamemation, lymphocyte suppression, and platelet activity—three key elements in the pathogenesis of thrombosis. First introduced in oncology as a prognostic marker in 2014 (18), the SII has since been validated in a broad range of inflammatory and vascular disorders, including ischemic stroke (10), non-alcoholic fatty liver disease (19), and coronary artery disease (20). It has proven reliable across different populations, with its prognostic performance confirmed by several meta-analyses (21). To our knowledge, the present study is among the first to investigate the utility of SII in neonates with CRT. To our knowledge, the present study is among the first to explore the application of SII in a neonatal cohort with CRT. Our findings demonstrate that SII levels are markedly elevated in CRT cases and remain moderately increased even in catheterized neonates without thrombosis when compared to healthy controls. This pattern suggests that SII may reflect both active thromboinflammatory states and a background predisposition to thrombosis, making it a sensitive and practical biomarker for clinical use in the NICU—especially where traditional thrombosis markers may be limited or impractical.

Recent literature supports the proposed link between neonatal inflammation and thrombosis. Bitsadze et al. described how inflammatory cytokines such as IL-6 and TNF-α can activate coagulation pathways in neonates, even in the absence of overt infection, by inducing endothelial dysfunction (22). Khizroeva et al. further highlighted the limited compensatory capacity of the neonatal hemostatic system, which may be tipped toward thrombosis by catheterization and

persistent low-grade inflammation (23). Additionally, Mineyko et al. showed that inflammatory biomarker profiles can help differentiate subtypes of neonatal stroke, lending further credence to the idea that markers such as SII may not only signal ongoing pathology but also reveal underlying susceptibility to thrombotic events (24).

We found no significant differences in absolute monocyte count (AMC) or monocyte-to-lymphocyte ratio (MLR) among the study groups. Although monocytes play a recognized role in thrombosis through tissue factor expression and inflammatory signaling (25,26), our results suggest that these conventional monocyte-based indices may have limited relevance in neonates. This discrepancy might reflect age-related differences in monocyte biology, as most prior data originate from adult or animal studies. Notably, the functional diversity of monocyte subsets is well-characterized in adults, yet their distribution and activity in neonates—particularly across gestational stages—remain poorly understood (27). Future studies characterizing monocyte subsets in the neonatal period could help clarify their contribution to vascular inflammation and thrombotic risk.

Although elevated hematocrit is a recognized risk factor for thrombosis due to increased blood viscosity (28–30), we did not observe polycythemia in CRT cases. On the contrary, baseline hemoglobin levels were lower, potentially related to lower Apgar scores and limited delayed cord clamping. While anemia is less commonly associated with thrombosis, emerging evidence in adult populations suggests that hypoxia-related endothelial injury and redox imbalance may contribute to prothrombotic states (31–33). In neonates, anemia may exacerbate tissue hypoxia and weaken antioxidant defenses, promoting erythrocyte membrane damage, microvesicle release, and platelet activation (34,35). These mechanisms raise the possibility that anemia, although often overlooked, could be a contributing factor to thrombotic risk in this vulnerable group.

In addition to clinical and laboratory markers, emerging evidence highlights the role of socio-demographic factors in neonatal thrombosis risk. A large U.S. cohort study by Easterlin et al. (36) reported higher rates of venous thromboembolism among NICU infants with public insurance and those of Hispanic ethnicity. While our dataset did not include such variables, future research should incorporate social determinants of health into thrombotic risk models to better understand their potential interplay with biological factors in shaping CRT outcomes.

While our findings are promising, the study's retrospective design and limited sample size require cautious interpretation. Larger, multicenter prospective studies are necessary to validate the predictive accuracy of SII and to confirm its utility in CRT risk stratification. At present, no pediatric-specific risk scoring system exists for catheter-related thrombosis. Developing such tools—tailored to the unique physiology and risk profiles of neonates—could enable earlier identification of at-risk infants and improve clinical decision-making. Furthermore, machine learning–based models may offer powerful solutions for integrating diverse clinical and laboratory parameters into personalized risk prediction frameworks for NICU populations.

Conclusion

This study is, to our knowledge, the first to evaluate the predictive role of the systemic immune-inflammation index (SII) in neonatal catheter-related thrombosis (CRT). Our findings suggest that serial increases in ANC, NLR, CRP, and especially SII are strongly associated with CRT development in the NICU setting. These markers—particularly SII—may offer enhanced predictive value over conventional CBC parameters and support their integration into early risk stratification protocols. The consistently rising trend of SII in CRT cases, as opposed to stable or decreasing levels in non-CRT infants, underscores its potential clinical utility. While promising, these results should be interpreted with caution due to the study's limited sample size. Larger prospective studies are warranted to confirm these findings and to establish SII as a reliable tool for early thrombosis detection and management in neonates.

Acknowledgments

None.

Conflicts of interest

No conflict of interest was declared by the authors.

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