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Inflammation, cognitive dysfunction, and suicidal ideation among patients with major depression

Mao-Hsuan Huang[1,2,3], Mu-Hong Chen[2,4]*, Ju-Wei Hsu[2,4], Kai-Lin Huang[2,4], Shih-Jen Tsai[2,3,4], Tung-Ping Su[2,3,4,5] and Ya-Mei Bai[2,3,4]*

[1]Department of Psychiatry, YuanShan and Suao Branches of Taipei Veterans General Hospital, Ilan, Taiwan, [2]Division of Psychiatry, Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, [3]Institute of Brain Science, National Yang Ming Chiao Tung University, Taipei, Taiwan, [4]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan, and [5]Department of Psychiatry, General Cheng Hsin Hospital, Taipei, Taiwan

Original Research

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***Authors for correspondence:**
Mu-Hong Chen, MD, PhD
Email: kremer7119@gmail.com
Ya-Mei Bai, MD, PhD
Email: ymbi@mail2000.com.tw

Abstract

Background. Dysregulated proinflammatory cytokines have been shown to be associated with suicidal behavior. Cognitive deficits in working memory and inhibitory control have been demonstrated in depressed patients and people with suicidal ideation (SI). However, the association between proinflammatory cytokines, SI, and cognitive deficits in patients with major depressive disorder (MDD) remains unclear.

Methods. A total of 77 patients with MDD and age-/sex-matched 60 healthy individuals were recruited. MDD patients were divided into two groups: with SI (n = 36) and no SI (n = 41). SI was defined by a score of ≥2 in item 3 of the 17-item Hamilton Rating Scale for Depression. Levels of proinflammatory cytokines, including soluble interleukin-6 receptor, soluble tumor necrosis factor-α receptor type 1, and C-reactive protein (CRP), were measured, and cognitive function was assessed using 2-back task and Go/No-Go task.

Results. Patients with SI had higher levels of CRP than those without SI and controls ($P = .007$). CRP was positively associated with SI ($\beta = 0.21$, $P = .037$), independent of cognitive function and depressive symptoms. Furthermore, SI was associated with cognitive deficits in working memory and inhibitory control after adjusting for confounding factors ($P < .05$).

Conclusion. Our findings suggest that higher levels of serum CRP and deficits in working memory and inhibitory control may be associated with higher SI among patients with MDD.

Introduction

Suicide is a major public health concern and is considered as a complex phenomenon with biological, psychological, and social causes.[1] Suicidal behavior includes suicidal ideation (SI), suicide attempts, and completed suicide. A history of suicide attempts or the presence of SI is an important risk factor and a major predictor of subsequent suicide.[2] The pathophysiological mechanisms of suicide had been investigated,[3,4] but the mechanisms leading to suicidal behavior remain unclear. Because more than half of patients with depression present SI, and one-third of patients with SI progress to committing a suicidal act,[5] identifying potential biomarkers of SI in patients with major depressive disorder (MDD) is crucial for suicide prevention.

Patients with depression have cognitive deficits in executive function, memory and attention compared to healthy controls.[6] People with a history of suicide attempts or with current SI have also been reported to have cognitive deficits in the above-mentioned neuropsychological domains.[7-9] Specifically, depressed participants with SI were found to have higher cognitive inhibition deficit compared with depressed participants without SI, assessed by using Go/No-Go task.[9] Among executive functions, cognitive inhibition serves to restrict access to irrelevant information from working memory, and suppresses irrelevant stimuli for the ongoing task. With impaired cognitive inhibition, a person lacks capacity to reduce the intrusion of SI and retrieval of incorrect information from working memory, resulting in sustained negative affect.[10]

In addition, accumulating evidence has indicated that dysregulated immune system and cytokines may contribute to depressive symptoms and suicide.[11,12] For instance, patients with MDD have been reported to exhibit elevated serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP).[13-15] Interleukin-6 (IL-6), a cytokine secreted by T-cells and macrophages, can bind to a soluble form of the IL-6 receptor (sIL-6R). The IL-6/sIL-6R complex can stimulate cells that only express glycoprotein 130, a process that displays mainly proinflammatory functions.[16] Therefore, serum levels of sIL-6R may be suited for assessing inflammatory activity in BD than IL-6.[17] TNF-α exerts its effects by binding two receptors, TNF-α receptor subtype 1 (TNF-αR1) and TNF-α receptor subtype 2, and the binding of TNF-α to

