Research Square

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Systemic Inflammatory Biomarkers and Non-Suicidal Self-Injury in Adolescents with Mental Disorders: A Threshold Effect Analysis

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Abstract

Background

Non-suicidal self-injury (NSSI) is a prevalent and serious psychiatric concern among adolescents. Emerging evidence implicates systemic inflammation in the pathophysiology of mood disorders and impulsivebehaviors; however, the specific association between peripheral inflammatory biomarkers and NSSI in adolescents remains poorly characterized. This study aimed to evaluate the predictive value of six systemic inflammatory indices for NSSI and to explore potential non-linear threshold effects in a clinical adolescent population.

Methods

This cross-sectional study enrolled 500 adolescents hospitalized with psychiatric disorders (316 with NSSI, 184 without NSSI) between June 2024 and June 2025. Six systemic inflammatory markers—neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), and Aggregate Index of Systemic Inflammation (AISI)—were calculated from routine blood tests. Multivariable logistic regression, generalized additive models (GAM), and two-piecewise linear regression were employed to assess both linear and non-linear associations after adjusting for potential confounders.

Results

Adolescents with NSSI exhibited significantly elevated levels of NLR, PLR, and SII compared to the non-NSSI group (allp < 0.05). After full adjustment, the highest tertiles of PLR (OR = 2.05), SII (OR = 2.30), SIRI (OR = 1.97), and AISI (OR = 2.39) were independently associated with increased NSSI risk. GAM analysis revealed significant non-linear relationships, and threshold effect analysis identified critical breakpoints for PLR (K = 73.26), SIRI (K = 1.72), and AISI (K = 616.92), below which NSSI risk increased sharply. Among all markers, SII demonstrated the highest predictive performance (AUC = 0.584).

Conclusions

Composite inflammatory indices, particularly SII and AISI, are robust independent predictors of NSSI in adolescents with mental disorders. The identification of non-linear threshold effects provides novel insights into the inflammation-NSSI relationship and supports the clinical utility of these cost-effective biomarkers for early risk stratification.

1. Introduction

Non-suicidal self-injury (NSSI) is a prevalent neuropsychiatric condition during adolescence [1]. It is defined as the deliberate, socially unacceptable destruction of one's own body tissue without suicidal intent, encompassing behaviors such as cutting, burning, biting, and scratching [2]. Epidemiological studies report a global NSSI prevalence of 17.7% among adolescents [3], while the rate in Chinese adolescents reaches up to

27.4% [4]. Notably, the incidence is substantially higher among adolescents with psychiatric disorders, frequently co-occurring with severe anxiety and depression. Although distinct from suicidal attempts, NSSI is intimately linked to suicide-related behaviors [5]. Adolescents with a history of NSSI face a greater than 7-fold increased risk of suicide and are over three times more likely to experience suicidal ideation and suicide attempts compared to their non-NSSI peers [6]. Consequently, NSSI has emerged as a critical public health issue severely compromising adolescent mental health.

Accumulating evidence suggests that immune dysregulation and systemic inflammation play a crucial role in the pathophysiology of depression and related psychiatric conditions. Peripheral pro-inflammatory cytokines can cross the blood-brain barrier to activate glial cells, thereby triggering neuroinflammation that directly affects mood and behavior [7–9]. This inflammatory cascade is deeply intertwined with several pathogenic mechanisms of major depressive disorder (MDD), including hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, glutamatergic dysfunction, impaired neuroplasticity, gut microbiota dysbiosis, and altered tryptophan metabolism [10–11]. Clinically, depressive symptoms are strongly correlated with low-grade systemic inflammation [12–13], and successful antidepressant treatment is often accompanied by a reduction in pro-inflammatory markers[14]. Thus, chronic inflammation is increasingly recognized as a significant risk factor for the development and exacerbation of psychiatric symptoms[15] .

In clinical practice, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) are widely utilized as cost-effective, easily accessible, and reproducible markers of systemic inflammation [16–18]. By reflecting the balance between distinct immune pathways, these ratios offer superior predictive value and are less susceptible to confounding physiological factors than individual cell counts [19]. Recently, novel composite indicators, such as the Systemic Immune-Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI), have been developed to provide a more comprehensive assessment by integrating neutrophil, monocyte, platelet, and lymphocyte counts [20–21]. Similarly, the Aggregate Index of Systemic Inflammation (AISI), originally designed to evaluate inflammatory status in idiopathic pulmonary fibrosis (IPF) [22], has proven valuable in reflecting the systemic immune-thrombosis network. Although initially applied to somatic conditions like rheumatoid arthritis[23] and hypertension[24], the utility of these multifaceted indices in neuropsychiatric research is gaining attention.

