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Interleukin-12 Dynamic Changes as a Predictive Biomarker of Antidepressant Response in Adolescents with MDD and Comorbid NSSI: A Prospective Longitudinal Study

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Abstract

Background

Non-suicidal self-injury (NSSI) is highly prevalent in adolescents with major depressive disorder (MDD) and poses a critical public health threat. While inflammatory dysregulation is implicated in both conditions, dynamic cytokine changes during treatment and their predictive value for therapeutic response remain unclear, especially for interleukin-12 (IL-12).

Methods

This prospective longitudinal study enrolled 68 psychotropic-naïve adolescent inpatients aged 12–17 years, all diagnosed with MDD and comorbid NSSI according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*.Participants were stratified into high- and low-inflammation groups based on median baseline C-reactive protein level (0.58 mg/L), and received 6 weeks of selective serotonin reuptake inhibitor (SSRI) monotherapy. Ten inflammatory cytokines were measured via enzyme-linked immunosorbent assay (ELISA) at baseline and follow-up, alongside validated clinical symptom assessments. Correlation and regression analyses identified predictors of treatment response.

Results

At baseline, the high-inflammation group had significantly lower self-esteem and perceived social support, higher suicide risk, and elevated TNF-α, IL-6, and IL-1 levels (all $P < 0.05$). After treatment, both groups showed improved depressive symptoms ($P = 0.001$), while only the high-inflammation group showed significant anxiety reduction ($P = 0.009$). Core pro-inflammatory cytokines were downregulated, with compensatory increases in anti-inflammatory factors. Notably, ΔIL-12 was positively correlated with Hamilton Depression Rating Scale (HAMD) ($r = 0.473$, $P = 0.011$) and Hamilton Anxiety Rating Scale (HAMA) ($r = 0.531$, $P = 0.004$) reduction rates, and was the sole independent predictor of symptomatic improvement ($\beta = 0.453$, $P = 0.037$; $\beta = 0.454$, $P = 0.030$).

Conclusions

Adolescents with MDD and comorbid NSSI exhibited a distinct hyperinflammatory phenotype. SSRI treatment restored inflammatory homeostasis, and ΔIL-12 independently predicted treatment response, supporting its potential as a novel dynamic biomarker for precision psychiatry in this population.

Background

Non-suicidal self-injury (NSSI), defined as deliberate self-inflicted harm without suicidal intent [1], is a critical public health concern, particularly among adolescents. The potential underlying motivations of NSSI in adolescents may be to eliminate life difficulties, release stress, or regulate emotions [2]. A meta-analysis pooling data from 62 studies (264,638 adolescents) reported that the aggregate prevalence of NSSI in a non-clinical sample of adolescents was similar between over a lifetime (22.0%, 95% CI 17.9–26.6) and during a 12-month period (23.2%, 95% CI 20.2–26.5) [3]. The estimated lifetime prevalence of NSSI among the Chinese youth

population is alarmingly high, at 24.7% (N = 1,088,433) [4]. The inclusion of NSSI as a distinct clinical condition in the DSM-5 underscores its clinical significance; however, its neurobiological mechanisms remain poorly understood.

China contributes to roughly 17% of the global burden of mental disorders, reflecting a substantial public health challenge [5]. In the past four decades, China witnessed dramatic socioeconomic changes driven by industrialization and urbanization, which have exerted adverse effects on the psychological well-being of children and adolescents across the nation [6]. According to the first nationwide psychiatric epidemiological survey in this demographic, the general prevalence of mental health disorders reached 17.5%, marking the highest recorded rate in China's history and underscoring the profound societal impact of these conditions [7]. Further evidence came from a clinical sample of 394 psychiatric inpatients in Beijing: 62.2% of them disclosed engaging in NSSI within the preceding year [8]. These elevated rates indicate that mental health disorders are a pressing concern in contemporary Chinese society. Potential contributing factors include heightened stress levels, negative life events, and poor interpersonal relationships [9], all of which may exacerbate psychological distress among vulnerable populations.

NSSI is strongly linked to depression [10]. While psychological factors such as emotional dysregulation, trauma, and social stressors are well-documented contributors to NSSI and mood disorders [11, 12], biological mechanisms, particularly inflammatory pathways, are underexplored [13]. Emerging evidence suggests that neuroinflammation and cytokine dysregulation underlie both mood disorders and self-harm behaviors [14, 15]. For instance, elevated interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are associated with depression severity and suicide risk [16]; however, their role in NSSI remains unclear.