TNF-αR1 has been related to apoptotic neuronal death.[18] The soluble forms of the TNF-α receptors prolong the half-life of TNF-α, and their circulating levels may be used to determine the overall production of TNF-α. Hence, the sTNF-αR1 is more reliable markers of proinflammatory activity.[19] Cytokine dysregulation has also been reported in the blood, cerebrospinal fluid, and postmortem brains of individuals with suicidal behavior compared with healthy controls.[20-22] However, previous investigations recruited participants with different psychiatric diagnoses, and participants with a history of suicide attempts and with the presence of SI were mixed in the analyses, which led to inconsistent findings.[13] Although patients with a history of suicide attempts have been included in many studies, only few studies have examined MDD patients with or without SI.[23] Furthermore, most studies on the correlation between suicidal behavior and proinflammatory biomarkers did not control for cognitive function. There is need to investigate the correlation between SI and proinflammatory cytokines among patients with MDD, as well as the confounding role of cognitive deficits.

In this study, we investigated the correlation between SI and proinflammatory cytokines among adult patients with MDD, with the adjustment of working memory and inhibitory control. We hypothesize that: (1) the levels of serum proinflammatory cytokines, namely CRP, sIL-6R, and sTNF-αR1, may be associated with SI after controlling for working memory and inhibitory control and (2) SI is correlated with impaired cognitive function in working memory and inhibitory control.

Methods

Our study was conducted in the psychiatric outpatient clinic of Taipei Veterans General Hospital. Consecutive outpatients aged between 20 and 64 years diagnosed with MDD based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, were enrolled. Age-, sex-, and body mass index (BMI)-matched normal controls were also recruited. Exclusion criteria included major physical disorder (ie, autoimmune/immune diseases, stroke, and epilepsy), a history of alcohol or substance misuse or dependence, and major psychiatric comorbidities such as schizophrenia, bipolar disorder, other major psychosis, intellectual disability, and organic mental disorder. We also excluded individuals who received electroconvulsive treatment in the past year before recruitment. All participants were not taking medications that could affect cytokine levels such as nonsteroidal anti-inflammatory drug or antibiotics. The healthy individuals were recruited by poster advertising in the clinic and in the community, and they underwent the Mini-International Neuropsychiatric Interview with a psychiatrist to rule out psychiatric illnesses. The detailed medical histories of all subjects were reviewed and physical examinations were taken to exclude any physical illness. Written informed consent was obtained from all patients prior to their inclusion in the study. The study was approved by the Institutional Review Board of the Taipei Veterans General Hospital and was conducted in accordance with the Declaration of Helsinki.

The severity of depression symptoms in all patients was assessed using the 17-item Hamilton Rating Scale for Depression (HAMD). Patients with MDD were classified as having SI if they scored ≥2 on item-3 of HAMD. The working memory (2-back) task and Go/No-Go task were the two cognitive tasks included in the computerized tests. In the working memory tasks, all participants were asked to respond as quickly as possible when they saw a number that appeared on a screen again separated by one other number (eg, if 31-45-31 was displayed in order, participants responded when 31 was displayed the second time). In the Go/No-Go task, participants were asked to respond as quickly as possible when the × symbol appeared. They were asked not to press the key when the + symbol appeared. After participants completed the pretest with all correct responses, formal tests were then administered to record their reaction times (mean), correct responses, commission errors, and omissions as performance parameters. Go/No-Go task was used to measure a participant's capacity for sustained attention and response control. Commission errors are related to disinhibition and increased impulsivity, while omission errors reflect one's deficiency in sustained attention to the task.

Proinflammatory cytokine levels of all subjects, including CRP, sIL-6R, and sTNF-αR1, were assessed using enzyme-linked immunosorbent assay (ELISA) kits (R&D systems, Minneapolis, MN). Fasting serum samples were collected in serum separator tubes, clotted for 30 minutes, and stored at −80°C until use. All assays were performed according to the manufacturer's instructions. The final absorbance of the mixture was measured at 450 nm, and the mixture was analyzed using an ELISA plate reader with Bio-Tek Power Wave Xs and Bio-Tek's KC junior software (Winooski, VT). The standard range was considered as per the manufacturer's instructions. A linear regression R-square value of ≥0.95 represented a reliable standard curve.

