Original Article

# C-reactive Protein and Suicidality in Patients with Treatment-resistant Depression

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## Abstract

**Objective:** Increasing evidence suggests a crucial rôle of C-reactive protein (CRP) in the pathological mechanisms of suicide. Whether CRP levels may be associated with suicidal ideation (SI) among patients with treatment-resistant depression (TRD) remains unclear. In this study, we intended to explore the relation between TRD and SI. **Methods:** Totally 36 patients with TRD and SI, 24 with TRD without SI, and 32 healthy controls were enrolled in the present study. SI was defined based on scores of ≥ 2 at the 17-item Hamilton Depression Rating Scale item 3. Fasting serum CRP levels were also measured. **Results:** The generalized linear model with gamma log link demonstrated that patients with TRD and SI had significantly higher CRP levels ($p < 0.05$) than the control group after adjusting for age, sex, and body mass index. **Conclusion:** Patients with TRD and SI, but not those without SI, were associated with increased CRP levels. Whether CRP may be a predictor of further suicidal risk among such high-risk patients would need further investigation.

**Key words: 17-item Hamilton Depression Rating Scale, biomarker, inflammatory theory of depression, predictor for suicide risk**
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## Introduction

According to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) research, up to 40% of patients with major depressive disorder (MDD)) – defined as treatment-resistant depression (TRD) – do not have a clinical remission after two trials of conventional antidepressants with adequate dose and treatment duration [1]. TRD has been associated with worsening clinical outcomes, including increased relapse rates, suicidality, and decreased psychosocial functioning and quality of life [2-4]. In Taiwan, the suicide death rate reached its highest point in 2006 (19.3/100,000) [5, 6]. After implementing a suicide prevention program in Taiwan in 2005, we saw a drop in the incidence of suicide death to 15.1/100,000 in the years that followed (2008–2011) [5, 6]. But in 2012, the rate of suicide death was increased again to around 16/100,000, and it stayed there until 2019 [5, 6].

Research results showed that pro-inflammatory cytokines, especially C-reactive protein (CRP), have a critical rôle in suicidality, which includes suicidal ideation (SI), attempts, and mortality [7, 8]. O'Donovan et al. demonstrated that patients with MDD and high SI have higher serum CRP levels than patients with low SI do [9]. Wiebenga et al. examined serum CRP levels among 1,749 patients with depressive and/or anxiety disorders and found that patients without current SI but with a previous history of suicide attempts and those with current SI and previous suicide attempts have increased serum CRP levels compared with patients without current SI and previous suicide attempts [10]. But patients with MDD with suicidal idea have not been found to be associated with increased serum CRP levels [11]. In a meta-analysis study of 2,772 patients with MDD and 237 healthy controls, an association exists between patients' high serum CRP levels and suicidality [12]. Miola et al. also found that compared to nonsuicidal people (either patients or healthy controls), serum CRP levels are greater in patients with high SI [12] and that

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in those who have had attempted suicide. But whether those findings could be generalized to patients with TRD remains unclear and would need further investigation.

In the present study, we attempted to explore the serum CRP levels between patients with TRD with or without SI compared with the healthy controls. We hypothesized that patients with TRD and SI would exhibit the highest CRP levels among the three groups.

# Methods

## Study participants

Totally we enrolled 60 adult patients aged between 20 and 64 years who were diagnosed with MDD based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, with inadequate response to at least two different antidepressants with adequate dosage and treatment duration in the present study. Patients with SI were those with scores of ≥ 2 at the 17-item Hamilton Depression Rating Scale (HDRS) item 3; patients without SI were those with scores of ≤ 1 at the HDRS item 3 [13]. The cutoff point of SI was defined as ≥ 2 of HDRS item 3 based on Vuorilehto et al.'s finding that the highest Kappa coefficient of HDRS item 3 ≥ 2 was considered suicide [14]. Furthermore, we enrolled 32 age- and sex-matched healthy controls who had neither a current without previous psychiatric diagnosis based on the Mini-International Neuropsychiatric Interview as a comparison group [15]. Exclusion criteria included major medical or neurological diseases or a history of alcohol or substance use disorders in the current study.

This study was approved two times by the Institutional Review Board of Taipei Veterans General Hospital (protocol IRB numbers = 2012-04-037B and 2016-08-001C as well as dates of approval = April 24, 2012, and August 17, 2016, respectively). All study participants were required to sign their informed consent before participating in the study.

