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Suicidality in civilian women with PTSD: Possible link to childhood maltreatment, proinflammatory molecules, and their genetic variations

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ABSTRACT

Background: Posttraumatic stress disorder (PTSD) is a robust risk factor for suicide. Studies have suggested an association between suicide and elevated inflammatory markers, although such evidence in PTSD is scarce. Suicide risk, PTSD, and inflammatory molecules are all shown to be associated with childhood maltreatment and genetic factors.

Methods: We examined the association between suicidal ideation/risk and inflammatory markers in 83 civilian women with PTSD, and explored the possible influence of childhood maltreatment and inflammatory genes. Suicidal ideation and risk were assessed using the Beck Depression Inventory-II and the Mini-International Neuropsychiatric Interview. Childhood maltreatment history was assessed with the Childhood Trauma Questionnaire (CTQ). Blood levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and high-sensitivity tumor necrosis factor-α were measured. Genetic polymorphisms of *CRP* rs2794520 and *IL6* rs1800796 were genotyped.

Results: Suicidal ideation was significantly positively correlated with hsCRP ($p = 0.002$) and IL-6 ($p = 0.015$) levels. Suicide risk weighted score was significantly positively correlated with hsCRP ($p = 0.016$) levels. The risk alleles of *CRP* rs2794520 and *IL6* rs1800796 leading to increased respective protein levels were dose-dependently associated with higher risk of suicide ($p = 0.007$ and $p = 0.029$, respectively). The CTQ total score was significantly correlated with suicidal ideation and risk, but not with inflammatory marker levels. Furthermore, a multivariate regression analysis controlling for PTSD severity and potential confounders revealed that rs2794520 and rs1800796, but not hsCRP or IL-6 levels, significantly predicted suicidal ideation ($p < 0.001$) and risk ($p = 0.007$), respectively.

Conclusion: Genetic variations within inflammatory genes might be useful in detecting PTSD patients at high risk of suicide.

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric condition that can develop after a major traumatic event, often leading to a chronic course with severe functional disability. PTSD is characterized by intrusion (or re-experiencing) symptoms, avoidance, negative

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alterations in cognitions and mood, and hyperarousal (APA, 2013). PTSD is considered to be a robust risk factor for suicide (Fox et al., 2021), as indicated by the relationship with completed suicide (Gradus et al., 2010), suicide attempt (Davidson et al., 1991), and suicidal ideation (Krysinska and Lester, 2010). This association between PTSD and suicide has been observed even after controlling for psychiatric comorbidities including comorbid depression (Davidson et al., 1991; Gradus et al., 2010) as well as demographic confounders (Davidson et al., 1991; Fox et al., 2021). However, prevention of suicidal behaviors in individuals with PTSD is usually difficult, which may be partly because there are no objective markers that can aid in the prediction of these behaviors.

There has been increasing evidence on the link between inflammation, suicide, and PTSD. Patients with PTSD are shown to exhibit elevated levels of circulating proinflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), compared to healthy controls (Hori and Kim, 2019; Imai et al., 2018; Miller et al., 2018; O'Donovan et al., 2017; Passos et al., 2015; Yang and Jiang, 2020). Suicide has also been associated with elevated levels of IL-6, TNF-α, and CRP (Black and Miller, 2015; Brundin et al., 2017; Janelidze et al., 2011; Miola et al., 2021; O'Donovan et al., 2013; Su et al., 2020; Yan et al., 2021). These findings suggest that inflammation can be involved in the biological mechanism of suicide in PTSD. To our knowledge, however, no study has reported the association of inflammatory markers with suicidality in patients with PTSD.

It is well known that a variety of environmental factors can influence the development of PTSD and risk of suicide. Among these, early-life adversity such as childhood maltreatment has been reliably associated with increased risk of PTSD (Scott et al., 2010) and suicidality (Felitti et al., 1998; Polanco-Roman et al., 2021) in later life. Adverse childhood experiences are also associated with increased levels of CRP, IL-6, and TNF-α in adulthood (Baumeister et al., 2016; Coelho et al., 2014; Hakamata et al., 2022; Wong et al., 2022). Based on these findings, it is suggested that dysregulation in the immune-inflammatory system may be a key mechanism linking early-life adversity to the development of neuropsychiatric disorders (Agorastos et al., 2019; Danese and Lewis, 2017). It is therefore possible that early trauma can influence the relationship between PTSD, suicide, and inflammation.