Research has highlighted the critical role of inflammatory dysregulation in both NSSI and suicidal ideation/behaviors [17]. Elevated pro-inflammatory cytokines, including C-reactive protein (CRP), IL-1, IL-6, and TNF-α, were consistently linked to NSSI frequency in adolescents with depression, mediated by corticostriatal reward circuit dysfunction[18]. Similarly, suicidal ideation and suicide attempts were associated with aberrant inflammatory dynamics under stress, such as elevated TNF-α levels and impaired stress-response plasticity [19]. Furthermore, systemic inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR) and high-sensitivity C-reactive protein (hs-CRP), have shown high predictive accuracy for NSSI, supporting their utility as peripheral biomarkers for early risk identification and targeted intervention [20]. These findings highlight the involvement of inflammation in the pathophysiology of depression [21] and NSSI, indicating a brain-immune interaction as a potential mechanism underlying self-injurious behavior [22].

Despite growing evidence linking inflammatory cytokines to NSSI, several challenges persist. Primarily, the lack of longitudinal studies hinders understanding of causality and temporal dynamics between inflammation and NSSI, with existing research being predominantly cross-sectional [20]. This impedes insight into whether inflammation precedes or follows NSSI behaviors. Additionally, there is considerable heterogeneity in studied inflammatory markers, complicating comparative analyses. Studies often focus on different cytokines, such as IL-6, IL-8, and TNF-α [16, 23], without consensus on which are most pertinent to NSSI, leading to fragmented findings. Another underexplored area is how genetic predispositions interact with environmental factors to influence inflammatory responses linked to NSSI. The role of psychosocial factors, including stress and trauma, in modulating these processes also warrants further investigation [12]. Finally, while targeting inflammatory pathways shows promise for treating NSSI, randomized controlled trials that confirm these hypotheses and

assess the efficacy of anti-inflammatory treatments are scarce. Addressing these gaps is essential for advancing knowledge and developing more effective interventions for individuals engaging in NSSI.

This study is the first to investigate inflammatory dysregulation in adolescents with major depressive disorder (MDD) and comorbid NSSI, with a dual focus on inflammatory stratification and treatment response. By integrating longitudinal biomarker profiling with clinical symptom trajectories, this study establishes a novel precision psychiatry framework for the clinical management of NSSI. Furthermore, it characterizes the utility of inflammatory thresholds to guide therapeutic decision-making, thereby addressing a critical unmet gap in adolescent mental health research.

Methods

Participants

The study protocol was approved by the Ethics Committee of Xi'an Jiaotong University (approval number XJTU1AF2022LSK-171). The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from legal guardians of all participants, and written assent was provided by all adolescent participants. We enrolled 68 psychotropic-naïve adolescent inpatients (aged 12–17 years) with a DSM-5 diagnosis of MDD and comorbid NSSI, who were hospitalized at the Department of Psychiatry of the First Affiliated Hospital of Xi'an Jiaotong University; all patients were assessed as requiring antidepressant treatment by certified child and adolescent psychiatrists.

Participant exclusion criteria were: (1) use of medications affecting serum inflammatory markers (e.g., antibiotics, nonsteroidal anti-inflammatory drugs) within 3 months prior to enrollment; (2) a history of manic/hypomanic episodes, neurological disorders, severe systemic disease, substance use disorder, or intellectual developmental disorder. Of the 68 eligible participants, 56 completed the paired pre- and post-treatment inflammatory marker assessments.

Study design and clinical procedures

This prospective longitudinal study adopted a naturalistic observational design to investigate the temporal associations between clinical symptom progression and inflammatory biomarker fluctuations in adolescents diagnosed with MDD and comorbid NSSI. Routine data collection, blood sample collection, and clinical symptom scale assessments were conducted at baseline; clinical symptom scale assessments and blood sample collection were repeated at follow-up after 6 weeks of treatment.

Clinical assessments

All participants completed a battery of clinical assessments including clinician-administered rating scales and self-reported questionnaires: the Hamilton Depression Rating Scale (HAMD)[24], Hamilton Anxiety Rating Scale (HAMA)[25], Insomnia Severity Index (ISI)[26], Rosenberg Self-Esteem Scale (RSES)[27], Automatic Thoughts Questionnaire (ATQ) [28, 29], Social Support Rating Scale (SSRS)[30], and the Suicide Risk Assessment Scale (SRAS), a 23-item clinician-rated scale widely used for suicide risk stratification in Chinese psychiatric inpatient settings, comprising three domains: psychological/clinical, demographic, and psychosocial factors. It assesses

depression, suicidal ideation, suicide attempts, hopelessness, social support, life events, and insight, with a total score of 0–43 classifying suicide risk into four levels (≤ 10, relatively safe; 11–20, at risk; 21–30, high risk; 31–43, extremely dangerous).