Patients' characteristics were analyzed using descriptive analysis. Chi-square tests were applied to compare categorical data. ANOVA with post hoc analysis was used to compare continuous data among the three groups (depressed patients without SI, depressed patients with SI, and controls). Linear regression analysis was used to examine the correlation between SI and inflammatory cytokines. Linear regression models were used to investigate the association between SI and cognitive function while controlling for confounding factors. Sensitivity analyses were performed with adjustment for age, sex, education, illness duration, and BMI in model 1, additional adjustment for the total HAMD score minus item 3 in model 2, and additional adjustment for cytokine levels in model 3. General linear models (GLMs) were used to assess proinflammatory cytokine levels between groups with the adjustment of age, sex, education, BMI, illness duration, and total HAMD score. The significance level was set at a $P < .05$. Statistical analysis was performed using SPSS 11.5 (SPSS Inc., Chicago, IL).

Results

In this study, 77 patients with MDD and 60 healthy subjects were recruited, and patients with MDD were divided into the SI group (n = 36) and the no SI group (n = 41). Patients with MDD had lower educational level than the controls ($P < .001$). Patients and SI had a longer duration of illness and higher total HAMD scores than controls and patients without SI ($P < .001$; Table 1). MDD patients with SI performed worse on 2-back task and Go/No-Go task than the other two groups (Table 1). GLMs for levels of proinflammatory cytokines with the adjustment of confounding factors revealed a higher level of CRP among patients with SI than the controls and patients without SI ($P = .004$; Figure 1).

Linear regression analyses showed that peripheral CRP level was positively associated with SI after controlling for demographic data, depression severity, working memory, and inhibitory control ($\beta = 0.21$, $P = .037$; Table 2). In addition, we found that the peripheral CRP level was negatively correlated with the correct

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Table 1. Demographic Data, Inflammatory Markers, and Cognitive Function Between MDD Patients With/Without Suicide Ideation and Controls

	Control (n = 60)	Patients Without SI (n = 41)	Patients With SI (n = 36)	*P*	Post Hoc
Age (years, SD)	30.18 (7.41)	31.80 (8.69)	33.36 (8.74)	.179	
Female (n, %)	38 (63.3)	33 (80.5)	25 (69.4)	.180	
Education (years, SD)	16.07 (2.04)	14.46 (2.67)	13.72 (2.41)	**<.001**	control > SI, no SI
BMI (SD)	22.48 (2.74)	23.43 (4.42)	23.92 (4.68)	.181	
Duration of illness (years, SD)	0 (0)	4.77 (5.63)	7.82 (6.99)	**<.001**	SI > no SI > control
HAMD total (SD)	0 (0)	11.76 (6.52)	22.97 (5.57)	**<.001**	SI > no SI > control
HAMD item 3 (SD)	0 (0)	0 (0)	2.17 (0.38)	**<.001**	SI > no SI, control
Proinflammatory markers (pg/mL, SD)					
CRP	868.10 (970.88)	1083.32 (1208.25)	2518.47 (3047.73)	**<.001**	SI > no SI, control
sIL-6R	32 220.56 (7368.64)	30 752.93 (9268.80)	28 116.64 (8590.76)	.073	
sTNF-αR1	859.46 (140.06)	826.64 (174.28)	755.95 (233.65)	**.028**	Control > SI
Working memory (2-back)					
Correct	13.87 (1.69)	12.38 (2.95)	9.83 (4.09)	**<.001**	Control > no SI > SI
Error	0.35 (0.63)	0.67 (1.64)	0.83 (1.44)	.169	
Omission	1.13 (1.69)	2.62 (2.95)	5.17 (4.09)	**<.001**	SI > no SI > control
Go/No-Go					
Correct	19.90 (0.44)	19.47 (2.17)	19.09 (19.6)	.056	
Error	0.22 (0.83)	0.26 (0.55)	1.31 (1.96)	**<.001**	SI > control
Omission	0.08 (0.42)	0.53 (2.17)	0.91 (1.96)	**.048**	SI > control

Note: Bold type indicates statistical significance.
Abbreviations: CRP, C-reactive protein; HAMD, 17-item Hamilton Depression Rating Scale; SD, standard deviation; SI, suicidal ideation; sIL-6R, soluble interleukin-6 receptor; sTNF-αR1, soluble tumor necrosis factor-α receptor type 1.

($\beta = -0.001$, $P = .001$) and positively correlated with the omission errors ($\beta = 0.001$, $P = .001$) in the working memory task. With respect to the neuropsychological correlates of SI, linear regression analyses adjusting for age, sex, education, illness duration, BMI, depression severity, and cytokine levels revealed that SI was positively associated with the omission errors ($\beta = 0.96$, $P = .002$) and negatively associated with the correct ($\beta = -0.96$, $P = .002$) in the working memory task (Table 3). SI was shown to be positively correlated with commission errors ($\beta = 0.38$, $P = .035$) in the Go/No-Go task (Table 3).