## Assessment of inflammatory makers

The serum CRP levels of all participants were assayed using enzyme-linked immunosorbent assay (ELISA) kits (R and D Systems, Minneapolis, Minnesota, USA). Fasting serum samples were collected in serum separator tubes and clotted for 30 min between 9: 00 a.m. and 12: 00 p.m. All specimens were then stored at −80°C until use. We did all according to the manufacturer's instructions. The final absorbance of the mixture was measured and analyzed at 450 nm using an ELISA plate reader with Bio-Tek Power Wave Xs and Bio-Tek's KC junior software (Winooski, Vermont, USA). The standard range depended on the manufacturer's instructions, and a linear regression, $R^2 \geq 0.95$ represented a reliable standard curve.

## Definition of treatment refractoriness

The Maudsley staging method (MSM), a points-based staging model, was used to quantify the degrees of treatment refractoriness since treatment refractoriness in depression encompasses several dimensions [16]. The MSM contains three factors: Severity of symptoms based on total scores of HDRS, duration of presenting episode, and treatment history (i.e., numbers of antidepressant treatment failures) [15].

## Statistical analysis

For between-group comparisons, the *F*-test was used for continuous variables, and Pearson's test was used for categorical variables. Due to the gamma distribution of CRP levels in the present study, the generalized linear model (GLM) with gamma log link was used to examine the CRP levels between groups after adjusting for age, sex, and body mass index (BMI). Furthermore, the partial correlation analysis model with adjustment of age, sex, BMI, duration of illness, and nonsuicidal depressive symptoms was done to investigate the associations between suicidal symptoms (HDRS item 3 scores) and total MSM scores among patients with TRD. The GLM with gamma log link was done to assess the association between HDRS item 3 scores and CRP levels among patients with TRD.

A two-tailed $p < 0.05$ was considered significant for differences between groups. For data processing and statistical analyses, we used the Statistical Package for the Social Science software version 17 for Windows (SPSS Inc., Chicago, Illinois, USA).

# Results

Totally we enrolled 36 patients with TRD and SI, and 24 patients with TRD without SI, and 32 healthy controls in the present study. As shown in Table 1, no differences were seen in age, sex, or BMI. Furthermore, total HDRS scores were higher in patients with TRD and SI than in those with TRD without SI ($p < 01$). The total MSM scores did not show a significant difference between the two TRD groups. As shown in Table 2, we found no association between serum CRP levels and the level of treatment refractoriness (Table 2).

As shown in Figure 1, age, sex, and BMI were taken into account in the GLM with gamma log link. Patients with TRD

**Table 1.** Demographic and clinical variables in control group, treatment-resistant depression without suicidal ideation group and treatment-resistant depression with suicidal ideation group

| | Mean ± SD | | |
|---|---|---|---|
| | Controls ($n$ = 32) | TRD without SI ($n$ = 24) | TRD with SI ($n$ = 36) |
| Age (years) | 42.03 ± 7.78 | 45.17 ± 9.65 | 42.47 ± 10.39 |
| Female, $n$ (%) | 21 (65.6) | 19 (79.2) | 24 (66.7) |
| BMI (kg/m$^2$) | 24.78 ± 4.10 | 22.30 ± 4.00 | 23.47 ± 4.65 |
| Duration of illness (years) | | 10.25 ± 6.62 | 10.90 ± 8.88 |
| Total HDRS scores | | 20.38 ± 2.68 | 22.97 ± 3.82** |
| HDRS item 3 scores | | 1.00 ± 0.00 | 2.31 ± 0.47*** |
| MSM scores | | 8.21 ± 1.53) | 9.08 ± 1.86 |

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; significantly different between the group tested using $t$-test of Chi-square test when appropriate.
TRD, treatment-resistant depression; SI, suicidal ideation; BMI, body mass index; HDRS, Hamilton Depression Rating Scale; MSM, Maudsley Staging Method; SD, standard deviation

**Table 2.** The associations of suicidal symptoms and treatment refractoriness with C-reactive protein levels among patients with treatment-resistant depression

| HDRS item 3 scores | MSM scores§ | HDRS item 3 scores | CRP levels+ |
|---|---|---|---|
| *r* | 0.12 | B | 0.17 |

*p*- values of CRP levels and MSM were nonsignificant.
§Partial correlation analysis was used after adjusting for age, sex, BMI, duration of illness, and nonsuicidal depressive symptoms;
+Generalized linear model with gamma log link was used after adjusting for age, sex, BMI, duration of illness, and nonsuicidal depressive symptoms.
CRP, C-reactive protein; HDRS, Hamilton Depression Rating Scale; MSM, Maudsley Staging Method; BMI, body mass index