To ensure the consistency of clinician-rated assessments, all raters completed standardized training prior to study initiation, and excellent inter-rater reliability (intraclass correlation coefficient, ICC > 0.85) was achieved for all clinician-administered scales.

Treatment protocol

All participants received selective serotonin reuptake inhibitor (SSRI) monotherapy with either sertraline (50–200 mg/day) or fluoxetine (20–60 mg/day). Dosage adjustments were implemented by the attending psychiatrists based on individual clinical response and treatment tolerability. Medication adherence was monitored via structured pill counts and intermittent plasma concentration testing.

Cytokine measurement

We measured 10 key inflammatory markers selected based on prior evidence [15, 20, 31]: tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-1 (IL-1), interferon-gamma (IFN-γ), interleukin-4 (IL-4), interleukin-17 (IL-17), interleukin-2 (IL-2), interferon-alpha (IFN-α), and interleukin-12 (IL-12). Following overnight fasting, venous blood specimens were collected and processed by centrifugation to obtain plasma aliquots, which were subsequently cryopreserved at -80°C until analysis. Quantitative determination of circulating cytokine levels was conducted using ELISA. All assays were performed in duplicate with intra-assay coefficient of variation < 10%.

Statistical analysis

Data were analyzed using SPSS 26.0 and R 4.1.0. Two-tailed tests were used throughout, with significance set at $P < 0.05$, and a stricter threshold of $P < 0.01$ for primary treatment-response outcomes. Participants were divided into high- and low-inflammation groups based on the median baseline C-reactive protein level (0.58 mg/L). Baseline comparisons employed independent-samples *t*-tests, Mann–Whitney *U* tests, chi-square tests, or Fisher's exact tests as appropriate. Longitudinal changes were assessed using paired t tests or Wilcoxon signed-rank tests. Between-group differences in symptom scale changes were examined via repeated-measures ANOVA, while between-group differences in cytokine changes were analyzed using analysis of covariance (ANCOVA) with baseline levels as covariates. Effect sizes are reported as partial η^2. Spearman correlations examined associations between symptom reduction rates (HAMD-RR, HAMA-RR) and cytokine changes (Δcytokine). Simple and multiple linear regression models tested the predictive value of ΔIL-12 for symptom improvement, with ΔIL-10 and ΔIL-4 included as covariates; multicollinearity was assessed via variance inflation factors (all VIF < 5). The analytical sample for correlational and regression analyses comprised 56 participants with complete pre- and post-treatment data.

Results

Demographic and baseline clinical characteristics

Using the median C-reactive protein level (0.58 mg/L) as the criterion, participants were divided into two groups: high-inflammation (*n* = 34) and low-inflammation (*n* = 34). Table 1 summarizes the participants' characteristics. Statistical analysis confirmed balanced demographic profiles between the high- and low-inflammation groups, validating the grouping approach and enabling adjustment for demographic confounders in subsequent analyses.

Table 1
Demographic and clinical characteristics of participants

Age (years, M ± SD)	**Low-inflammation group (n = 34)**	**High-inflammation group (n = 34)**	**χ^2/t**	***P***
	14.771 ± 1.763	**15.057 ± 1.749**	**-0.700**	**0.487**
Male, n (%)	5 (14.7)	4(11.8)	NA	1.000
Smoking/Drinking, n (%)	10 (29.4%)	16 (47.1%)	2.242	0.134
Physical comorbidities, n (%)	4 (11.8%)	7 (20.6%)	0.976	0.323
Only child, n (%)	13 (38.2%)	18 (52.9%)	1.482	0.223
Urban household registration, n (%)	22 (64.7%)	21 (61.8%)	0.063	0.801
Single parent family, n (%)	12 (35.3%)	10 (29.4%)	0.269	0.604
Paternal education ≥ high school, n (%)	17 (50.0%)	20 (58.8%)	0.534	0.465
Maternal education ≥ high school, n (%)	17 (50.0%)	18 (52.9%)	0.059	0.808
Family history of mental illness, n (%)	4 (11.8%)	3 (8.8%)	*NA*	1.000

Note: Data are presented as mean ± SD, n (%), or n.

P values were obtained from *t*-test, χ^2 test, or Fisher's exact test.
All *P*-values are two-tailed.

Compared with the low-inflammation group, the high-inflammation group showed significantly lower RSES and SSRS scores, and higher ATQ and SRAS scores (all $P < 0.05$), indicating systemic inflammation correlates with lower self-esteem, less perceived social support, more negative automatic thoughts, and higher suicide risk (Table 2).