Discussion

We found that MDD patients with SI had higher levels of CRP than controls and patients without SI. Higher levels of serum CRP were found to be associated with higher SI after controlling for confounding factors. We also found that MDD patients with SI exhibited deficits in working memory and inhibitory control in the computerized 2-back task and Go/No-Go task, respectively. In addition, SI was found to be correlated with deficits in working memory and inhibitory control.

Our study demonstrated a positive correlation between serum CRP levels and SI. The result corroborated previous observations supporting the relationship between CRP and SI.[24-26] O'Donovan et al found that MDD patients with SI had higher CRP levels than those with low SI and healthy controls.[24] By contrast, Courtet et al found no significant differences in CRP levels between depressed patients with high SI and those with low SI in an inpatient population.[27] However, they did not compare CRP levels between patients and healthy controls. Increased expression of proinflammatory mediators may contribute to the pathophysiology of depression and suicidal behavior through increased tryptophan metabolism via the kynurenine pathway, HPA axis dysregulation and altered monoamine metabolism.[11,28] Inflammatory cytokines are able to activate the indoleamine-2,3-dioxygenase, decreasing the concentrations of tryptophan and increasing the concentrations of kynurenine, and changes in the kynurenine pathway have been proposed to be involved in MDD and suicidal behavior.[11,28] However, the literature is ambiguous regarding the change in peripheral tryptophan and kynurenine levels in depressed individuals. While some reported no association between kynurenine levels and MDD,[29] others found lower concentrations of kynurenine.[30] More investigations are needed to examine the kynurenine pathway in the pathophysiology of MDD. Furthermore, we found an association between serum CRP level and working memory, and it has been speculated that working memory may mediate increased SI and negative affect.[10,31] Additional studies are necessary to elucidate the underlying mechanisms of CRP for suicidal behavior and cognitive dysfunction among patients with MDD.

We found no significant differences between groups in the levels of sIL-6R and sTNF-αR1 in this study. High circulating levels of IL-6 have been reported to be associated with increased SI[24] and suicide attempts.[32] However, the results of previous studies were contradictory. Some studies found no differences in IL-6 levels between individuals with and without a history of suicide attempts.[33,34] Contrarily, Kim et al found a lower IL-6 production in MDD patients who had recently attempted suicide than those without history of suicide within 1 year.[35] The inconsistent findings may be due to many factors. For example, elevated levels of IL-6

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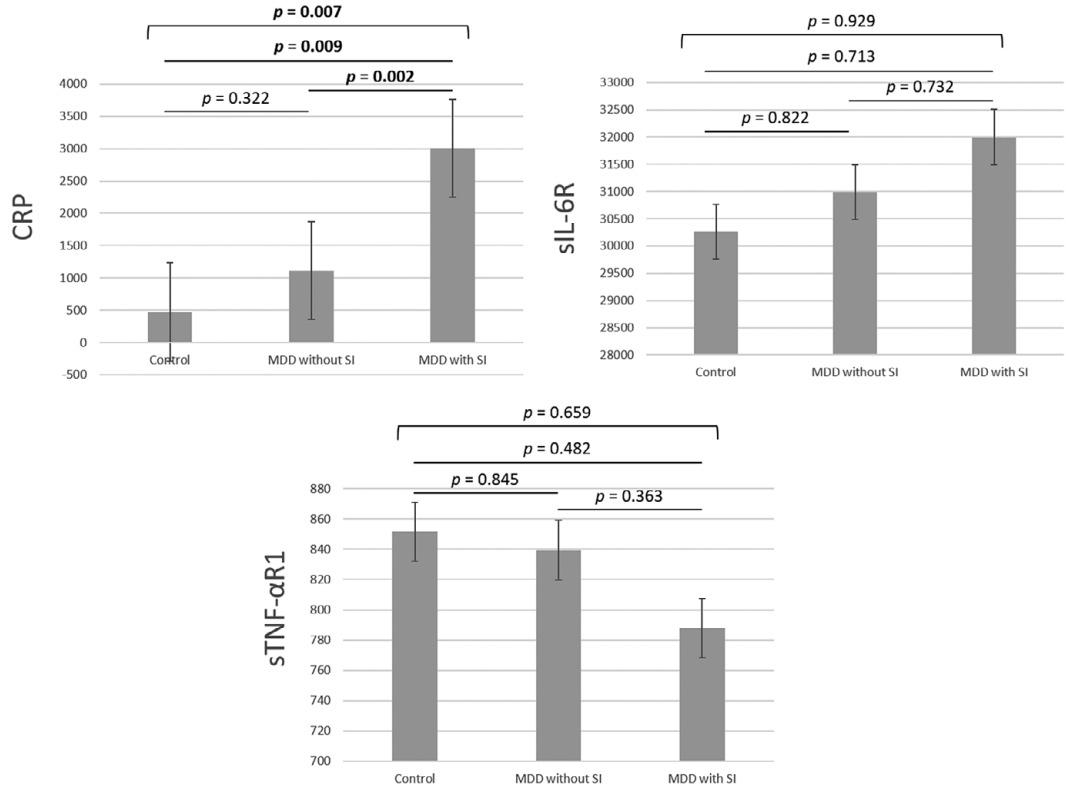