Previous studies have demonstrated altered inflammatory profiles in psychiatric inpatients, particularly those diagnosed with schizophrenia and bipolar disorder [25]. In pediatric populations, significantly elevated NLR, PLR, and MLR have been observed in children with attention-deficit/hyperactivity disorder (ADHD) and adolescents with anxiety disorders compared to healthy controls [26]. Regarding self-harming behaviors, Ekinci et al. proposed that NLR could serve as a biological marker for suicide vulnerability in patients with MDD [27]. Furthermore, Puangsri et al. found that depressed adolescents with a history of suicide attempts exhibited higher MLR levels, and both MLR and NLR were positively correlated with the severity of suicidality[28].

Despite these insights, the specific association between peripheral inflammatory markers and NSSI—a behavioral phenotype distinct from suicide—remains underexplored in hospitalized adolescents with mental disorders. Moreover, the predictive capacity of novel composite indices (SII, SIRI, and AISI) for NSSI has never been evaluated in this population. Most importantly, previous psychiatric research has largely assumed a strict

linear relationship between inflammation and clinical symptoms, overlooking potential threshold effects of immune activation. Therefore, this study aims to comprehensively analyze six inflammatory indicators (NLR, PLR, MLR, SII, SIRI, and AISI) in a cohort of psychiatric adolescents. By exploring both independent linear associations and non-linear threshold effects, we seek to validate the clinical utility of these biomarkers as objective diagnostic and risk-stratification tools for NSSI.

2. Materials and Methods

2.1. Study Design and Participants

This cross-sectional observational study consecutively recruited 500 adolescent patients hospitalized at Hainan Anning Hospital between June 2024 and June 2025. The study protocol was approved by the Institutional Review Board of Hainan Anning Hospital (Approval No. : HYMLL-2025-159) and was conducted in strict accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and their legal guardians prior to enrollment.

The inclusion criteria were as follows: (1) age between12 and 18 years; (2) a primary diagnosis of psychiatric disorders according to the International Classification of Diseases, 10th Revision (ICD-10), including major depressive disorder (MDD), bipolar disorder (BD), anxiety disorders (AD), or behavioral and emotional disorders with onset usually occurring in childhood and adolescence; (3) engaging in non-suicidal self-injury (NSSI) behavior, defined according to DSM-5 criteria, with at least one episode of self-harm in the past month. Participants were categorized into the NSSI group and the non-NSSI group based on their history of self-injury, which was ascertained through direct clinical interviews and medical record reviews.

The exclusion criteria included: (1) presence of severe somatic diseases, particularly those associated with systemic inflammatory responses such as active infections, fever, or acute/chronic endocrine disorders; and (2) use of anti-inflammatory drugs, corticosteroids, or antipyretics within two weeks prior to admission.

2.2. Clinical Data Collection and Symptom Assessment

Sociodemographic and clinical characteristics were collected using a structured questionnaire administered by specially trained psychiatric nurses. The collected data included age, gender, ethnicity, disease duration, diagnosis, family history of mental illness, history of aggression, and suicidal behaviors (suicide attempts and current suicidal ideation). All questionnaire data were subsequently cross-validated with the hospital's electronic medical record system, and patient identities were de-identified to ensure confidentiality.

The severity of depressive and anxiety symptoms over the past week was evaluated using the 17-item Hamilton Depression Rating Scale (HAMD-17) [29]and the 14-item Hamilton Anxiety Rating Scale (HAMA-14)[30], respectively. Both scales are widely validated instruments in psychiatric assessments. In the present study sample, the scales demonstrated acceptable internal consistency, with Cronbach's alpha coefficients of 0.716 for the HAMD-17 and 0.819 for the HAMA-14.

2.3. Laboratory Measurements and Inflammatory Biomarkers

Fasting peripheral venous blood samples were collected from all participants between 6:00 AM and 8:00 AM on the first day of admission (following an overnight fast of at least 8 hours). Blood samples were drawn into

EDTA-containing tubes and promptly analyzed using an automated hematology analyzer to obtain complete blood counts, including absolute numbers of white blood cells, neutrophils (N), lymphocytes (L), monocytes (M), and platelets §.

Based on these absolute counts, six systemic inflammatory indices were calculated as follows:

NLR = N / L;MLR = M / L□PLR = P / L□SII = (P × N) / L□SIRI = (N × M) / L

AISI = (N × M × P) / L

2.4. Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were expressed as frequencies and percentages. Baseline group differences in inflammatory markers and clinical characteristics were compared using the independent-samplest-test or Chi-square test, as appropriate.

To identify independent associations between inflammatory indices and NSSI, multivariable logistic regression analyses were conducted across three hierarchical models: Model 1 was unadjusted; Model 2 was adjusted for sociodemographic factors (age, gender, and ethnicity); and Model 3 was fully adjusted for variables showing clinical relevance or significance in univariate analyses (age, gender, ethnicity, diagnosis, disease duration, suicidal ideation, suicide attempt history, history of aggression, and HAMD/HAMA severity). Furthermore, to evaluate the dose-response relationship, the continuous inflammatory markers were transformed into categorical variables (tertiles), andP for trendwas calculated.