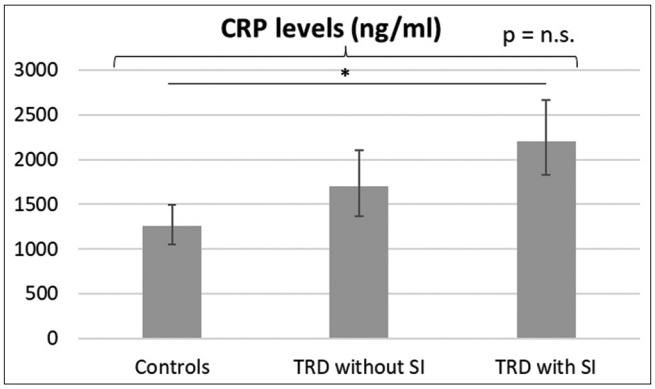


**Figure 1.** Generalized linear regression model with gamma log link for the estimated C-reactive protein levels (means, standard errors) between groups after adjusting for age, sex, and body mass index. *$p < 0.05$, significantly different between the groups tested using Wald Chi-square test. CRP, C-reactive protein; TRD, treatment-resistant depression; SI: suicidal ideation.

and SI had significantly higher CRP levels than the control group ($p < 0.05$).

Finally, we found no significant associations between the HDRS item 3 scores and the CRP levels or the total MSM scores among patients with TRD (Table 2).

## Discussion

Our study findings (Table 1) supported the study hypothesis that patients with TRD and SI but not those without SI, had significantly higher serum CRP levels than the control group ($p < 0.01$). CRP was an independent factor of SI regardless of age, sex, and BMI among patients with TRD. As mentioned, increasing evidence has shown an association between CRP and suicidality, including SI, suicide attempts, and suicide death [7, 8]. Turkheimer et al. examined the levels of the translocator protein (TSPO), a proxy of microglial activation, using (11C) PK11195 positron emission tomography imaging and also assessed a biomarker of blood–brain barrier (BBB) leakage S100β among patients with depression [17]. They discovered that peripheral inflammation (increased CRP levels) is associated with the increase in TSPO and the reduction in BBB permeability [17]. Su et al. found higher blood CRP levels and elevated TSPO levels in brain regions associated with depression, such as the anterior cingulate cortex, in patients with depression compared with the controls [18]. Furthermore, Holmes et al. revealed that whereas TSPO is not increased among patients with depression who did not have suicidal thoughts, it is much higher in those with suicidal thoughts, especially in the anterior cingulate cortex and insula [19]. Gonçalves de Andrade et al. hypothesized neuroinflammation (i.e., microglial activation) as a hub for suicide neuropathology, and further suggested that intervention targeting neuroinflammation is a possible therapeutic strategy against suicidality [20]. In the present study (Table 1), we found that patients with TRD and SI showed significantly highest CRP levels compared with the other groups ($p < 0.01$). This finding needs to further confirm the rôle of CRP in the pathophysiology of suicide.

We found no association between CRP levels and the level of treatment refractoriness (Table 2 and Figure 1), which was consistent with Fischer et al.'s findings of the lack of an association between low-grade systemic inflammation and antidepressant resistance [21]. Fischer et al. explored the associations between serum CRP levels and response to antidepressant treatment among patients with major affective disorders in a 6-week inpatient setting [21]. They indicated that the baseline serum CRP levels are not associated with the treatment response to antidepressants among patients with major depression [21]. But Khonglah et al. reported that a higher proportion of patients with major depression who have low CRP levels at baseline attend attained remission than patients with higher CRP levels after a 12-week antidepressant treatment [22]. A Mendelian randomization study of the UK Biobank (about 500,000 individuals) identified an independent causal effect of BMI on TRD not through CRP [23]. This finding may imply that an overall systemic low-grade inflammation condition, such as obesity, but not a single inflammatory marker, including CRP, may play a crucial rôle in the pathological mechanisms of antidepressant resistance among patients with major depression [23]. However, BMI did not differ between the three groups in our study. Further studies would be required to clarify the separate or additive role of obesity and CRP in the levels of antidepressant refractoriness.

### Study limitations

The readers are warned against over-interpret the study data because this study has two major limitations:

- During the CRP test, patients did not stop taking their psychotropic medications. It was ethically right to let patients maintain their prescriptions to avoid making their depression and suicidal thoughts worse. This decision also guaranteed the data's veracity. To verify our results, nevertheless, a drug-free study design would be necessary
- We found no associations between serum CRP levels and the HDRS item 3 scores as well as the total MSM scores, which may partially imply a homogeneity of our TRD samples. Whether the predictive role of CRP on suicidality

may emerge in a sample of patients with mixed depression severity would need further investigation

- Patients with TRD and SI had slightly but significantly higher total HDRS scores than did those without SI, which may imply the possibility of an association between increased serum CRP levels and overall depression severity. Despite the high collinearity between suicide and depression severity, further studies would be required to clarify whether increased serum CRP levels may be independently associated with suicidality.