Table 2
Psychological scale scores in the two groups

Measure	Low-inflammation group (Mean ± SD)	High-inflammation group (Mean ± SD)	*t*	*P*
HAMD	47.36 ± 10.91	50.03 ± 10.27	-1.022	0.310
HAMA	32.48 ± 11.21	34.12 ± 9.57	-0.638	0.526
ISI	15.88 ± 6.25	18.39 ± 6.25	-1.636	0.107
RSES	19.85 ± 6.04	16.42 ± 3.97	2.721	0.008
ATQ	112.52 ± 29.60	125.06 ± 18.29	-2.071	0.043
SSRS	47.67 ± 17.25	37.79 ± 12.13	2.691	0.009
SRAS	26.85 ± 5.39	29.76 ± 4.23	-2.441	0.017

Note: HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; ISI, Insomnia Severity Index; RSES, Rosenberg Self-Esteem Scale; ATQ, Automatic Thoughts Questionnaire; SSRS, Social Support Rating Scale; SRAS, Suicide Risk Assessment Scale.

Baseline inflammatory cytokine differences

The high-inflammation group showed significantly higher levels of TNF-α, IL-6, and IL-1 compared to the low-inflammation group (all $P < 0.05$; Table 3). No other cytokine differences were significant. These findings suggest a link between peripheral cytokines and inflammation-based stratification in adolescent depression, pending further causal clarification.

Table 3
Comparison of inflammatory cytokine levels between the two groups

Inflammatory cytokines (pg/mL)	Low-inflammation group Median (IQR)	High-inflammation group Median (IQR)	*Z*	*P*
TNF-α	3.46(2.45,4.04)	3.94(3.10,5.73)	-2.059	0.039
IL-6	1.71(1.28,2.33)	2.05(1.52,4.99)	-2.580	0.010
IL-10	1.08(0.87,1.21)	0.99(0.83,1.21)	-0.109	0.913
IL-1	2.77(2.59,2.99)	3.19(2.59,3.40)	-2.343	0.019
IFN-γ	10.90(10.69,12.94)	10.90(10.90,12.32)	-0.191	0.848
IL-4	3.32(2.02,3.32)	3.32(1.81,3.32)	-1.313	0.189
IL-17	3.46(3.06,4.38)	3.46(2.69,3.69)	-1.287	0.198
IL-2	6.39(4.68,7.54)	5.78(4.72,7.06)	-0.745	0.456
IFN-α	2.00(1.70,2.00)	2.00(1.70,2.00)	-0.661	0.508
IL-12	150.45(129.96,150.45)	129.96(110.96,150.45)	-1.493	0.136

Note: Mann–Whitney U tests (non-parametric) were used to compare inflammatory cytokine levels between the low-inflammation and high-inflammation groups. Data are presented as median (IQR), with *Z* and *P* values reported. Statistical significance was set at $P< 0.05$.

Clinical symptom improvement after 6 weeks of treatment

After six weeks of treatment, HAMD scores improved significantly in both groups (both $P = 0.001$). For HAMA scores, a significant reduction was observed only in the high-inflammation group ($P = 0.009$), whereas the low-inflammation group showed no significant change ($P = 0.158$). There were no significant between-group differences in post-treatment HAMD or HAMA scores (both $P > 0.05$), with small effect sizes (partial $\eta^2 = 0.039$ and 0.035, respectively) (Table 4).

Table 4
Changes in HAMD and HAMA scores after 6 weeks of treatment

Index	Group	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	Within-group *Z* (*P*)	Between-group *F* (*P*)	Partial η^2
HAMD	Low-inflammation	43.15 ± 11.22	23.00 ± 14.21	−3.183 (0.001)	1.047 (0.316)	0.039
	High-inflammation	49.87 ± 9.60	24.33 ± 9.39	−3.410 (0.001)		
HAMA	Low-inflammation	29.31 ± 9.39	23.77 ± 12.67	−1.413 (0.158)	0.944 (0.340)	0.035
	High-inflammation	33.93 ± 8.82	25.13 ± 8.28	−2.615 (0.009)		

Note: Data are expressed as mean ± standard deviation (SD). Wilcoxon signed-rank test was performed for within-group pre-post comparisons. Repeated-measures ANOVA was used for between-group overall effect comparisons, with effect sizes reported as partial η^2. A *P* value < 0.05 was considered statistically significant.

Group-specific changes in plasma inflammatory cytokine levels

Post-treatment, TNF-α, IL-6, and IL-10 levels decreased significantly in both the low-inflammation and high-inflammation groups (all $P < 0.05$), while IL-4 and IFN-α levels increased significantly in both groups (all $P < 0.05$). IL-1 decreased significantly only in the high-inflammation group ($P = 0.002$), with no significant change in the low-inflammation group ($P = 0.115$). No significant pre–post changes were observed for IL-12, IFN-γ, IL-17, or IL-2 in either group (all $P > 0.05$). No significant between-group differences were found for any cytokines after adjusting for baseline levels (all $P > 0.05$, Table 5).