To explore potential non-linear relationships, Generalized Additive Models (GAM) and smooth curve fitting were applied. If non-linearity was detected, a two-piecewise linear regression model was utilized to calculate the threshold effect (breakpointK). The log-likelihood ratio test was used to compare the fit of the piecewise model against the standard linear model.

Finally, Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the biomarkers. Data normalization was completed prior to the ROC analysis to minimize the impact of individual variations and systematic errors. All statistical analyses were executed using R software (version 4.1.3) and SPSS version 26.0. A two-tailedp-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics of Participants

The demographic and clinical characteristics of the study population are summarized in Table 1. A total of 500 adolescents were included, with 316 (63.2%) in the NSSI group and 184 (36.8%) in the non-NSSI group. Compared with the non-NSSI group, the NSSI group was characterized by a significantly higher proportion of females (82.6% vs. 68.5%,p < 0.001) and a longer disease duration (p = 0.001). Clinical assessments showed that adolescents with NSSI exhibited more severe depressive symptoms (Severe depression: 68.4% vs. 48.4%), higher levels of anxiety, and a significantly higher prevalence of suicide attempt history (37.7% vs. 13.6%) and current suicidal ideation (86.4% vs. 59.2%) (allp < 0.001).

In terms of laboratory indicators, the NSSI group demonstrated markedly higher systemic inflammatory levels, including SII (723.63 ± 1078.54 vs. 443.69 ± 539.52,$p < 0.001$), NLR (2.01 ± 2.56 vs. 1.45 ± 1.71,$p = 0.004$), and PLR (142.10 ± 100.19 vs. 124.13 ± 81.59,$p = 0.030$). Significant intergroup differences were also observed in absolute counts of white blood cells ($p = 0.040$), neutrophils ($p = 0.019$), and platelets ($p = 0.035$), while no significant difference was found for MLR ($p = 0.649$).

Table 1
Demographic characteristics of the NSSI group and the non-NSSI group

Variables	NSSI (n = 316)	Non-NSSI (n = 184)	Z/χ^2	P
MLR	0.28 ± 1.02	0.33 ± 1.72	0.456	0.649
NLR	2.01 ± 2.56	1.45 ± 1.71	-2.930	0.004
PLR	142.10 ± 100.19	124.13 ± 81.59	-2.180	0.030
SIRI	1.329 ± 3.581	1.036 ± 3.586	1.042	0.379
SII	723.63 ± 1078.54	443.69 ± 539.52	-3.859	<0.001
AISI	468.25 ± 1189.71	308.80 ± 990.36	3.107	0.108
Age	15.00 ± 1.74	14.78 ± 1.77	-1.321	0.187
Gender			13.248	< 0.001
Male	55(17.4)	58(31.5)		
Female	261(82.6)	126(68.5)		
Ethnicity			3.525	0.172
Han	287(90.8)	174(94.6)		
Ethnic minorities	29(9.2)	10(5.4)		
Disease Duration			14.345	0.001
<1 year	51(16.1)	54(29.3)		
1–3 year	196(62.0)	105(57.1)		
>3 year	69(21.8)	25(13.6)		
Diagnosis			71.725	< 0.001
Moderate to severe depression	234(74.1)	111(60.3)		
Schizophrenia	12(3.8)	39(21.2)		
Bipolar disorder	52(16.5)	9(4.9)		
Other mental disorders	18(5.3)	25(13.6)		
Family History of Mental Illness			0.266	0.606
No	291(92.1)	167(90.8)		
Yes	25(7.9)	17(9.2)		
History of Aggression			0.165	0.685
No	296(98.3)	180(97.8)		
Yes	5(1.7)	4(2.2)		

Variables	NSSI (n = 316)	Non-NSSI (n = 184)	Z/χ²	P
Suicide Attempt History			32.686	<0.001
No	188(62.3)	159(86.4)		
Yes	114(37.7)	25(13.6)		
Suicidal Ideation			47.553	< 0.001
No	43(13.6)	75(40.8)		
Yes	273(86.4)	109(59.2)		
Hamilton Depression Rating			32.352	< 0.001
Normal	11(3.5)	15(8.2)		
Possible depression	34(10.8)	51(27.7)		
Definite depression	55(17.4)	29(15.8)		
Severe depression	216(68.4)	89(48.4)		
Hamilton Anxiety Rating			27.422	< 0.001
No significant anxiety	63(19.9)	75(40.8)		
Mild anxiety	99(31.3)	46(25.0)		
Moderate anxiety	99(31.3)	47(25.5)		
Severe anxiety	55(17.4)	16(8.7)		
WBC (10^3/μL)	7.06 ± 1.89	6.71 ± 1.67	-2.056	0.040
LYM (10^3/μL)	2.86 ± 1.92	2.64 ± 0.67	-2.005	0.061
MON (10^3/μL)	0.71 ± 3.13	0.76 ± 3.10	0.171	0.864
NEU (10^3/μL)	4.72 ± 5.40	3.67 ± 4.42	-2.349	0.019
PLT (10^3/μL)	356.99 ± 249.24	293.71 ± 62.76	-2.117	0.035

MLR, Monocyte-to-Lymphocyte Ratio;NLR, Neutrophil-to-Lymphocyte Ratio;PLR, Platelet-to-Lymphocyte Ratio;SII, Systemic Immune-Inflammation Index;SIRI, Systemic Inflammation Response Index;AISI, Aggregate Index of Systemic Inflammation;WBC, White Blood Cell Count;LYM, Lymphocyte Count;MON, Monocyte Count;NEU, Neutrophil Count;PLT, Platelet Count.