Figure 1. Levels (pg/mL) of cytokines between major depressive disorder (MDD) patients with or without SI and the controls with the adjustment of age, sex, education, BMI, illness duration, and total HAMD score. CRP, C-reactive protein; HAMD, 17-item Hamilton Depression Rating Scale; SI, suicidal ideation; sIL-6R, soluble interleukin-6 receptor; sTNF-αR1, soluble tumor necrosis factor-α receptor type 1.

Table 2. Linear Regression Models for the Association Between Suicide Ideation and Cytokine

	Model 1		Model 2	
	HAMD Item 3		HAMD Item 3	
Proinflammatory Cytokine Level	*β* (95% CI)	*P*	*β* (95% CI)	*P*
Log CRP	0.20 (0.01, 0.39)	**.036**	0.21 (0.01, 0.40)	**.037**
Log sIL-6R	−0.01 (−0.96, 0.94)	.987	−0.01 (−0.96, 0.94)	.985
Log sTNF-αR1	−0.80 (−2.11, 0.52)	.232	−0.80 (−2.12, 0.52)	.234

Note: Model 1: Adjusted by age, sex, education, illness duration, and total HAMD score minus item 3. Model 2: Model 1 additionally adjusted by working memory and cognitive control. Bold type indicates statistical significance.
Abbreviations: CRP, C-reactive protein; HAMD, 17-item Hamilton Depression Rating Scale; sIL-6R, soluble interleukin-6 receptor; sTNF-αR1, soluble tumor necrosis factor-α receptor type 1.

may be related to depression severity instead of suicidal behavior, and genotypic differences may interfere with individual inflammatory responses.[36] The relationship between SI and peripheral TNF-α levels remains unclear. Li et al found that the plasma TNF-α level equally increased in 33 suicidal and 19 nonsuicidal MDD patients compared with 64 healthy subjects. They suggested that the elevated levels of TNF-α may be associated with depression instead of suicide.[37]

To our knowledge, no study has compared working memory between patients with and without SI by using the *n*-back test. We found that adult depressed patients with SI had less correction and more errors in working memory 2-back task, compared to controls and depressed participants without SI. Participants with SI also had more commission and omission errors in Go/No-Go task, indicating their disinhibition and increased impulsivity. The results are consistent with those of previous studies, which evidenced the relationship between SI and cognitive deficits.[9,38,39] Working memory comprises a range of cognitive and affective functions, including emotional regulation and optimal affective information processing.[40] MDD patients with a history of suicide attempts have been shown to perform worse on *n*-back task than nonattempters.[7] Future studies should generalize findings from the *n*-back test to other stimuli and from working memory to other cognitive processes. By using the Go/No-Go paradigm similar to that in the present study, Westheide et al found that depression inpatients with recent suicide attempts and current SI had more commission errors and fewer correct responses in the Go/No-Go task compared with patients without SI.[9] Cognitive deficits have been demonstrated to play a role in the progression from SI to suicide attempts.[41] Moreover, our results may add to the evidence for impairments in inhibitory control in each stage of suicide: depression without SI, depression with SI, and suicide attempt.