Table 5
Inflammatory cytokine levels before and after treatment by group

Index	Group	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	Within-group *Z* (*P*)	Between-group *F* (*P*)	Partial η²
TNF-α	Low-inflammation	3.48 ± 0.94	2.67 ± 0.92	-2.902 (0.004)	3.755 (0.064)	0.126
	High-inflammation	4.71 ± 1.96	3.45 ± 1.97	-2.329 (0.020)		
IL-6	Low-inflammation	2.09 ± 1.19	1.29 ± 0.37	-2.274 (0.023)	3.781 (0.063)	0.127
	High-inflammation	3.26 ± 1.95	1.38 ± 0.33	-3.409 (0.001)		
IL-10	Low-inflammation	0.92 ± 0.39	0.74 ± 0.42	-2.517 (0.012)	1.143 (0.295)	0.042
	High-inflammation	1.13 ± 0.34	0.80 ± 0.35	-3.124 (0.002)		
IL-1	Low-inflammation	2.78 ± 0.51	2.60 ± 0.37	-1.578 (0.115)	3.140 (0.088)	0.108
	High-inflammation	3.76 ± 1.59	2.41 ± 0.29	-3.069 (0.002)		
IFN-γ	Low-inflammation	12.12 ± 2.33	11.13 ± 2.84	-1.294 (0.196)	0.088 (0.769)	0.003
	High-inflammation	11.97 ± 3.26	11.93 ± 4.81	-1.765 (0.078)		
IL-4	Low-inflammation	2.97 ± 1.23	7.20 ± 2.41	-3.188 (0.001)	0.126 (0.725)	0.005
	High-inflammation	2.74 ± 1.86	7.03 ± 1.65	-3.361 (0.001)		
IL-17	Low-inflammation	3.49 ± 0.60	3.36 ± 0.51	-0.456 (0.648)	0.444 (0.511)	0.017
	High-inflammation	3.25 ± 0.77	3.32 ± 0.95	-0.171 (0.864)		
IL-2	Low-inflammation	5.70 ± 2.03	5.53 ± 1.27	-0.664 (0.507)	0.238 (0.630)	0.009
	High-inflammation	5.47 ± 1.69	5.20 ± 1.66	-0.824 (0.410)		
IFN-α	Low-inflammation	1.93 ± 0.37	2.21 ± 0.29	-2.091 (0.036)	0.057 (0.814)	0.002
	High-inflammation	1.95 ± 0.20	2.22 ± 0.22	-3.070 (0.002)		

Index	Group	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	Within-group *Z* (*P*)	Between-group *F* (*P*)	Partial η²
IL-12	Low-inflammation	134.69 ± 22.60	135.83 ± 21.58	-0.595 (0.552)	3.623 (0.068)	0.122
	High-inflammation	127.55 ± 21.64	118.37 ± 18.99	-1.080 (0.280)		

Note: Data are presented as mean ± SD. Within-group comparisons were performed using the Wilcoxon signed-rank test. Between-group comparisons were conducted using analysis of covariance (ANCOVA) with pre-treatment values as covariates. Partial η² is reported as the effect size. A two-tailed $P < 0.05$ was considered statistically significant.

Correlations between cytokine changes and symptom improvement

Spearman correlation analysis revealed that ΔIL-12 was positively correlated with both HAMA ($r = 0.53$, $P<0.01$) and HAMD reduction rates ($r = 0.47$, $P<0.05$), while ΔIL-4 was negatively correlated with HAMA reduction rate (RR) ($r = -0.40$, $P<0.05$). Other cytokines showed weak or non-significant associations (Fig. 1).

Regression analysis of inflammatory cytokine changes on symptom reduction rates

In simple regressions, only ΔIL-12 significantly predicted HAMD-RR ($\beta = 0.517$, $P = 0.005$) and HAMA-RR ($\beta = 0.510$, $P = 0.006$); ΔIL-10 and ΔIL-4 showed non-significant trends. In multiple regressions, both models were significant (HAMD-RR: $F(3,52) = 3.41$, $P = 0.034$, adj. $R^2 = 0.211$; HAMA-RR: $F(3,52) = 4.40$, $P = 0.013$, adj. $R^2 = 0.274$). ΔIL-12 remained the only significant independent predictor ($\beta = 0.453$, $P = 0.037$ and $\beta = 0.454$, $P = 0.030$, respectively). Neither ΔIL-10 nor ΔIL-4 was significant (all $P > 0.05$), though ΔIL-4 showed a trend in the HAMA model ($\beta = -0.301$, $P = 0.082$) (Table 6).