3.2. Association Between Inflammatory Biomarkers and NSSI

Multivariable logistic regression was employed to evaluate the independent associations between inflammatory markers and NSSI (Table 2). In the fully adjusted model (Model 3),NLRanalyzed as a continuous variable remained significantly associated with NSSI (OR = 1.23, 95% CI: 1.02–1.48,p = 0.0313).

When biomarkers were analyzed as tertiles, the highest tertiles (T3) of PLR, SII, SIRI, and AISI demonstrated significant positive associations with NSSI risk compared to the lowest tertiles (T1). Specifically, the adjusted ORs in Model 3 were2.05(95% CI: 1.21–3.48,p = 0.0077) forPLR,2.30(95% CI: 1.34–3.96,p = 0.0026) forSII,1.97(95% CI: 1.16–3.34,p = 0.0119) forSIRI, and2.39(95% CI: 1.39–4.12,p = 0.0016) forAISI. Trend tests further confirmed that the risk of NSSI increased significantly with rising levels of PLR (P for trend = 0.008), SII (P for trend = 0.0037), SIRI (P for trend = 0.012), and AISI (P for trend = 0.0018). MLR did not show a significant association in any model.

Table 2
Multivariable logistic regression analysis of the association between inflammatory biomarkers and NSSI.

Index	Continuous.or.categories	Model1		Model2		Model3	
		OR(95%CI)	P	OR(95%CI)	P	OR(95%CI)	P
NLR	Continuous variable	1.19(1.02, 1.38)	0.0254	1.20 (1.03, 1.39)	0.0212	1.23 (1.02, 1.48)	0.0313
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	0.68(0.43, 1.06)	0.085	0.67 (0.43, 1.06)	0.0903	0.69 (0.42, 1.14)	0.1478
	Tertile 3	1.10(0.70, 1.75)	0.6697	1.18 (0.73, 1.88)	0.5031	1.31 (0.77, 2.22)	0.3214
	P for trend	0.6790		0.5255		0.3520	
PLR	Continuous variable	1.00(1.00, 1.01)	0.0869	1.00 (1.00, 1.01)	0.1159	1.00 (1.00, 1.01)	0.1474
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	0.96(0.62, 1.50)	0.8723	0.98 (0.62, 1.53)	0.9206	1.15 (0.69, 1.90)	0.5959
	Tertile 3	1.93(1.21, 3.07)	0.0055	1.91 (1.19, 3.07)	0.0072	2.05 (1.21, 3.48)	0.0077
	P for trend	0.0062		0.0081		0.008	
MLR	Continuous variable	0.97(0.85, 1.11)	0.6323	0.96 (0.84, 1.10)	0.5469	0.92 (0.81, 1.06)	0.257
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	0.82(0.53, 1.29)	0.3989	0.89 (0.56, 1.41)	0.6124	0.98 (0.59, 1.63)	0.9413
	Tertile 3	1.00(0.64, 1.57)	1	1.15 (0.72, 1.84)	0.5489	1.25 (0.74, 2.12)	0.3992
	P for trend	1		0.5471		0.4048	
SII	Continuous variable	1.00(1.00, 1.00)	0.0037	1.00 (1.00, 1.00)	0.0043	1.00 (1.00, 1.00)	0.0039
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	0.73(0.47, 1.14)	0.1636	0.75 (0.48, 1.18)	0.2089	0.75 (0.45, 1.24)	0.2621
	Tertile 3	1.91(1.19, 3.07)	0.0069	2.08 (1.28, 3.38)	0.0032	2.30 (1.34, 3.96)	0.0026
	P for trend	0.0087		0.004		0.0037	
SIRI	Continuous variable	1.02(0.96, 1.09)	0.491	1.03 (0.96, 1.10)	0.472	1.00 (0.94, 1.07)	0.9147

	Tertile 1	Reference		Reference		Reference	
	Tertile 2	1.10(0.71, 1.72)	0.6704	1.21 (0.77, 1.92)	0.4111	1.32 (0.79, 2.20)	0.2897
	Tertile 3	1.60(1.01, 2.52)	0.0433	1.79 (1.12, 2.86)	0.0151	1.97 (1.16, 3.34)	0.0119
	P for trend	0.0445		0.0152		0.012	
AISI	Continuous variable	1.00(1.00, 1.00)	0.2351	1.00 (1.00, 1.00)	0.207	1.00 (1.00, 1.00)	0.4788
	Tertile 1	Reference		Reference		Reference	
	Tertile 2	0.85(0.55, 1.32)	0.4702	0.91 (0.58, 1.43)	0.683	0.99 (0.60, 1.64)	0.966
	Tertile 3	1.89(1.19, 3.02)	0.0074	2.05 (1.27, 3.31)	0.0033	2.39 (1.39, 4.12)	0.0016
	P for trend	0.0087		0.0037		0.0018	

In sensitivity analysis, MLR, NLR, PLR, SII, SIRI, and AISI, were converted fromcontinuous variablesto categorical variables (tertiles).

