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The role of cytokines in predicting the therapeutic effect of non-suicidal self-injury in adolescents: a longitudinal study

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Abstract

Background Neuroinflammatory processes are directly involved in the pathogenesis of non-suicidal self-injury (NSSI) among adolescents. However, their role in predicting the outcome of adolescent NSSI is unknown. This study aimed to explore the relationship between inflammatory cytokines and their effect on NSSI treatment through a prospective investigation.

Methods Thirty-two healthy adolescents and 199 adolescents who had engaged in NSSI were recruited. Blood samples were obtained from all participants to determine the concentration of inflammatory cytokines at enrollment. Thereafter, the NSSI group completed surveys on their NSSI behaviors after 3, 6, and 12 months. The outcomes of their NSSI behaviors were evaluated using the indexes of NSSI number and NSSI impulsivity.

Results The results showed that the mean NSSI number and NSSI impulsivity of the participants both showed a decline tendency over time. However, regarding the NSSI number, the significant treatment effect only emerged after 6 months. The abnormal rates of IL-1βand IL-8 levels of the NSSI group were significantly higher than those of healthy controls ($\chi^2 = 3.945, 27.394$; $P < 0.05$). In the regression models, high IL-8 level (β: 0.225, 95% CI: 0.001, 0.005; $p = 0.001$), high TNF-α level (β: 0.157, 95% CI: 0.023, 0.244; $p = 0.018$), and low IL-10 level (β: −0.261, 95% CI: −2.678, −0.901; $p = 0.017$) could predict the treatment effect of NSSI number. High level of IL-8 (β: 0.233, 95% CI: 0.002, 0.009; $p = 0.001$) and long duration of medical treatment (β: 0.285, 95% CI: 0.234, 0.649; $p < 0.001$) could predict the treatment effect of NSSI impulsivity. When considering the two indexes together, the role of screened-out cytokines, IL-8 (OR = 1.065, 95% CI: 1.032,1.099; $p < 0.001$), TNF-α (OR = 1.839, 95% CI: 1.063, 3.182; $p = 0.029$) and IL-10 (OR = 0.031, 95% CI: 0.002, 0.541; $p = 0.017$), were still stable.

Conclusions Employing the assessment of inflammatory cytokines among adolescents who engage in NSSI may be helpful in predicting their treatment outcome and designing other suitable treatment schemes in advance.

Trial registration registered in https://www.medicalresearch.org.cn/. Retrospectively registered: registered in https://www.chictr.org.cn/. Registration number: ChiCTR2500097375. Date of registration: 18th February, 2025.

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Keywords Adolescent, NSSI, Inflammatory cytokines, Treatment effect, Longitudinal study

Introduction

Non-suicidal self-injury (NSSI) refers to a behavior of deliberate and direct destruction of one's body tissue without the intention to die [1]. It may include various self-harm behaviors, such as cutting, scratching, burning, and impinging any body part [2]. NSSI is becoming prevalent among the adolescent population worldwide, with a global lifetime prevalence rate of 17–18% [3]. The rate, reported to be as high as 60%, is higher among adolescent patients with psychiatric disorders [4]. NSSI can present in several psychiatric diseases [5]. It has been found to play an important role in the chronicity of psychiatric diseases and increasing risk of suicide [6]. Several studies have investigated the risk factors of NSSI among adolescents, regarding the psychosocial, demographic, and neurobiological perspectives [7, 8, 9, 10]. However, studies focusing on factors related to treatment outcome of NSSI among adolescents are rare.

It has been shown that oxidative stress and inflammation play an important role in the development of many psychiatric disorders which include the symptoms of suicide or NSSI [11, 12]. It is reported that among these psychiatric disorders, emotional disorders often suffered by adolescents who engage in NSSI also showed obvious association with the dysregulation of the immune-inflammatory response system [13, 14, 15]. Several studies have indicated the increased inflammation in individuals who experienced childhood adversity and chronic stress. These stresses are also seen in adolescences engaged in NSSI [16]. Moreover, one study even pointed out that neuroinflammation processes are directly involved in the pathogenesis of NSSI among adolescents [17]. Neuroinflammation has been observed to play an important role in the development of NSSI among adolescents. The typical neuroinflammatory markers include the expression of inflammatory cytokines, such as pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-1β, IL-2, IL-6, and IL-8) and anti-inflammatory cytokines (IL-4 and IL-10). Furthermore, studies have revealed the varying relationships between inflammatory cytokines and NSSI. For example, Zheng et al. [18] reported that systemic inflammation was strongly associated with adolescent NSSI. Westling [19] found that the increase in IL-1β reactivity may play a role in the pathogenesis of NSSI. Kim [20] discovered that an increased TNF-α level was related to NSSI, whereas Russell reported no association between IL-6 and NSSI [21]. Although these studies analyzed the role of inflammatory cytokines in NSSI, few studies reveal their role in predicting the prognosis or outcome of adolescent NSSI. To our knowledge, previous studies only focused on the predictive role of inflammatory cytokines in suicide [22, 23]. Due to the increasing prevalence of NSSI among adolescents and the significant role of NSSI in predicting suicide attempt [24], exploration of the predictive role of inflammatory cytokines in adolescent NSSI remains necessary. Among adolescents, fewer variables may confound the role of inflammatory responses than among adults. Moreover, inflammatory cytokine levels are lower during adolescence than during adulthood [25]. Therefore, we expect that these differences may improve the accuracy of our findings.