The results of our study indicate that dysregulated proinflammatory cytokines, especially serum CRP levels, may play a crucial

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Table 3. Linear Regression Models for the Association Between Suicidal Ideation and Cognitive Function

	Correct		Error		Omission	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Working Memory (2-Back)						
Model 1: Adjusted by age, sex, education, illness duration, and BMI						
HAMD item 3	−1.22 (−1.81, −0.65)	**<.001**	0.179 (−0.07, 0.43)	.154	1.22 (0.65, 1.81)	**<.001**
Model 2: Model 1 additionally adjusted by HAMD total score minus item 3						
HAMD item 3	−1.17 (−1.89, −0.45)	**.002**	0.19 (−0.12, 0.50)	.224	1.17 (0.45, 1.89)	**.002**
Model 3: Model 2 additionally adjusted by CRP, sIL-6R, and sTNF-αR1						
HAMD item 3	−0.96 (−1.76, −0.15)	**.02**	0.10 (−0.26, 0.47)	.572	0.96 (0.15, 1.76)	**.002**
Go/No-Go						
Model 1: Adjusted by age, sex, education, illness duration, and BMI						
HAMD item 3	−0.11 (−0.43, 0.21)	.503	0.39 (0.14, 0.63)	**.002**	0.11 (−0.21, 0.43)	.493
Model 2: Model 1 additionally adjusted by HAMD total score minus item 3						
HAMD item 3	0.17 (−0.22, 0.56)	.381	0.40 (0.09, 0.70)	**.012**	−0.17 (−0.56, 0.21)	0.376
Model 3: Model 2 additionally adjusted by CRP, sIL-6R, sTNF-αR1						
HAMD item 3	0.14 (−0.32, 0.60)	.550	0.38 (0.03, 0.73)	**.035**	−0.15 (−0.61, 0.31)	.530

Note: Bold type indicates statistical significance.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; HAMD, 17-item Hamilton Depression Rating Scale; sIL-6R, soluble interleukin-6 receptor; sTNF-αR1, soluble tumor necrosis factor-α receptor type 1.

role in the identification of individuals at suicide risk. Therefore, patients with SI may be biologically distinguished from other subgroups of depressive patients. These results may have implications for the classifications of depression into more homogeneous groups and for developing different treatment strategies; future studies are warranted to investigate the efficacy of cytokine measures in suicide risk-assessment. For many individuals, suicidal behavior and SI denote impairment in executive function, which includes working memory and inhibitory cognitive control. A thorough understanding of this neuropsychological framework may suggest novel targets for treatment approaches to suicide, such as executive function training and problem-solving techniques.[42]

Some study limitations should be addressed. First, our study results are limited by the cross-sectional design, and individuals with depression included were not medication-free. The enrolled patients were receiving psychotropic medications during the cognitive function assessment and cytokine examination, which could have influenced the results, because some studies have suggested the anti-inflammatory properties of antidepressant drugs.[37,43] Allowing the patients to continue medications was more ethical and may prevent relapse and recurrence. Because our study had a cross-sectional design, a causal link between proinflammatory cytokine levels and suicide risk could not be established. Second, given that both MDD and suicide are associated with emotion, the enrolled patients who were sufficiently calm to complete the assessment might have caused recruitment bias and an overestimation of cognitive deficits. Third, we only assessed neuropsychological domains using the go/no-go and 2-back tasks. Future studies should use other neuropsychological measures used in previous studies or include more than one measure to allow the comparison of findings. For example, people with major affective disorders have been shown to have extreme sensory processing patterns, assessed by using Adult/Adolescent Sensory Profile, and the involvement of altered sensory perception may be linked with higher depression, impulsivity, and hopelessness, which are major indicators of suicidal behavior.[44] Fourth, the levels of proinflammatory cytokines, including TNF-α, may have diurnal variations.[45] We did not collect blood samples of the participants at the same time of the day, which may confound our findings. Fifth, the participants' SI in our study was not assessed through standardized scales that measure the attitudes, preparations, and behaviors to suicide, such as the Scale for Suicide Ideation and the Beck Scale for Suicide Ideation.[46,47] Future studies may consider applying the abovementioned widely used scales when investigating suicidal behavior in order increase the validity of assessment, and to maintain comparability with previous work. Finally, information on the history, recency, and frequency of suicide attempts was not collected. Individuals with recent suicide attempts have been found to self-report more cognitive impairment than individuals with nonrecent suicide attempts.[48] In addition, individuals with multiple suicide attempts have been reported to have higher comorbid health risks than those with a single suicide attempt or those without suicide attempts.[49] The differences in cognitive function and levels of inflammatory cytokines between groups in our study may have thus been distorted.

Conclusion

In summary, the present study indicates that serum levels of CRP have distinct differences between MDD patients with or without SI. Higher levels of serum CRP and deficits in working memory and inhibitory control may be associated with higher SI among patients with MDD.