Model 1: No covariates were adjusted.

Model 2: Adjusted for age, gender, and ethnicity.

Model 3: Adiusted for age, gender, ethnicity, disease duration, diagnosis, family history of mental illness, history of aggression, suicide attempt history, suicidal ideation, hamilton depression rating, and hamilton anxiety rating.

3.3. Non-linear Relationships and Threshold Effect Analysis

Smoothing curve fitting using GAM revealed that the associations between inflammatory biomarkers and NSSI in hospitalized adolescents with mental disorders were non-linear (Fig. 1). Threshold effect analysis (Table 3) identified significant breakpoints (K) for PLR, SIRI, and AISI.

For PLR, the breakpoint was 73.26; below this threshold, the OR was 0.94 (95% CI: 0.89–0.99,p = 0.013), and above it, the OR became 1.00 (95% CI: 1.00–1.01,p = 0.009). ForSIRI, a significant threshold effect was found at1.72(pfor log-likelihood ratio test = 0.011); below the breakpoint, the OR was 1.67 (95% CI: 1.12–2.50,p = 0.012), while the association was non-significant above it.AISIalso exhibited a marked threshold effect at616.92(pfor log-likelihood ratio test < 0.001), showing a significant positive association only below the breakpoint.

Table 3
Threshold effect analysis of inflammatory biomarkers on NSSI risk using two-piecewise linear regression.

Variables	NLR	PLR	MLR	SII	SIRI	AISI
Standard linear model						
OR	1.23 (1.02, 1.48)	1.00 (1.00, 1.01)	0.92 (0.81, 1.06)	1.00 (1.00, 1.00)	1.00 (0.94, 1.07)	1.00 (1.00, 1.00)
P	0.0313	0.1474	0.257	0.0039	0.9147	0.4788
Fitting by two-piecewise linear model						
Breakpoint (K)	1.64	73.26	0.11	1000.72	1.72	616.92
OR1 (< K)	0.78 (0.46,1.34)	0.94 (0.89,0.99)	4.36(0.14,137.17)	1.00(1.00, 1.00)	1.67(1.12, 2.50)	1.00(1.00, 1.00)
	0.375	0.013	0.403	0.002	0.012	<0.001
OR2 (> K)	1.32 (1.05,1.65)	1.00 (1.00,1.01)	0.96 (0.84, 1.10)	1.00(1.00, 1.00)	0.99(0.94, 1.05)	1.00(1.00, 1.00)
	0.016	0.009	0.601	0.294	0.859	0.840
OR2/OR1	1.68 (0.88,3.22)	1.07 (1.02,1.13)	0.22 (0.01, 6.99)	1.00(1.00, 1.00)	0.59(0.39, 0.91)	1.00(1.00, 1.00)
	0.117	0.009	0.392	0.060	0.016	<0.001
Logarithmic likelihood ratio test p-value	0.108	0.001	0.261	0.076	0.011	<0.001

3.4. Evaluation of Predictive Performance

The ROC analysis was used to compare the predictive capacity of the inflammatory biomarkers for NSSI behavior (Fig. 2). As shown in Table 4, the AUC values for PLR, SII, SIRI, and AISI were all statistically significant ($p < 0.05$). Among them,SII exhibited the highest AUC (0.584, 95% CI: 0.534–0.634), followed by AISI(AUC: 0.583, 95% CI: 0.533–0.633),PLR(AUC: 0.566, 95% CI: 0.516–0.616), and SIRI(AUC: 0.549, 95% CI: 0.498–0.600).

The ROC analysis was used to evaluate the discriminatory capacity of the inflammatory biomarkers for NSSI (Fig. 2, Table 4). Among all markers, SII exhibited the highest AUC (0.584, 95% CI: 0.534–0.634), followed by AISI (0.583), PLR (0.566), and SIRI (0.549), all reaching statistical significance ($p < 0.05$). Although the AUC values were modest, they indicate potential utility as accessible screening biomarkers when combined with clinical assessment.

Table 4
Predictive performance of inflammatory biomarkers for NSSI based on ROC analysis.