In addition to the above-mentioned phenomena, previous studies have found that one of the core ingredients of NSSI is impulsivity [26, 27, 28], which plays an important predictive role in the treatment outcome of NSSI among adolescents [29, 30]. Moreover, impulsivity has been shown to be associated with inflammatory cytokines [31, 32]. Because inflammation plays a key role in self-regulation [33], and the poor ability in self-regulation is the typical expression of high impulsivity, analysis of the role of inflammatory cytokines in predicting the outcome of NSSI from the perspective of impulsivity is necessary. Substance abusers have been found to have high impulsivity and low self-regulation, and it has been reported that the increased inflammatory response in them may become the biomarker to predict treatment response at different stages of treatment [34]. Furthermore, due to the lack of targeted treatment methods, the current treatment of adolescent NSSI behavior is mainly aimed at the treatment of its primary diseases, such as depression and anxiety disorders, with anti-depressants as the main method. According to a previous report, inflammation might moderate the role of central neurotransmitters, including dopamine and serotonin, on NSSI [32]. These neurotransmitters are the key elements through which antidepressants exert their effects. Additionally, antidepressants decrease pro-inflammatory cytokine levels [35, 36]. Considering the findings, we hypothesized that inflammatory cytokines may play an important role in predicting the treatment outcome of adolescent NSSI.

To verify our hypothesis, we conducted a 1-year longitudinal study among a sample of psychotropic drug-naive adolescents who engaged in NSSI to understand (1) the differences in inflammatory cytokines between adolescents who engaged in NSSI and healthy controls; (2) whether the level of inflammatory cytokines before treatment could affect the treatment outcome of NSSI; and (3) establish a prediction model to predict the outcome of adolescent NSSI.

Materials and methods

Participants

In this 1-year prospective study, we recruited 202 adolescents who engaged in NSSI (NSSI group) and were admitted to the Clinical Psychology Ward of The Fourth People's Hospital of Chengdu for treatment from January 2019 to December 2020. They were evaluated at the time of enrollment and re-evaluated after 3 months, 6 months, and 1 year. Among these participants, two participants committed suicide successfully before the first follow-up visit, and one participant dropped out of the study at the second follow-up due to unwillingness to follow her doctor's prescription. The demographic data of these three participants were not significantly different from those of the remaining 199 participants who completed the study ($p > 0.05$). To prevent attrition, the participants completed the enrollment evaluation and joined a special WeChat group set up for their follow-ups. When the time for follow-up was due, we sent them an electronic link to the questionnaire to gather data on their statuses.

All participants in the NSSI group had to meet the following inclusion criteria: (1) Age of 12–18 years; (2) Treatment naivety for psychiatric diseases in the past 6 months; (3) ≥ 2 events of self-injury in the past month; (3) diagnosis of NSSI behavior according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, the fifth version) criteria (NSSI was assessed by experienced psychiatrists working in the ward at the time of their admission through psychiatric interviews). The exclusion criteria were (1) diagnosis of serious psychosis illnesses, including schizophrenia, substance abuse, and developmental disorder spectrum disease; (2) diagnosis of physical diseases associated with systemic inflammatory responses; (4) and use of immunity-affecting medications in the past 6 months.

We also recruited 32 healthy adolescents as the control group to determine whether the cytokine levels of the NSSI group differed from those of the healthy controls. All healthy controls underwent psychiatric examination to exclude the presence of any psychiatric diagnosis and NSSI behaviour. They also need to meet the exclusive criteria listed above.

Consent to participate in our study was obtained from the guardians of all subjects via a written informed consent.The study was approved by the institutional review board (IRB) of the Fourth People's Hospital of Chengdu.

Measures

Questionnaires and follow-up process

All participants, including the control group, completed the demographic questionnaire at the point of enrollment. The questionnaire was used to obtain data on sex, age, height, weight, and family history of psychosis. This questionnaire was self-administered and only needed to be completed once.

The clinical characteristics of the NSSI group were recorded by one of the authors according to the psychiatric interviews. They included duration of disease, number of onset episodes, psychiatric diagnosis (according to the International Classification of Diseases, ICD, the tenth version), and the duration of medical treatment (the total number of months of medicine treatment during the 1-year follow-up). Additionally, we used the NSSI questionnaire, as adapted from Wan's scale, which is focused on investigating the behavior and function of NSSI. This scale has been proven to be of good reliability and validity [37]. We chose the first part of this scale to understand the type and number of NSSI behaviors in the previous 2 weeks. It included 12 types of self-injury behavior and requested participants to provide the specific frequency of each type of self-injury. Thereafter, we added another item based on a 10-point evaluation. It evaluated the degree of NSSI impulsivity in the last 2 weeks, with a score of 0 representing no impulsivity and a score of 10 indicating a want to harm oneself all the time. This scale was also self-reported and patients were required to complete it at each follow-up visit through our network link. Thereafter, they provided information on treatment compliance and duration. The concrete contexts included whether they followed the prescription of their resident physicians and whether they were still taking medications to sustain their treatment. If they had stopped taking medication, was it at the suggestion of their physicians or was it due to an individual factor? They were also required to provide the total length of time they had been taking medications for their treatment during the follow-up.

To prevent the complicated influence of other factors on the treatment effect, the NSSI group underwent a similar treatment scheme as that received during their hospitalization. The choice of treatment included sertraline/fluoxetine (which was used to improve emotional symptoms), valproate sodium/lithium (which was used to stabilize mood and control impulsivity), and the fixed group psychotherapy.

Determination of cytokine concentration

The concentrations of the following cytokines were determined: IL-1, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, and TNF-α. The C-reactive protein (CRP) was detected as a control factor to exclude participants who were in acute infection. The CRP results of all participants did not exceed the normal range. Because our hospital's laboratory was limited, a normal CRP result was listed as < 10 mg/L without displaying the detailed values. Hence, it was not included as one of the independent variables in the regression model.