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References

1. Turecki G, Brent DA. Suicide and suicidal behaviour. *Lancet*. 2016;**387**(10024):1227–1239.
2. Garcia de la Garza A, Blanco C, Olfson M, *et al.* Identification of suicide attempt risk factors in a national US survey using machine learning. *JAMA Psychiatry*. 2021;**78**(4):398–406.
3. Niculescu AB, Le-Niculescu H, Levey DF, *et al.* Precision medicine for suicidality: from universality to subtypes and personalization. *Mol Psychiatry*. 2017;**22**(9):1250–1273.
4. Serafini G, Canepa G, Adavastro G, *et al.* The relationship between childhood maltreatment and non-suicidal self-injury: a systematic review. *Front Psychiatry*. 2017;**8**:149.
5. Nock MK, Hwang I, Sampson NA, *et al.* Mental disorders, comorbidity and suicidal behavior: results from the national comorbidity survey replication. *Mol Psychiatry*. 2010;**15**(8):868–876.
6. Rock PL, Roiser JP, Riedel WJ, *et al.* Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Med*. 2014;**44**(10):2029–2040.
7. Keilp JG, Gorlyn M, Russell M, *et al.* Neuropsychological function and suicidal behavior: attention control, memory and executive dysfunction in suicide attempt. *Psychological Med*. 2013;**43**(3):539–551.
8. Marzuk PM, Hartwell N, Leon AC, *et al.* Executive functioning in depressed patients with suicidal ideation. *Acta Psychiatr Scand*. 2005;**112**(4):294–301.
9. Westheide J, Quednow BB, Kuhn KU, *et al.* Executive performance of depressed suicide attempters: the role of suicidal ideation. *European Arch Psychiatry Clin Neurosci*. 2008;**258**(7):414–421.
10. Richard-Devantoy S, Gorwood P, Annweiler C, *et al.* Suicidal behaviours in affective disorders: a deficit of cognitive inhibition? *Can J Psychiatry*. 2012;**57**(4):254–262.
11. Brundin L, Bryleva EY, Thirtamara Rajamani K. Role of inflammation in suicide: from mechanisms to treatment. *Neuropsychopharmacology*. 2017;**42**(1):271–283.
12. Courtet P, Giner L, Seneque M, *et al.* Neuroinflammation in suicide: toward a comprehensive model. *World J Biol Psychiatry*. 2016;**17**(8):564–586.
13. Dowlati Y, Herrmann N, Swardfager W, *et al.* A meta-analysis of cytokines in major depression. *Biological Psychiatry*. 2010;**67**(5):446–457.
14. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry*. 2016;**21**(12):1696–1709.
15. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;**71**(2):171–186.
16. Scheller J, Chalaris A, Schmidt-Arras D, *et al.* The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim Biophys Acta*. 2011;**1813**(5):878–888.
17. Bai YM, Su TP, Li CT, *et al.* Comparison of pro-inflammatory cytokines among patients with bipolar disorder and unipolar depression and normal controls. *Bipolar Disord*. 2015;**17**(3):269–277.
18. Chen G, Goeddel DV. TNF-R1 signaling: a beautiful pathway. *Science*. 2002;**296**(5573):1634–1635.
19. Huang MH, Chen MH, Tu PC, *et al.* Elevated tumor necrosis factor-alpha receptor subtype 1 and the association with abnormal brain function in treatment-resistant depression. *J Affect Disord*. 2018;**235**:250–256.
20. Ducasse D, Olie E, Guillaume S, *et al.* A meta-analysis of cytokines in suicidal behavior. *Brain Behav Immun*. 2015;**46**:203–211.
21. Black C, Miller BJ. Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. *Biological Psychiatry*. 2015;**78**(1):28–37.
22. Serafini G, Parisi VM, Aguglia A, *et al.* A specific inflammatory profile underlying suicide risk? Systematic review of the main literature findings. *Int J Environ Res Public Health*. 2020;**17**(7):2393.
23. Gananca L, Oquendo MA, Tyrka AR, *et al.* The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology*. 2016;**63**:296–310.
24. O'Donovan A, Rush G, Hoatam G, *et al.* Suicidal ideation is associated with elevated inflammation in patients with major depressive disorder. *Depress Anxiety*. 2013;**30**(4):307–314.
25. Gibbs HM, Davis L, Han X, *et al.* Association between C-reactive protein and suicidal behavior in an adult inpatient population. *J Psychiatr Res*. 2016;**79**:28–33.
26. Park RJ, Kim YH. Association between high sensitivity CRP and suicidal ideation in the Korean general population. *European Neuropsychopharmacol*. 2017;**27**(9):885–891.
27. Courtet P, Jaussent I, Genty C, *et al.* Increased CRP levels may be a trait marker of suicidal attempt. *European Neuropsychopharmacol*. 2015;**25**(10):1824–1831.
28. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006;**27**(1):24–31.
29. Bradley KA, Case JA, Khan O, *et al.* The role of the kynurenine pathway in suicidality in adolescent major depressive disorder. *Psychiatry Res*. 2015;**227**(2–3):206–212.
30. Pompili M, Lionetto L, Curto M, *et al.* Tryptophan and kynurenine metabolites: are they related to depression? *Neuropsychobiology*. 2019;**77**(1):23–28.
31. Bauer BW, Gustafsson HC, Nigg J, *et al.* Working memory mediates increased negative affect and suicidal ideation in childhood attention-deficit/hyperactivity disorder. *J Psychopathol Behav Assess*. 2018;**40**(2):180–193.
32. Lindqvist D, Janelidze S, Hagell P, *et al.* Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biological Psychiatry*. 2009;**66**(3):287–292.
33. Isung J, Mobarrez F, Nordstrom P, *et al.* Low plasma vascular endothelial growth factor (VEGF) associated with completed suicide. *World J Biol Psychiatry*. 2012;**13**(6):468–473.
34. Vargas HO, Nunes SO, Pizzo de Castro M, *et al.* Oxidative stress and lowered total antioxidant status are associated with a history of suicide attempts. *J Affect Disord*. 2013;**150**(3):923–930.
35. Kim YK, Lee SW, Kim SH, *et al.* Differences in cytokines between non-suicidal patients and suicidal patients in major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;**32**(2):356–361.
36. Kim YK, Hong JP, Hwang JA, *et al.* TNF-alpha -308G>A polymorphism is associated with suicide attempts in major depressive disorder. *J Affect Disord*. 2013;**150**(2):668–672.
37. Li Z, Qi D, Chen J, *et al.* Venlafaxine inhibits the upregulation of plasma tumor necrosis factor-alpha (TNF-alpha) in the Chinese patients with major depressive disorder: a prospective longitudinal study. *Psychoneuroendocrinology*. 2013;**38**(1):107–114.
38. Kim SJ, Kang SG, Cho IH, *et al.* The relationship between poor performance on attention tasks and increased suicidal ideation in adolescents. *Eur Child Adolesc Psychiatry*. 2015;**24**(11):1361–1368.
39. Kasckow J, Youk A, Anderson SJ, *et al.* Trajectories of suicidal ideation in depressed older adults undergoing antidepressant treatment. *J Psychiatric Res*. 2016;**73**:96–101.
40. Schmeichel BJ, Volokhov RN, Demaree HA. Working memory capacity and the self-regulation of emotional expression and experience. *J Pers Soc Psychol*. 2008;**95**(6):1526–1540.