Besides environmental factors, genetic background is implicated in PTSD (Koenen et al., 2008) and suicide (Roy et al., 1991). Recently, immune/inflammatory system-related genes and pathways have been identified as the most dysregulated in patients with PTSD compared to controls in hypothesis-free, data-driven genomics studies such as genome-wide association (Stein et al., 2016; Maihofer et al., 2022), blood DNA methylome (Uddin et al., 2010), and blood transcriptome (Breen et al., 2018) studies. Inflammation-related genes and pathways have also been identified in genome-wide association (Galfalvy et al., 2015) and blood transcriptome (Le-Niculescu et al., 2013) studies of suicidality. Moreover, inflammation-related genes such as *CRP* and *IL6* have been associated with both PTSD symptomatology (Michopoulos et al., 2015; Miller et al., 2018) and suicide (Bokor et al., 2021; Suchankova et al., 2013). Notably, previous studies including ours have demonstrated that the single nucleotide polymorphism (SNP) rs2794520 of *CRP* is associated with blood CRP levels and PTSD symptom severity (Michopoulos et al., 2015; Otsuka et al., 2021). In addition, rs1800795 of *IL6*, which is in strong linkage disequilibrium with rs1800796, is known to affect circulating IL-6 levels (Terry et al., 2000) and has been associated with suicidal behaviors (Bokor et al., 2021; Eftekharian et al., 2018).

The present study investigated the relationship of suicide risk with blood levels of CRP, IL-6, and TNF-α in patients with PTSD, and further explored possible effects of childhood maltreatment history and genetic variations of *CRP* (rs2794520) and *IL6* (rs1800796). We focused on women with PTSD, considering that the vast majority of participants enrolled in our research project were women and that sex differences may exist in the relation between inflammation and suicide in PTSD (Lombardo, 2021). Indeed, it is well known that the prevalence of PTSD is higher in women than in men (Kessler et al., 1995). It is also suggested that the heritability of PTSD is different between sexes (Sartor et al., 2011) and that PTSD is one of the women-specific risk factors for suicide attempts (Miranda-Mendizabal et al., 2019). We hypothesized that 1) PTSD patients with high risk of suicide would show higher levels of inflammatory makers, 2) childhood maltreatment history in PTSD patients would be associated with increased levels of inflammatory markers, and 3) PTSD patients carrying the *CRP* and *IL6* alleles that increase circulating protein levels would show higher suicide risk.

2. Methods

2.1. Participants

This study was conducted as part of our ongoing research project, and results on the association between inflammatory markers and PTSD symptomatology have been partially reported elsewhere (Imai et al., 2018; Otsuka et al., 2021); however, the focus of these previous studies was not on suicidality, and the data on suicide have not been reported thus far. Data collection for the present study was conducted between 2015 and 2021.

A total of 93 civilian patients with PTSD (age range: 18–59 years) participated in this study. This sample size was determined by referring to previous studies on inflammatory markers in relation to suicidality (reviewed in Miola et al., 2021). The patients were recruited at 3 institutes and their affiliated hospitals/clinics in a consecutive manner, with their attending doctors having been asked to inform the researcher of all potentially eligible patients. All patients were regularly visiting a psychiatric hospital/clinic and had already been diagnosed as having PTSD by their attending clinicians. The diagnosis was confirmed by the Posttraumatic Diagnostic Scale (PDS; Foa, 1995), a well-established self-report questionnaire to assess PTSD diagnosis. The Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was also administered to identify any other Axis-I disorders as well as PTSD. The MINI evaluation was supported by National Center of Neurology and Psychiatry biobank (Ethics Committee approval number: A2012-091).