All blood samples (10 mL) were drawn at 07:00–08:00 AM after overnight fasting. The EDTA blood was then centrifuged at 3000 rpm for 15 min after collection. After centrifugation, serum was drawn off and frozen at – 80∘C until assayed. Assays were performed at the third-party laboratory (Chengdu DiAn medical inspection office co., Ltd). The level of IL-1 in serum was determined by double antibody sandwich enzyme-linked immunosorbent assay (ELISA) according to the instructions of the manufacturers (Boster Biotechnology Company, Wuhan, China). The levels of IL-2, IL-1β, IL-4, IL-6, IL-8, IL-10, and TNF-α in serum were determined by Chemiluminescence immunoassay sandwich method according to the instructions of the manufacturers (Xieguang Biotechnology Co., Ltd.). The automatic chemiluminescence analyzer (marque: Sharay 4000) and cytokine combined detection kit (magnetic particle chemiluminescence method) were used. The detection limits of this method for each cytokine and the normal ranges are listed in Table 1.

The assignment of independent and dependent variables

The aim of our study was to discover the role of cytokines in predicting treatment effect. Therefore, we deemed all cytokines to be independent variables. According to the test results, we found that only IL-8 and TNF-α values could be reported as specific numbers for all participants. Therefore, they were entered into the regression model as continuous variables. Most of the results of other cytokines were under the detection limits. As a result, we divided their results into three categories: those below the lower limit that could not be detected, those that could be detected as specific values but did not exceed the normal range, and those above the upper limit of the normal range. They were deemed to be categorical variables in the regression model, and the rule of assignment of these variables was that scores of 0, 1, and 2 represented "cannot be tested out", "in normal range", and "over the normal range", respectively.

The treatment effect was manifested by two indexes, the degree of change in NSSI number and NSSI impulsivity. For the change in NSSI number, the relative change value was used because the total number of NSSI events varied for each subject at different time points. The rule of conversion was the discrepancy value between different time points and baseline divided by the total number of NSSI events at baseline. For example, the Change of NSSI number on the time point of 3 month was calculated like this: (the total number of NSSI events at baseline - the total number of NSSI events at 3 month) / the total number of NSSI events at baseline. Similarly, the Change of NSSI number on the time point of 6 month was calculated as follows: (the total number of NSSI events at baseline - the total number of NSSI events at 6 month) / the total number of NSSI events at baseline. For the change in NSSI impulsivity, we only calculated the difference in value between the NSSI impulsivity score at baseline and those measured at each follow-up to represent the treatment effect of NSSI impulsivity, because this score was set within a fixed range. For example, for the change in NSSI impulsivity at 3 months, the specific calculation was that the NSSI impulsivity score at baseline reduced the corresponding score at 3 months.

Table 1 The limits of detection and normal range of cytokines in our study

Item	Detection limits (pg/mL)	Normal range (pg/mL)
IL-1	1.00	0–3.90
IL-1β	5.00	< 5.00
IL-2	7.00	0–31.30
IL-4	10.00	0–31.30
IL-6	1.50	< 7.00
IL-8	0.78	≤ 62.00
IL-10	5.00	≤ 9.10
TNF-α	0.78	≤ 8.10

Statistical analysis

All continuous variables were reported as means ± SD, whereas categorical variables were reported as frequencies (%). Student's t-test or Pearson χ^2 test was used to compare group means and frequencies of variables, including sex, age, BMI (weight / height^2), and history of psychosis. The χ^2 test for crosstab was used to analyze the differences in abnormal rate of cytokines between the NSSI group and control group. Because some samples in the crosstab had a small sample size and their expected values were < 5, Fisher's Exact Test was used. To describe the longitudinal change of the NSSI number's relative value and the score on NSSI impulsivity, the repeated-measures ANOVA was used. If the results of the Mauchly test led to a spherical rejection, Greenhouse-Gaither correction was used to adjust the degree of freedom of significance average test. Additionally, we used the post hoc test to do the pairwise comparisons to determine which NSSI numbers / NSSI impulsivity were significantly different from others at different time points. To determine the role of cytokines in influencing the final treatment effect (NSSI number or NSSI impulsivity as the single dependent variable), we used multiple linear regression with the backward method and included all cytokines as independent variables to build two models. Sex, age, and BMI have been reported to have an effect on cytokine level [38, 39, 40]. Therefore, we included these demographic variables and other potential factors that may influence treatment effect in the models to obtain comprehensive results.

Because we considered treatment effect to include two indexes, the NSSI number and NSSI impulsivity,

and sought to determine the factors that may cause an improvement in these indexes, we divided the treatment effect into two categories according to these rules: 1 for no improvement/worsening effect (the NSSI number in the last follow-up increased/did not change + the NSSI impulsivity in the last follow-up increased/did not change); and 2 for improvement (the NSSI number in the last follow-up decreased/did not change + the NSSI impulsivity in the last follow-up decreased or the NSSI number in the last follow-up decreased + the NSSI impulsivity in the last follow-up did not change). After re-valuing the dependent variable, we used the binary logistic regression models with the forward stepwise method to determine whether the cytokines still had significant influence on the final treatment effect. The odds ratio (OR) and 95% confidence intervals (CIs) were shown to indicate the associations between these factors and the outcomes. SPSS software, version 23.0 (IBM-SPSS Inc., Armonk, NY, USA) was used for all analyses. A P-value < 0.05 was considered statistically significant.