### *Summary*

In our study, patients with TRD and SI had the highest CRP levels compared with those with TRD without SI and the control group. Identifying an optimal biomarker of suicide is clinically important and challenging. Further prospective follow-up studies would be required to investigate whether CRP may predict further suicidal risk, such as worsening SI and suicide attempts, among patients with TRD.

## Data Availability Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to Taiwan's clinical trial ethical regulation. But this study related data are available from the corresponding author on a reasonable request.

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## Conflicts of Interest

The authors declare no conflicts of interest in writing this article.

## References

1. Howland RH: Sequenced Treatment Alternatives to Relieve Depression (STAR*D). Part 2: Study outcomes. *J Psychosoc Nurs Ment Health Serv* 2008; 46: 21-4.
2. Dignam P: Treatment-resistant depression. *Aust N Z J Psychiatry* 2009; 43: 87.
3. Fekadu A, Wooderson SC, Markopoulo K, et al.: What happens to patients with treatment-resistant depression? a systematic review of medium to long term outcome studies. *J Affect Disord* 2009; 116: 4-11.
4. Little A: Treatment-resistant depression. *Am Fam Physician* 2009; 80: 167-72.
5. Snowdon J, Chen YY, Zhong B, et al.: A longitudinal comparison of age patterns and rates of suicide in Hong Kong, Taiwan and Japan and two Western countries. *Asian J Psychiatr* 2018; 31: 15-20.
6. Chen YY, Yang CT, Pinkney E, et al.: The age-period-cohort trends of suicide in Hong Kong and Taiwan, 1979-2018. *J Affect Disord* 2021; 295: 587-93.
7. Black C, Miller BJ: Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. *Biol Psychiatry* 2015; 78: 28-37.
8. Ganança L, Oquendo MA, Tyrka AR, et al.: The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology* 2016; 63: 296-310.
9. 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: 307-14.
10. Wiebenga JX, Heering HD, Eikelenboom M, et al.: Associations of three major physiological stress systems with suicidal ideation and suicide attempts in patients with a depressive and/or anxiety disorder. *Brain Behav Immun* 2022; 102: 195-205.
11. Huang TL, Lin FC: High-sensitivity C-reactive protein levels in patients with major depressive disorder and bipolar mania. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31: 370-2.
12. Miola A, Dal Porto V, Tadmor T, et al.: Increased C-reactive protein concentration and suicidal behavior in people with psychiatric disorders: a systematic review and meta-analysis. *Acta Psychiatr Scand* 2021; 144: 537-52.
13. Carrozzino D, Patierno C, Fava GA, et al.: The hamilton rating scales for depression: a critical review of clinimetric properties of different versions. *Psychother Psychosom* 2020; 89: 133-50.
14. Vuorilehto M, Valtonen HM, Melartin T, et al.: Method of assessment determines prevalence of suicidal ideation among patients with depression. *Eur Psychiatry* 2014; 29: 338-44.
15. Sheehan DV, Lecrubier Y, Sheehan KH, et al.: The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59 Suppl 20: 22-33.
16. Fekadu A, Wooderson SC, Markopoulou K, et al.: The Maudsley staging method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. *J Clin Psychiatry* 2009; 70: 952-7.
17. Turkheimer FE, Althubaity N, Schubert J, et al.: Increased serum peripheral C-reactive protein is associated with reduced brain barriers permeability of TSPO radioligands in healthy volunteers and depressed patients: implications for inflammation and depression. *Brain Behav Immun* 2021; 91: 487-97.
18. Su L, Faluyi YO, Hong YT, et al.: Neuroinflammatory and morphological changes in late-life depression: the NIMROD study. *Br J Psychiatry* 2016; 209: 525-6.
19. Holmes SE, Hinz R, Conen S, et al.: Elevated translocator protein in anterior cingulate in major depression and a role for inflammation in suicidal thinking: a positron emission tomography study. *Biol Psychiatry* 2018; 83: 61-9.
20. Gonçalves de Andrade E, González Ibáñez F, Tremblay MÈ: Microglia as a hub for suicide neuropathology: future investigation and prevention targets. *Front Cell Neurosci* 2022; 16: 839396.
21. Fischer KF, Simon MS, Elsner J, et al.: Assessing the links between childhood trauma, C-reactive protein and response to antidepressant treatment in patients with affective disorders. *Eur Arch Psychiatry Clin Neurosci* 2021; 271: 1331-41.
22. Khonglah D, Pal A, Mallik N, et al.: A prospective hospital-based study on C-reactive protein as a response predictor of antidepressant treatment in drug naïve patients with major depressive disorder. *Indian J Psychiatry* 2023; 65: 472-6.
23. Karageorgiou V, Casanova F, O'Loughlin J, et al.: Body mass index and inflammation in depression and treatment-resistant depression: a mendelian randomisation study. *BMC Med* 2023; 21: 355.