41. Huber RS, Hodgson R, Yurgelun-Todd DA. A qualitative systematic review of suicide behavior using the cognitive systems domain of the research domain criteria (RDoC) framework. *Psychiatry Res*. 2019;**282**: 112589.
42. Hopko DR, Funderburk JS, Shorey RC, *et al.* Behavioral activation and problem-solving therapy for depressed breast cancer patients: preliminary support for decreased suicidal ideation. *Behav Modif*. 2013;**37**(6): 747–767.
43. Hiles SA, Baker AL, de Malmanche T, *et al.* Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. *Psychological Med*. 2012;**42** (10):2015–2026.
44. Serafini G, Gonda X, Pompili M, *et al.* The relationship between sensory processing patterns, alexithymia, traumatic childhood experiences, and quality of life among patients with unipolar and bipolar disorders. *Child Abuse Negl*. 2016;**62**:39–50.
45. Naidu KS, Morgan LW, Bailey MJ. Inflammation in the avian spleen: timing is everything. *BMC Mol Biol*. 2010;**11**:104.
46. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the scale for suicide ideation. *J Consult Clin Psychol*. 1979;**47**(2):343–352.
47. Beck AT, Steer RA, Ranieri WF. Scale for suicide ideation: psychometric properties of a self-report version. *J Clin Psychol*. 1988;**44**(4):499–505.
48. Saffer BY, Klonsky ED. The relationship of self-reported executive functioning to suicide ideation and attempts: findings from a large U.S.-based online sample. *Arch Suicide Res*. 2017;**21**(4):577–594.
49. Rosenberg HJ, Jankowski MK, Sengupta A, *et al.* Single and multiple suicide attempts and associated health risk factors in New Hampshire adolescents. *Suicide Life-Threat Behav*. 2005;**35**(5):547–557.

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