Results

The demographic characteristics of both groups

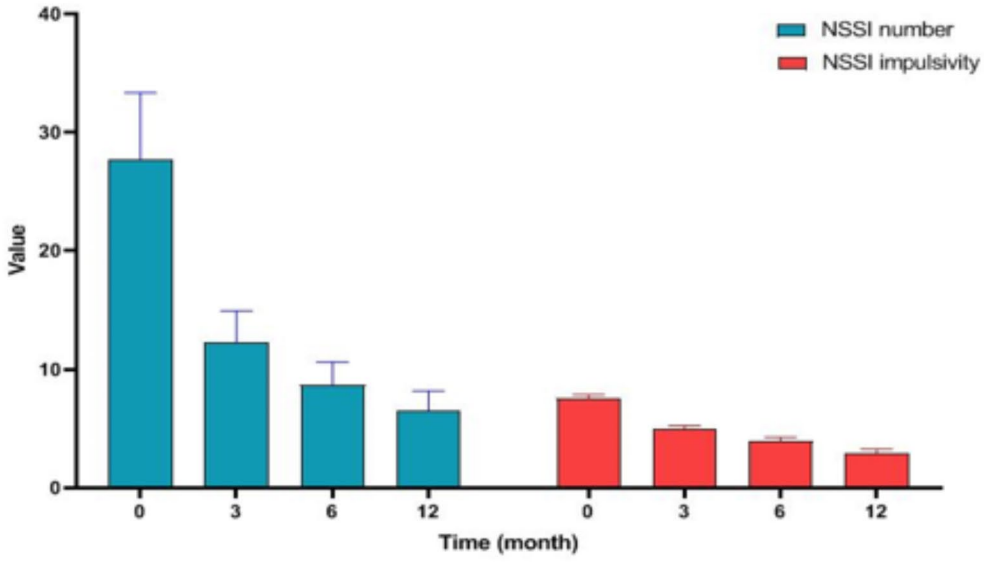
The NSSI group had significantly more female participants than the control group. Age, BMI, and history of psychosis were not significantly different between both groups. The clinical characteristics, including the duration of disease, number of onset episodes, diagnosis, and duration of medical treatment, are all shown in Table 2.

The outcome of NSSI number and NSSI impulsivity over time

The mean NSSI number ($F(1.27, 250.70) = 50.59$, $p < 0.001$, $\eta^2=0.20$) and NSSI impulsivity ($F(1.97, 390.06) = 345.07$, $p < 0.001$, $\eta^2=0.64$) of participants decreased over the time they were under treatment (Fig. 1). To detect the difference in treatment effect among different time points, we analyzed the degree of change in NSSI number and NSSI impulsivity at different time points (Fig. 2). The results showed that with time, the degree of treatment effect of NSSI impulsivity generally increased ($F(1.58, 313.43) = 159.82$, $p < 0.001$, $\eta^2=0.45$). The paired comparison among the three time points corroborated this finding. The difference between the scores at the 3-and 6-month, the difference between the scores at the 3-and 12-month, and the difference between the scores at the 6-and 12-month were all significant (please see the note of Table 3 for details for the paired comparison). The degree of treatment effect of NSSI number showed differences among the three time points ($F(1.74, 343.55) = 10.53$, $p < 0.001$, $\eta^2=0.05$). However, the paired comparison revealed no significant difference between the indexes at the 3-and 6-month time points; both were significantly lower than the values at the 12-month time point. The details of the paired comparison are shown in Table 3.

Table 2 Demographic and clinical characteristic of subjects from NSSI group and control group

Variables and assignment	NSSI group ($n = 199$) Mean (SD) *N* (%)	Control group ($n = 32$) Mean (SD) *N* (%)	χ^2	t	*P*
Sex			20.142		< 0.001
Male (0)	24 (12.1)	14 (43.8)			
Female (1)	175 (87.9)	18 (56.3)			
Age (years)	15.44 ± 1.95	15.59 ± 1.50		0.419	0.675
BMI (Kg/m^2)	20.15 ± 2.92	20.78 ± 1.44		1.181	0.239
History of psychosis			1.934		0.164
Yes (1)	22 (11.1)	1 (3.1)			
No (0)	177 (88.9)	31 (96.9)			
Duration of disease (years)	2.74 ± 2.28	-			
Number of onset episodes	1.56 ± 1.04	-			
Diagnosis		-			
Depressive disorders (1)	87 (43.7)	-			
Behavioural and emotional disorders that usually occur in childhood and adolescenct (2)	59 (29.6)	-			
Anxiety disorders (3)	33 (16.6)	-			
Post-traumatic stress disorder (4)	8 (4.0)	-			
Bipolar disorder (5)	6 (3.0)	-			
Personality disorders (6)	4 (2.0)	-			
Obsessive-compulsive disorder (7)	1 (0.5)	-			
Conversion disorder (8)	1 (0.5)	-			
Duration of medical treatment (month)	11.2 ± 1.82	-			



	Enrollment (Mean ± SD)	3 month (Mean ± SD)	6 month (Mean ± SD)	12 month (Mean ± SD)
NSSI number	27.69 ± 40.04	12.29 ± 19.01	8.67 ± 13.93	6.46 ± 12.18
NSSI impulsivity	7.50 ± 2.48	4.92 ± 2.29	3.93 ± 2.49	2.90 ± 2.63

Fig. 1 The change tendency of mean NSSI number and NSSI impulsivity over time. Legend: The ANOVA analysis was used to test the differences among different time points, which showed that the difference in NSSI number and that in NSSI impulsivity among the 4 time points were both significant ($p < 0.001$)

The comparison of cytokine between the NSSI and control groups

We compared all the cytokine indexes between the two groups and found that the IL-8 value of most participants in the NSSI group was above the normal range, and the ratio of abnormality of IL-1β and IL-8 between the two groups had significantly differences ($\chi^2 = 3.945$, 27.394; $P < 0.05$). The detailed results of the comparison are shown in Table 4. Because IL-8 and TNF-α values of all participants could be determined, we compared their mean values between both groups and found the average IL-8 value in the NSSI group (103.89 ± 111.93) to be higher than that in the control group (33.81 ± 25.25) (t = 3.521, $p = 0.001$). The average TNF-α value in the NSSI group (7.44 ± 1.77) was not different from that in the control group (7.90 ± 2.06) (t = 1.331, $p = 0.184$).