Table 6
Regression analysis of ΔIL-12, ΔIL-10, and ΔIL-4 as predictors of symptom reduction

Dependent variable	Predictor	Simple regression			Multiple regression					
		B (95% CI)	*β*	*P*	B (95% CI)	*β*	*P*	VIF	Adj. R^2	Model F (*P*)
HAMD-RR	ΔIL-12	0.004 (0.001, 0.007)	0.517	0.005	0.004 (0.000, 0.007)	0.453	0.037	1.436	0.211	*F*(3,52) = 3.41, *P* = 0.034
	ΔIL-10	0.264 (−0.007, 0.535)	0.366	0.056	0.067 (−0.241, 0.375)	0.093	0.658	1.460		
	ΔIL-4	−0.019 (− 0.056, 0.018)	−0.205	0.295	−0.014 (−0.047, 0.019)	−0.150	0.396	1.025		
HAMA-RR	ΔIL-12	0.007 (0.002, 0.012)	0.510	0.006	0.006 (0.001, 0.012)	0.454	0.030	1.436	0.274	*F*(3,52) = 4.40, *P* = 0.013
	ΔIL-10	0.427 (−0.035, 0.890)	0.349	0.069	0.063 (−0.437, 0.564)	0.052	0.797	1.460		
	ΔIL-4	−0.055 (− 0.115, 0.004)	−0.350	0.068	−0.048 (−0.102, 0.007)	−0.301	0.082	1.025		

Note. B = unstandardized coefficient; CI = confidence interval for B; β = standardized coefficient. HAMD-RR = Hamilton Depression Rating Scale reduction rate; HAMA-RR = Hamilton Anxiety Rating Scale reduction rate; VIF = variance inflation factor. The multiple regression model included ΔIL-12, ΔIL-10, and ΔIL-4 entered simultaneously.

Discussion

This study employed a prospective longitudinal design to investigate adolescents with MDD and comorbid NSSI, systematically examining the associations between inflammatory cytokine levels, clinical symptoms, suicide risk, and SSRI treatment response. This is the first study to establish the predictive value of changes in IL-12 levels for the improvement of depressive and anxiety symptoms, providing new insights into the neuroinflammatory mechanisms and clinical interventions for this comorbid condition.

Our findings revealed a significant link between systemic inflammation and a distinct clinical phenotype in adolescents with comorbid MDD and NSSI. Patients in the high-inflammation group demonstrated markedly lower self-esteem, less perceived social support, and higher suicide risk scores compared to those in the low-inflammation group, underscoring the importance of psychosocial factors in the context of depressive and self-injurious behaviors [32–34]. Family functioning, a core psychosocial determinant, influences suicide risk in

adolescents who self-harm via sequential well-being-depression mediation [35]; this suggests that improving family communication can help improve emotion regulation abilities and lower depressive symptoms, and subsequently, suicide risk [35, 36]. Elevated levels of TNF-α, IL-6, and IL-1 collectively characterized this hyperinflammatory state, implicating them as potential core biomarkers. These findings are consistent with previous studies [23, 37], further validating the connection between dysregulation of these pro-inflammatory cytokines and the specific pathological phenotype in this adolescent cohort [38]. Mechanistically, we postulate that these cytokines may disrupt the blood-brain barrier [39], enter the central nervous system (CNS), and interfere with corticostriatal reward processing. Such disruptions could lead to impaired emotion regulation [40], diminished self-worth, and reduced ability to engage with social support systems.

Excessive activation of pro-inflammatory cytokines mediates aberrant connectivity in the adolescent corticostriatal reward pathway, thereby compromising emotion regulation capabilities [22, 41]. Following systematic treatment, core pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1, were markedly downregulated, effectively reversing the hyperinflammatory state, a finding consistent with previous studies. IL-10 levels decreased concomitantly after treatment, aligning with the inflammatory dynamic model proposed by Arishi et al. [42], in which these cytokines interact to form a stable negative feedback loop. Suppression of core pro-inflammatory cytokines likely reduces the compensatory demand for the anti-inflammatory cytokine IL-10, collectively restoring inflammatory homeostasis. The epigenetic regulation of inflammatory response genes by IL-10, as elucidated by Mishra et al. [43], further supports the plausibility of this regulatory mechanism. Moreover, a study by Shen et al. [44] involving adolescents with depression confirmed the presence of specific peripheral cytokine dysregulation and inflammatory regulatory patterns in this population.