Variables	AUC	OR(95%CI)	Cut-off	Sensitivity(%)	specificity(%)	P
NLR	0.470	0.419–0.521	1.026	32.9	70.1	0.485
PLR	0.566	0.516–0.616	148.496	34.5	81.5	<0.001
MLR	0.506	0.454–0.557	0.194	56	50.5	0.157
SII	0.584	0.534–0.634	521.365	38	79.3	<0.001
SIRI	0.549	0.498-0.600	1.239	20.9	91.3	<0.001
AISI	0.583	0.533–0.633	271.137	41.8	75.5	<0.001

4. Discussion

4.1. Principal Findings To our knowledge, this is the first study to comprehensively evaluate both traditional (NLR, PLR, MLR) and novel composite (SII, SIRI, AISI) systemic inflammatory indices in relation to non-suicidal self-injury (NSSI) among adolescents with psychiatric disorders. Beyond confirming the overall elevation of inflammatory markers in the NSSI group, our multivariable analysis established that composite indices—specifically SII and AISI—are superior independent predictors of NSSI risk. Most notably, we identified distinct non-linear threshold effects for PLR, SIRI, and AISI, revealing a critical “inflection point” where the risk of self-harming behavior escalates sharply.

4.2. Inflammatory Ratios: Bridging the Gap Between Depression, Suicidality, and NSSI Extensive literature has established a baseline of immune-inflammatory activation in mood disorders. Meta-analyses by Mazza[31]and Su[32] confirmed that elevated NLR and PLR are robustly associated with the pathophysiology of bipolar disorder and major depressive disorder (MDD). However, our findings suggest that inflammatory dysregulation in NSSI extends beyond mere depressive symptomatology. Recent evidence indicates that severe self-harming behaviors, particularly suicidal ideation (SI) and suicide attempts (SA), possess distinct immunological profiles.Daray[33]and Moshfeghinia[34] demonstrated broad alterations in peripheral immune cells, notably increased NLR and MLR, in depressed patients with suicidal behaviors compared to non-suicidal counterparts. Similarly,Pethő proposed NLR as a biomarker for acute suicide risk[35], while Puangsri highlighted elevated MLR and monocyte counts in depressed adolescents with a history of SA[36]. Interestingly, while our NSSI cohort exhibited significantly elevated NLR and PLR, MLR did not emerge as an independent predictor in the fully adjusted model. This discrepancy is theoretically profound: NSSI and SA, though highly comorbid, are driven by different immediate psychological motives (affect regulation vs. intent to die). The predominance of neutrophil- and platelet-driven indices (NLR, PLR) in our NSSI cohort, as opposed to the monocyte-driven pattern (MLR) often seen in SA, implies that NSSI may represent a specific subtype of acute psycho-neuroimmunological stress response rather than a direct equivalent of suicidal vulnerability.

4.3. The Superior Predictive Capacity of Composite Indices (SII, SIRI, AISI)A major methodological advancement of this study is the integration of multiparametric indices.Liu et al.recently explored novel leukocyte-derived ratios in unmedicated MDD, noting significant alterations in systemic immune networks[37].

Building upon this, our data unequivocally show that SII (OR = 2.30) and AISI (OR = 2.39) in the highest tertiles outperform single-cell ratios in predicting NSSI. Biologically, indices like AISI integrate neutrophils, monocytes, lymphocytes, and platelets, thereby capturing the complex interplay between the innate immune response and the coagulation cascade (immune-thrombosis). The superior predictive power of AISI suggests that adolescent NSSI is not merely a localized neurochemical imbalance, but is accompanied by a profound, system-wide mobilization of multiple inflammatory pathways.

4.4. Mechanistic Interpretation of Non-Linear Threshold Effects The most striking finding of our study is the non-linear relationship between inflammation and NSSI, characterized by specific breakpoints. Most previous psychiatric research assumed a strict linear correlation. However, our piecewise regression indicates a "tolerance limit" within the adolescent neuro-immune axis. This threshold effect can be elucidated through recent neurobiological models. As demonstrated by Norman in murine models of spared nerve injury, peripheral somatic stress induces the upregulation of pro-inflammatory cytokines (such as IL-1β), which subsequently cross the blood-brain barrier to trigger depressive-like behaviors via glial activation[38]. In the context of adolescents,Wu et al.recently utilized spatial transcriptomics to reveal that specific neurobiological subtypes of adolescent depression are driven by microglial activation and astrocytic dysregulation, leading to severe emotional dysregulation and heightened impulsivity[39]. Synthesizing these concepts, we hypothesize that below the inflammatory threshold, the adolescent blood-brain barrier and compensatory glial mechanisms maintain homeostatic resilience. However, once peripheral inflammation breaches this critical "tipping point," a cascade of neuroinflammation ensues—disrupting frontoparietal networks and monoaminergic pathways. This abrupt synaptic interference clinically manifests as the intense affective instability and impaired impulse control that precipitate acute NSSI episodes.