The multiple linear regression analysis of influencing factors of NSSI number and NSSI impulsivity

To explore the long-term influencing factors of NSSI number and NSSI impulsivity, we only chose the relative change values on the time point of 12 month as the dependent variables. All cytokines and demographic characteristics were included in the regression models as independent variables. The assignments of the categorical variables in the model are shown in Table 2. The numbers in parenthesis indicated after the variable names represent the specific values.

In the regression model of NSSI number, we found that the higher levels of IL-8, TNF-α, and lower levels of IL-10, which might not be tested out, predicted better treatment effect of adolescents' NSSI number. The F-values (5,193) in the regression model was 8.671. The coefficient of determination (expressed as R^2) was 0.162. The detailed results are shown in Table 5. In the regression model of NSSI impulsivity, we found that only the higher level of IL-8 and longer duration of medical treatment could predict better treatment effect of adolescents' NSSI impulsivity. The F-values (2,196) in the regression model was 12.889, and R^2 was 0.107. The detailed results are shown in Table 6.

The logistic regression analysis of influencing factors of treatment effect of NSSI

The results of the logistic regression model showed that the duration of medical treatment (OR = 1.655, 95% CI: 1.121, 2.442, $p = 0.011$), level of IL-8 (OR = 1.065, 95% CI: 1.03, 1.099, $p < 0.001$), and level of TNF-α (OR = 1.839, 95% CI: 1.063, 3.182, $p = 0.029$) were the protective factors for the treatment of NSSI among adolescents. Whereas the level of IL-10 (OR = 0.031, 95% CI: 0.002, 0.541, $p = 0.017$) was the risk factor. These findings