In the current study, IL-4 exhibited the greatest absolute increase among the upregulated cytokines, indicating successful activation of endogenous anti-inflammatory pathways. This finding is consistent with evidence supporting the anti-inflammatory role of IL-4 signaling, and suggests that IL-4 may synergize with exogenous suppression of pro-inflammatory cytokines to collectively restore inflammatory homeostasis [45]. The significant elevation of IFN-α further enhanced immunomodulation, highlighting the multi-target regulatory advantage of the intervention. Meanwhile, IFN-γ and IL-12 showed only moderate reductions, which may be attributed to the relative stability of cytokine expression during adolescent immune development—a speculation consistent with the findings of Buytaert et al. [46], who emphasized age-dependent cytokine expression and differential regulatory flexibility in adolescents. In contrast, IL-17 and IL-2 exhibited no significant changes, indicating that the intervention exerted selective and targeted effects on inflammatory cytokines. This is consistent with the findings of Su et al. [47], who demonstrated that anti-inflammatory interventions can specifically modulate core inflammatory mediators in depressive disorders.

IL-10 decreased uniformly across participants, representing a generalized anti-inflammatory response with limited inter-individual variability, and consequently, showed no predictive value. By contrast, ΔIL-12 displayed substantial inter-individual variation despite non-significant group-level changes, thereby capturing the variance necessary to predict differential clinical outcomes.

IL-12 is a key pro-inflammatory cytokine that drives T helper 1 (Th1)-mediated immune responses. Elevated IL-12 levels have been consistently reported in patients with MDD and are associated with greater severity of the disorder [48, 49]. However, evidence regarding its dynamic changes during treatment and their association with clinical outcomes is limited [50]. The present study provides preliminary evidence that, in adolescents with NSSI,

ΔIL-12 independently predicts symptomatic improvement, suggesting that antidepressant treatment may exert its effects, at least in part, by modulating the Th1/Th2 immune balance. A moderate reduction in IL-12 levels may reflect an attenuated neuroinflammatory burden, thereby facilitating the restoration of affective circuit function [51]. These findings align with a meta-analysis by Köhler et al. [52], which showed that reductions in pro-inflammatory cytokines, including IL-12, paralleled clinical improvement following antidepressant therapy.

Although IL-4 levels increased significantly after treatment, its changes showed only a weak correlation with symptom reduction rates ($r \approx -0.3$). This pattern suggests that IL-4 may contribute to therapeutic effects primarily through neuroprotective mechanisms—such as promoting hippocampal neurogenesis [37, 53]—rather than acting as a direct dynamic marker of treatment response. In contrast, changes in other inflammatory markers (e.g., IL-6, TNF-α) showed weak correlations with symptom reduction rates ($|r| < 0.3$).

This study provides preliminary prospective longitudinal evidence for the value of IL-12 as a potential predictor of antidepressant treatment response in adolescents with comorbid MDD and NSSI, and its clinical application potential warrants further investigation.

Study limitations

This study has several limitations. The relatively small single-center sample, partially constrained by the ethical requirement of guardian consent for adolescent participants, limits the generalizability of findings. Adolescent developmental hormonal fluctuations and unassessed dietary and nutritional factors may introduce confounding effects on inflammatory levels. In addition, the naturalistic design without a placebo control cannot fully distinguish direct drug-induced inflammatory changes from secondary effects of symptom improvement, and peripheral cytokine measurements cannot directly reflect central neuroinflammatory status. Larger multi-center studies with stricter confounding control are warranted to validate our results.

Conclusions

This study shows that adolescents with MDD and comorbid NSSI present a peripheral inflammatory profile characterized by elevated pro-inflammatory cytokines (TNF-α, IL-6, and IL-1). Following standardized SSRI treatment, these pro-inflammatory cytokines decreased while anti-inflammatory factors (IL-4 and IFN-α) increased, suggesting that treatment may restore immune homeostasis through coordinated immunoregulatory pathways. Importantly, regression analyses revealed that only ΔIL-12 independently predicted improvement in both depressive and anxiety symptoms, indicating its potential utility as a dynamic biomarker for monitoring treatment response. These findings provide preliminary longitudinal evidence for peripheral inflammatory dysregulation in this comorbid condition and offer a basis for future mechanistic studies and personalized intervention strategies.