4.5. Clinical Utility Given the high prevalence of NSSI in psychiatric adolescents, identifying objective, accessible biomarkers is imperative. The parameters required to calculate SII and AISI are derived from routine, low-cost complete blood counts (CBC). Our findings suggest that clinicians should remain highly vigilant when a patient's inflammatory indices approach the identified thresholds, as this may signal an impending escalation in impulsivity and self-harm risk, warranting preemptive psychological or pharmacological intervention.

4.6. Limitations Several limitations must be acknowledged. First, the cross-sectional design precludes causal inferences between systemic inflammation and NSSI. Second, as highlighted by Puangsri, psychotropic medications—particularly SSRIs—can significantly alter CBC parameters, including reductions in MLR and neutrophil counts[36]. Although we adjusted for diagnostic categories and symptom severity, the heterogeneous medication status of our hospitalized cohort may have residually confounded the inflammatory profiles. Future longitudinal studies in drug-naïve cohorts, supplemented with specific cytokine assays (e.g., IL-6, TNF-α), are required to validate the inflammatory thresholds identified herein.6

5. Conclusion

Systemic inflammatory dysregulation is intricately linked to the pathogenesis of non-suicidal self-injury (NSSI) in adolescents with mental disorders. Among the evaluated biomarkers, the multifaceted composite indices—specifically SII andAISI—emerged as the most robust independent predictors of NSSI risk, outperforming traditional single-cell ratios. Crucially, the identification of significantnon-linear threshold effectsfor PLR, SIRI,

and AISI reveals a critical window where NSSI vulnerability escalates rapidly during the initial stages of inflammatory elevation. By integrating these accessible, cost-effective hematological markers into predictive models, clinicians can achieve more objective risk stratification, thereby facilitating early screening and targeted interventions for this high-risk population.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Hainan Anning Hospital (Approval No.: HYMLL-2025-159). Written informed consent was obtained from all participants and their legal guardians prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

CAO Xinyi and GAO Xueyi designed the study and wrote the manuscript. ,LIN Yin and HE Yan collected and analyzed the data. All authors read and approved the final manuscript.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