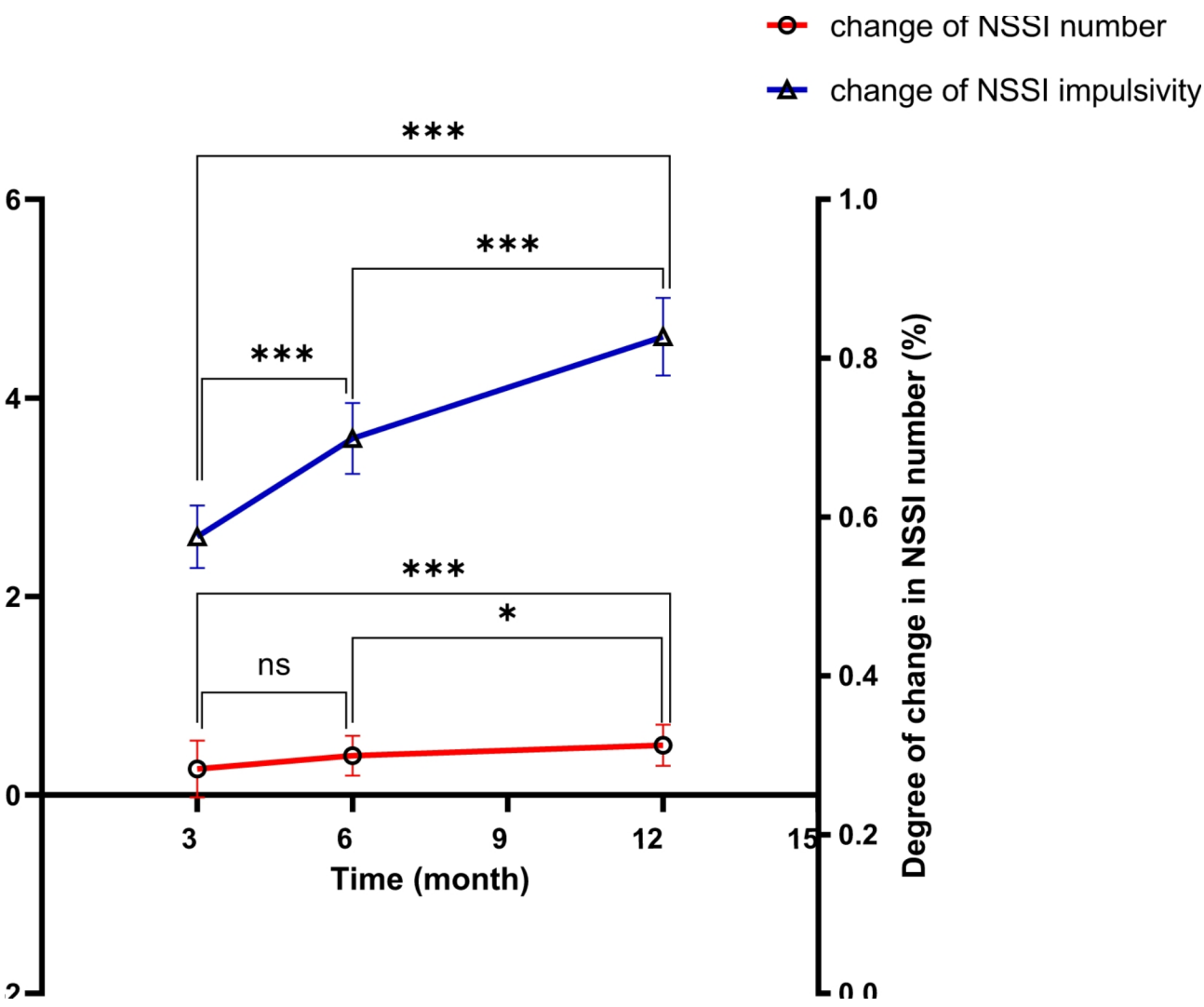


Fig. 2 The change tendency of treatment effect size of NSSI number and NSSI impulsivity over time. Legend: The Y-axis on the left represents the results of the degree of change in NSSI number, and the unit is percentage. The Y-axis on the right represents the results of the degree of change in NSSI impulsivity, and the unit is score. The repeated-measures ANOVA was used to test the degree of change in NSSI number and NSSI impulsivity at different time points, which showed that the difference in the degree of change in NSSI number and that in NSSI impulsivity among the 4 time points were both significant ($p < 0.001$). The significance results of the paired comparison between different time points are also shown inFig. 2. * stands for $p < 0.05$, ***stands for $p < 0.001$, ns stands for no significance

Table 3 The paired comparison of change of NSSI number and impulsivity among different time points

	Time point	M ± SD	P^1	95% CI	P^2	95% CI	P^3	95% CI
Change of NSSI number	3 month	0.26 ± 2.06	0.074	−0.025, 0.552	< 0.001	−0.365,−0.107	0.037	−0.202,−0.004
	6 month	0.40 ± 1.44						
	12 month	0.50 ± 1.50						
Change of NSSI impulsivity	3 month	2.60 ± 2.26	< 0.001	−1.192,−0.788	< 0.001	−2.342,−1.688	< 0.001	−1.298,−0.752
	6 month	3.59 ± 2.56						
	12 month	4.62 ± 2.81						

Note: P^1 stands for the significance between 3 month and 6 month; P^2 stands for the significance between 3 month and 12 month; P^3 stands for the significance between 6 month and 12 month. *95% CI*

stands for the Confidence interval of difference between different time points

Table 4 The comparison of abnormal rate of cytokines between NSSI group and control group

	NSSI group ($n=199$) Number (%)			Control group ($n=32$) Number (%)			χ^2	*P*
	Cannot be tested out	In normal range	Over normal range (abnormal)	Cannot be tested out	In normal range	Over normal range (abnormal)		
IL-1	171 (85.9)	27 (13.6)	1 (0.5)	27 (84.4)	5 (15.6)	0	0.797	0.814
IL-1β	157 (78.9)	0	42 (21.1)	30 (93.8)	0	2 (6.3)	3.945	0.047
IL-2	191 (96.0)	7 (3.5)	1 (0.5)	30 (93.8)	2 (6.3)	0	1.502	0.452
IL-4	198 (99.5)	1 (0.5)	0	32 (100.0)	0	0	-	1.000
IL-6	156 (78.4)	39 (19.6)	4 (2.0)	30 (93.8)	2 (6.3)	0	3.687	0.183
IL-10	189 (95.0)	10 (5.0)	0	32 (100.0)	0	0	-	0.365
IL-8	0	70 (35.2)	129 (64.8)	0	27 (84.4)	5 (15.6)	27.394	< 0.001
TNF-α	0	141 (70.9)	58 (29.1)	0	26 (81.3)	6 (18.8)	1.487	0.223

Table 5 The multiple linear regression analysis of influencing factors of NSSI number

Variable	Regression coefficients	Standard error of regression coefficient	Standardized regression coefficient	t	*P*	95% CI
Constant	−1.362	0.761		−1.789	0.075	(−2.863, 0.139)
IL−8	0.003	0.001	0.225	3.396	0.001	(0.001, 0.005)
TNF-α	0.133	0.056	0.157	2.376	0.018	(0.023, 0.244)
IL−10 (category)	−1.789	0.450	−0.261	−3.972	< 0.001	(−2.678,−0.901)

F (5, 193) = 8.671 ($P<0.001$), $R=0.183$, $R^2=0.162$

Table 6 The multiple linear regression analysis of influencing factors of NSSI impulsivity

Variable	Regression coefficients	Standard error of regression coefficient	Standardized regression coefficient	t	*P*	95% CI
Constant	−0.934	1.230		−0.760	0.448	(−3.360,1.491)
IL−8	0.006	0.002	0.233	3.433	0.001	(0.002, 0.009)
Duration of medical treatment	0.441	0.105	0.285	4.201	< 0.001	(0.234, 0.649)

F (2, 196) = 12.889 ($P<0.001$), $R=0.116$, $R^2=0.107$

Table 7 The logistic regression analysis of influencing factors of treatment effect of NSSI

Variable	Regression coefficients	Standard error of regression coefficient	Wald	Exp(B)	95% CI	*P*
Constant	−17.019	7.176	5.625	0.000		0.018
Duration of medical treatment	0.504	0.199	6.425	1.655	(1.121, 2.442)	0.011
IL−10 (category)	−3.472	1.458	5.669	0.031	(0.002, 0.541)	0.017
IL−8	0.063	0.016	15.068	1.065	(1.032, 1.099)	< 0.001
TNF-α	0.609	0.280	4.739	1.839	(1.063, 3.182)	0.029

suggested that the longer the participants received medical treatment, the higher the IL-8 and TNF-α values, and the lower the IL-10 value, the long-term treatment effect of NSSI was better. The detailed results are shown in Table 7.