Abbreviations

ATQ: Automatic Thoughts Questionnaire

CRP: C-reactive protein

CNS: Central nervous system

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition

ELISA: Enzyme-linked immunosorbent assay

HAMD: Hamilton Depression Rating Scale

HAMA: Hamilton Anxiety Rating Scale

ICC: Intraclass correlation coefficient

IFN-α: Interferon-alpha

IFN-γ: Interferon-gamma

IL-1: Interleukin-1

IL-2: Interleukin-2

IL-4: Interleukin-4

IL-6: Interleukin-6

IL-10: Interleukin-10

IL-12: Interleukin-12

IL-17: Interleukin-17

ISI: Insomnia Severity Index

MDD: Major depressive disorder

NSSI: Non-suicidal self-injury

RSES: Rosenberg Self-Esteem Scale

SSRI: Selective serotonin reuptake inhibitor

SSRS: Social Support Rating Scale

SRAS: Suicide Risk Assessment Scale

Th1: T helper 1

TNF-α: Tumor necrosis factor-alpha

VIF: Variance inflation factor

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Xi'an Jiaotong University (approval number XJTU1AF2022LSK-171). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and their legal guardians prior to study enrollment.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare no relevant financial or non-financial conflicts of interest that could influence the presented work.

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Authors' contributions

Binglong Wen: Writing-review**,** Funding acquisition, Data curation,Formal analysis. **Yajuan Fan**Writing-original draft,Formal analysis. **Binbin Zhao**Writing–review, Conceptualization**,** Formal analysis. **Xiawei Dang**Data curation,Funding acquisition**,** Validation, editing. **Wenhui Jiang:**Resources, Investigation. **Min Jia**Methodology**,** Data curation. **Qingyan Ma:**Software **,**Formal analysis. **Wei Wang:** Investigation, Project administration. **Xiancang Ma:**Supervision, Conceptualization, Project administration.

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Figures

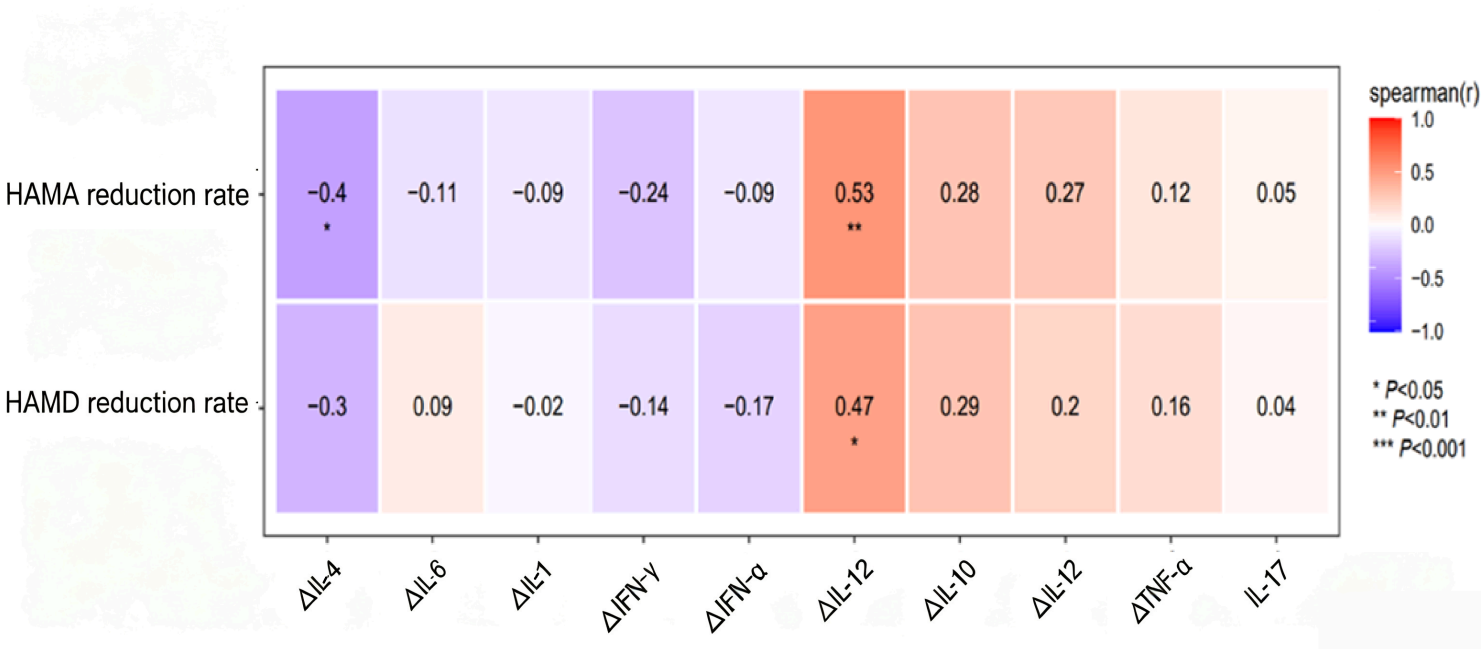


Figure 1

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