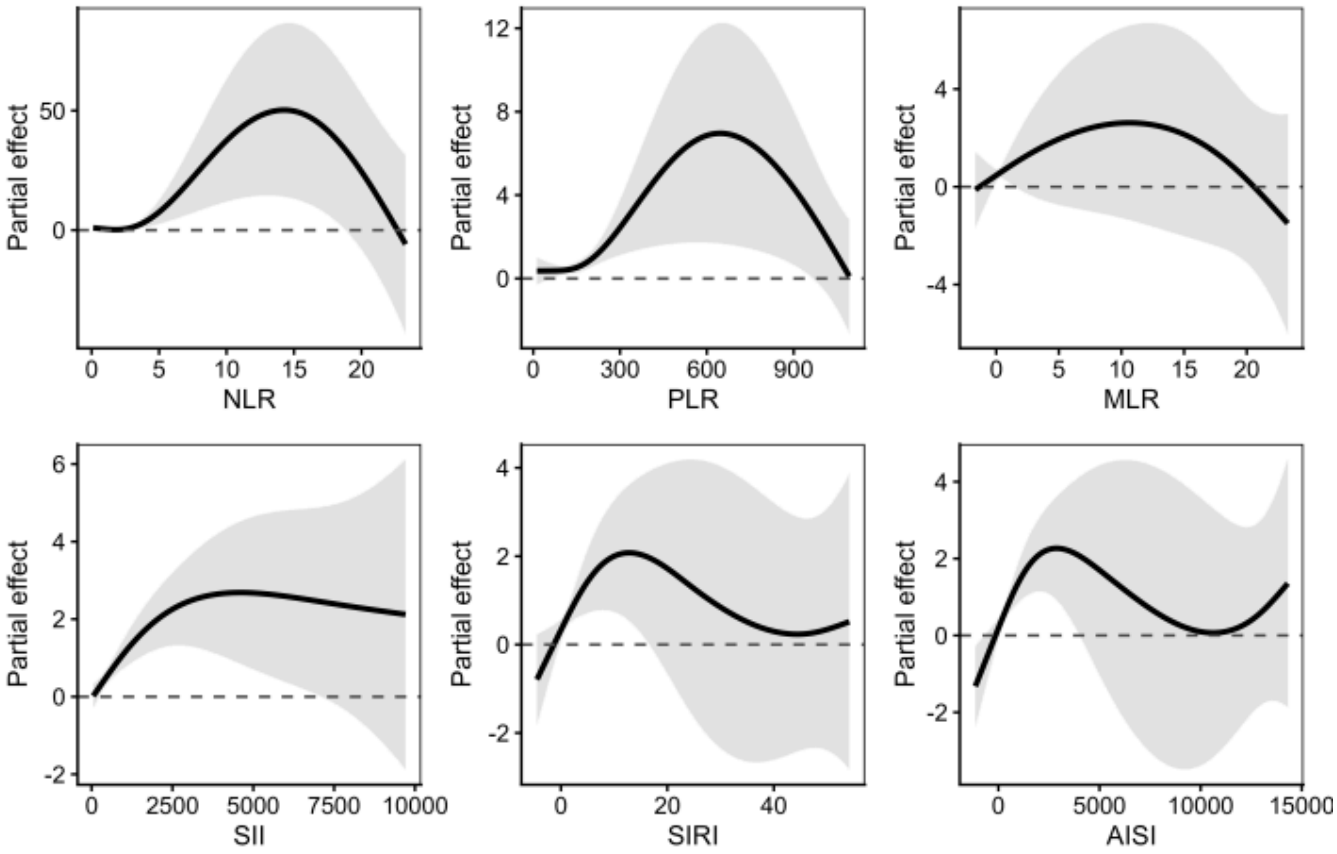

Figure 1

Dose-response relationships between inflammatory biomarkers and the risk of NSSI using generalized additive models (GAM).

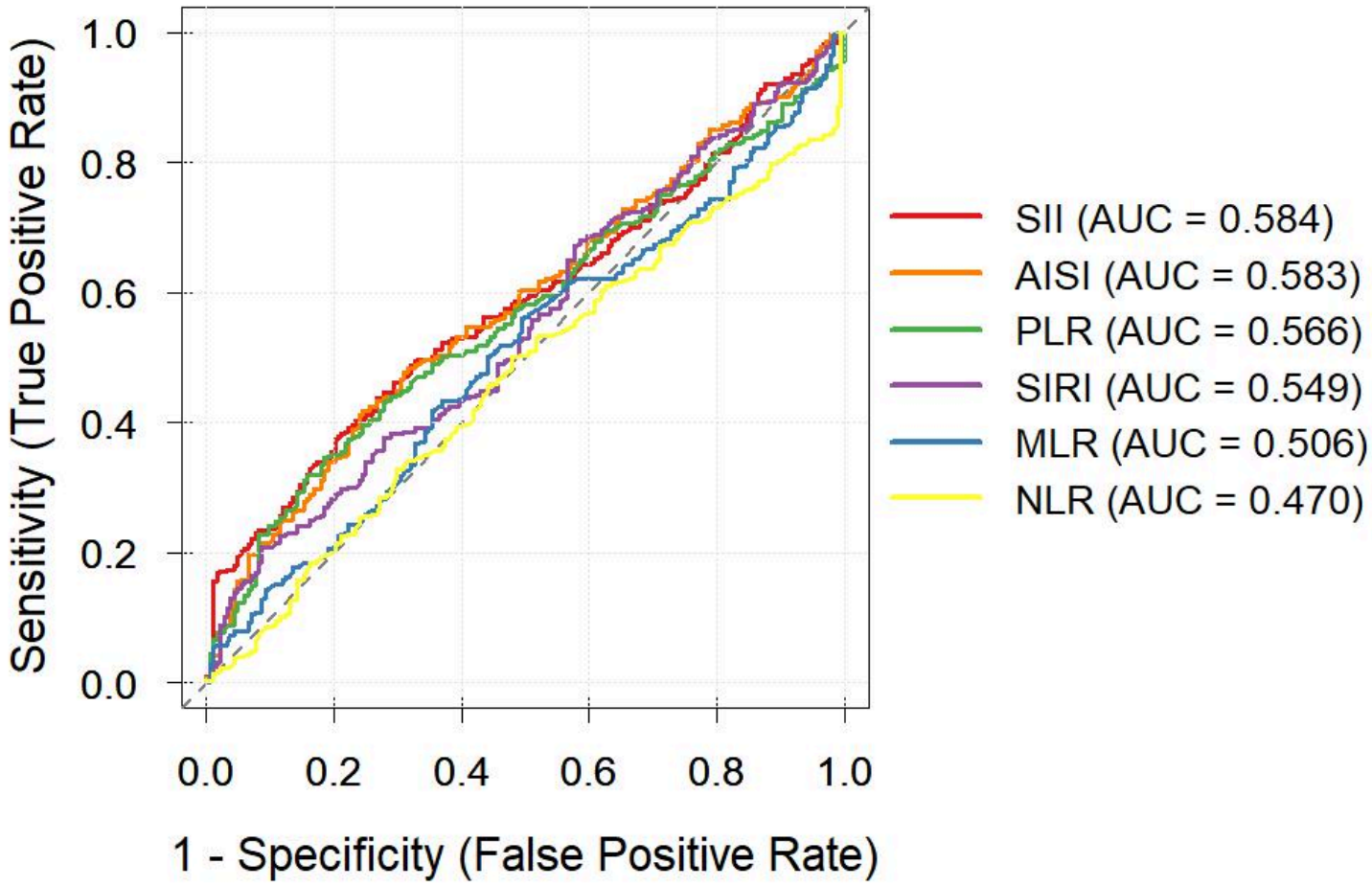

Figure 2

Receiver operating characteristic (ROC) curves of inflammatory biomarkers for predicting NSSI in adolescents.