Discussion

This study sought to mainly understand the role of inflammatory cytokines in predicting the treatment effect of adolescent NSSI. We found that the pro-inflammatory cytokines (IL-8 and TNF-α) and anti-inflammatory cytokine, IL-10, together with the duration of medical treatment, might influence the long-term outcome of adolescent NSSI treated mainly with sertraline/fluoxetine and valproate sodium/lithium, which could help psychiatrists in designing targeted interventions in the future.

Although the DSM-5 has proposed NSSI as an independent diagnosis [41], there are few studies regarding treatment of this common behavior among adolescents who suffer emotional disorders. In this study, the participants were still treated with psychotropic drugs, which seemed to be the main therapy. Though till now there

is no literature has verified the effectiveness of pharmacological agents on adolescent NSSI [42], our results showed that the mean NSSI number and NSSI impulsivity degree both decreased over time. The reason might be that most of the subjects in our study have emotional symptoms, and the anti-depressant could alleviate their depressed emotion [43], in which condition they might need less NSSI to resist their negative emotions [44]. The use of mood stabilizers can also help to decrease impulsivity [45], and may have contributed to the decrease in NSSI impulsivity. The analysis of the treatment effect of NSSI from the perspective of the relative value of NSSI number and NSSI impulsivity revealed that the effect was generally greater over time on impulsivity. The significant effect on NSSI number only emerged 6 months later, suggesting that the treatment effects of NSSI number and NSSI impulsivity were asynchronous. Although the prefrontal cortex function tends to improve with increasing age, lowering impulsivity [46], the frequency of NSSI events has been reported to decline from late adolescence and early adulthood [47]. As a result, the obvious treatment effect on NSSI frequency emerged later in the follow-up period.

Analysis of the inflammatory cytokine levels of the NSSI group and healthy controls at enrollment revealed that adolescents who engaged in NSSI were more prone to have abnormal index scores for IL-1β and IL-8. Their mean level of IL-8 was also significantly higher. IL-1β and IL-8 are known pro-inflammatory cytokines, which are upregulated during infection to stimulate cellular functions. Additionally, they can interact with the brain, regarding the body's health or challenged status [48]. Subjects with NSSI are prone to report more stressful experiences which often made them under the challenged status [49]. Otherwise, the main sources of IL-8 are epithelial cells and macrophages, while epithelial cells cover the whole skin. When the skin is damaged, it stimulates epithelial cells to secrete IL-8, thus attracting and activating more neutrophils to repair the wound [50]. Therefore, observation of high pro-inflammatory cytokine levels in such participants was not surprising. Moreover, the NSSI group had more female participants than the control group. Compared to men, the immune responses in women tend to be stronger when facing environmental stress, resulting in increased inflammatory response [51]. This may explain the high levels of pro-inflammatory cytokines in the NSSI group.

Regarding the role of inflammatory cytokines in predicting the long-term treatment effect on adolescent NSSI, we found that the high IL-8 and TNF-α levels, and the low IL-10 level could predict better treatment effect of adolescents' NSSI number. Among these cytokines, IL-8 could predict the treatment effect of NSSI impulsivity. In evaluating the treatment effect from both perspectives, the above findings remained stable. Previous studies have mainly focused on the association between baseline cytokine levels and response to antidepressant treatment. For example, Lanquillon et al. reported that higher levels of IL-6 might predict a worse response to antidepressant treatment [52]. Liu et al. concluded that patients diagnosed with major depressive disorder (MDD) who responded to antidepressant treatment had lower baseline IL-8 levels than the non-responders, and they also pointed out that the elevated cytokine levels of TNF-α may mean no improvement in clinical symptoms in MDD patients receiving antidepressant treatment [53]. The difference in our results may be due to the different sample we chose. The subjects in previous studies were all adults, and their cytokines could be confounded by smoking, obesity, and other lifestyle factors. So the data from treatment-naive adolescents seems to be more meaningful. The high level of pro-inflammatory cytokines has been reported to indicate a more developed defense mechanisms among the youth [54], under which condition individuals tend to have a reduced likelihood of using self-inflicted injuries to cope with stress [55]. Furthermore, antidepressants can play a role in improving depression symptoms by downregulating pro-inflammatory cytokines levels [35]. The initial low pro-inflammatory cytokine level might prevent antidepressants from decreasing them further, leading to the limited effect. As a result, clinicians have resorted to the use of anti-inflammatory drugs for the treatment of depression in recent years [56]. Our results suggest that the key to treating adolescent NSSI might depend on inflammatory reaction. Moreover, most subjects in our study were diagnosed with depression disorder, which is reported to have a close association with a disturbed hypothalamic–pituitary–adrenal (HPA) axis and inflammatory reaction [57]. The neurobiological models of NSSI indicate an involvement of the HPA axis [58]. Under stressful conditions, the HPA axis is activated, and the release of cortisol may affect the homeostasis of the immune system, leading to increased pro-inflammatory cytokine levels [59]. At this time, patients may be in the early stage of the disease. During this stage, the level of pro-inflammatory cytokine might be positively related to the severity of body damage [60]. Therefore, the treatment effect will be ideal. When stress persists or becomes chronic, the function of the HPA axis tends to be exhausted, losing its effect in activating pro-inflammatory cytokines. Therefore, although the patient still has serious self-injury, the level of pro-inflammatory cytokines might decrease further. As a result, the disease state may deteriorate, and the effect of antidepressant treatment will be unsatisfactory.

Analysis of the inflammatory cytokines indicated above revealed that among them, IL-8 plays a more prominent

role, and its increase implies a better treatment outcome in terms of both NSSI number and impulsivity. Till now, only one study could be found to reveal the role of cytokines (TNF-a, IL-6, and IL-1β) in predicting the response to antidepressant fluoxetine treatment in children. However, their results differed from ours. They found that higher cytokine levels were associated with refractoriness of depression and anxiety to treatment. The reason for the discrepancy may be related to the numerous methodological dissimilarities among studies [61]. However, we could explain the results in our study by the role and generation of pro-inflammatory cytokine. IL-8, an important pro-inflammatory cytokine, is produced at the early phase of inflammatory response [62]. It is discovered to show different immune actions, which is more associated with proinflammatory states [56]. A high IL-8 level before treatment indicates that a patient's disease might be in the early state, corroborating our explanation provided in the previous paragraph. Additionally, Moriarity et al. [56] reported that a higher IL-8 level could predict fewer symptoms of depression among adolescents after a 31-month follow-up study. Some of our study participants were treated with mood stabilizers, a typical drug used to improve the impulsivity of bipolar disorder [63]. This drug has been proven to have a positive treatment effect with the level of IL-8 [64]. Another pro-inflammatory cytokine, TNF-α, had a similar role as IL-8. A meta-analysis study indicated that the role of antidepressants in reducing cytokine levels in adults was mainly reflected in TNF-α level [65]. A similar study found that adolescents with depression administered with selective serotonin reuptake inhibitors had lower levels of cytokines than those ones who were untreated [66]. That report supports our conclusion.

The unique finding of our study showed that the lower the IL-10 level, the better the outcome of adolescent NSSI. IL-10 is known to be an anti-inflammatory cytokine, which has an inherent balance with the level of pro-inflammatory cytokines [67]. Hence, a low IL-10 level indicates that the disease is still at the early phase, and the compensatory immune regulatory system (CIRS), which is thought to be expressed in patients with emotional disorders, has yet to be activated [68]. This state of inactivation can be confirmed by the finding that a high IL-10 level might predict a more serious emotional symptoms over time [69]. As a result, a low IL-10 level predicts better treatment outcome.

In the regression model, in addition to the inflammatory cytokines screened above, we found that the longer the duration of medical treatment, the better the outcomes, which shows that drug maintenance treatment is important for managing adolescent NSSI. After all, a longer duration of drug maintenance treatment lowers recurrence rate and improves curative effect [70].

Limitations

Our study should be interpreted in light of the following limitations. First, the hormone secretion level of the HPA axis, which is closely related to inflammatory cytokines, was not included in the analysis. Although the role of inflammatory cytokines was known, the mechanism of its action could only be inferred from the relationship between the HPA axis and inflammatory cytokines. We had no data to verify the HPA level. Second, the effect size of our regression was relatively low, indicating that the inflammatory cytokines could only play a part role in predicting the outcome. Because the influencing factors of NSSI were complicated, a more robust and evidenced-based study is needed to understand the prediction model in the future. Third, follow-up of the control subjects was not conducted, so it is not possible to determine whether some of them might also develop mental health problems or engage in NSSI during the 1-year period. Fourth, because the concentration of pro-inflammatory cytokines might be associated with the severity of physical injury, it is important to conduct a three-arm comparison, including adolescents with non-NSSI wounds and healthy controls, to more accurately determine the changes in pro-inflammatory cytokines due to self-injury. However, according to the clinical fact, the vast majority of adolescents admitted to our hospital in the last two years had engaged in NSSI, so it was difficult to recruit subjects without NSSI. Considering that the sample size of this group of subjects may be too small for further statistical analysis, we did not include this group as a negative control group in our study. Additionally, due to the limitation of our current conditions, we can not report specific values of cytokines below the detection limit, which may influence the sensitivity and specificity of predictive role of cytokines. This also led to some limitations in the conclusions drawn from our study.

Although our study has some limitations, it is still the innovative study that explores the association between the primary inflammatory cytokines and the treatment outcome of adolescent NSSI. The statistical analysis method used was appropriate enough to obtain the results, and to make the results closer to reality, the confounding factor that might influence the level of cytokines was also considered. Although the conclusion could be drawn in some limited conditions, it could still give us some meaningful inspiration in designing the treatment plan for adolescent NSSI in the future.

Conclusions

In this study, we found that inflammatory cytokines played an important role in predicting the treatment effect of adolescent NSSI, therefore the influence of neuroimmunological factors should be considered before commencing therapy. Moreover, the detection

of inflammatory cytokines is simple, feasible, and worth popularizing in future clinical practice. This would help in the design of other auxiliary treatment schemes to treat adolescent patients engaged in NSSI to improve their treatment efficacy in the future.

Abbreviations

NSSI	Non-suicidal self-injury
TNF-α	Tumor necrosis factor-α
IL-1	Interleukin-1
IL-1β	Interleukin-1β
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-4	Interleukin-4
IL-10	Interleukin-10
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, the fifth version
IRB	Institutional review board
ICD	International Classification of Diseases
CRP	C-reactive protein
ELISA	Enzyme linked immunosorbent assays

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Not applicable.

Author contributions
ND and YX designed the research protocol; ND and YL1 conducted the study; CL, YL2, JC, XL, and YL3 analysed the data; ND and YX drafted the manuscript; YZ, LL, and PW critically revised the manuscript; and ND provided the funding resources. All authors have accepted responsibility for the entire content of this submitted manuscript and have approved its submission.

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

Declarations

Ethics approval and consent to participate
All methods of the study has been performed in accordance with the Declaration of Helsinki and has been approved by ethics committee which named Medical Ethics Committee of The Fourth People's Hospital of Chengdu. Consent to participate in our study was obtained from the guardians of all subjects via a written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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