In addition, 119 non-trauma-exposed healthy volunteers (20–64 years) were enrolled. They were recruited from the community through advertisements in free local magazines, our website, and university campuses. The PDS and MINI were also administered to healthy volunteers in order to ascertain the absence of traumatic experiences or any Axis-I disorders; if present, they were excluded from this study. The data of healthy controls were used only for comparing demographic, psychological, and biological characteristics with the patients, but not for examining their relationships with suicidality, since the control individuals exhibited virtually no suicidality.

All participants, both patients and healthy volunteers, were Japanese women who resided in metropolitan areas in Japan, including Tokyo and Nagoya. Additionally, both patients and controls were excluded if they had severe physical illness or intellectual disability, or were non-native Japanese speakers. There were no participants who presented clinically apparent signs/symptoms of acute infection.

This study was approved by the ethics committees of the 3 institutes involved, including National Center of Neurology and Psychiatry (Ethics Committee approval number: A2014-060, A2014-113, A2018-140, A2018-126), Tokyo Women's Medical University (3339, 281), and Nagoya City University (1123, 191, 60-19-0142, 70-00-0191), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after they had received a detailed explanation of the study.

2.2. Questionnaires

2.2.1. PDS (Foa, 1995)

The PDS was created in accordance with the diagnostic criteria of

PTSD in DSM-IV. It comprises 4 parts that evaluate traumatic experiences (Parts 1 & 2), PTSD symptom severity during the past month (Part 3), and associated functional impairments (Part 4). The assessment of PTSD symptom severity in Part 3 consists of 17 items, each scored on a 4-point Likert scale of symptom frequency, with higher scores indicating greater symptoms. In the present study, we used the validated Japanese version of PDS (Itoh et al., 2017; Nagae et al., 2007). We have previously confirmed a sufficiently high concordance rate (i.e., 95.1%, $\kappa = 0.90$; Itoh et al., 2017) between the PDS and the Clinician-Administered PTSD Scale (Blake et al., 1995), a structured interview for the diagnosis of PTSD.

2.2.2. *Childhood Trauma Questionnaire* ***(CTQ)*** *(Bernstein et al., 2003)*

Childhood maltreatment history was assessed with our Japanese version (Nakajima et al., 2022) of the CTQ, a widely used questionnaire for assessing history of childhood maltreatment. It is a 28-item self-report measure (25 clinical items and 3 validity items) and comprises 5 subscales that assess different types of maltreatment, including emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. All items are rated on a 5-point Likert scale (i.e., 1–5) and can be summed to generate the 5 subscale scores as well as the total score, with higher scores indicating more severe childhood maltreatment. While cut-off scores for the CTQ subscales are defined in the manual (Bernstein and Fink, 1998), we used the raw (continuous) data since our primary hypotheses were tested by correlation and regression analyses.

2.3. *Assessment of suicidal ideation and risk*

2.3.1. *The Beck Depression Inventory-II (BDI-II), item-9 (Beck et al., 1996)*

We used the validated Japanese version (Kojima et al., 2002) of BDI-II, a 21-item self-report measure of depressive symptoms during the past 2 weeks, in order to assess suicidal ideation in patients and controls. The item-9 of BDI-II is often used to briefly evaluate suicidal ideation (Green et al., 2015; Shiner et al., 2016). This item is rated on a 4-point Likert scale, i.e., (0) "I don't have any thought of killing myself", (1) "I have thought of killing myself, but would not carry them out", (2) "I would like to kill myself", and (3) "I would kill myself if I had the chance", with higher scores indicating greater suicidal ideation.

2.3.2. *The MINI suicidality module (Sheehan et al., 1998)*

We used the validated Japanese version (Otsubo et al., 2005) of MINI, and its suicidality module was administered to patients in order to further examine their suicide risk. The data of suicidality assessed with MINI were available for 79 patients of the total 93 patients. For the healthy controls, we did not perform further detailed assessment of suicidality using MINI since the item-9 of BDI-II revealed virtually no suicidality in these individuals.

This module has 6 items pertaining to suicidality that are answered by "yes" or "no". The questions 1–5 ask whether suicidal thoughts and events (e.g., suicidal ideation or suicide planning) occurred during the last month, and the question 6 is for lifetime suicide attempt. These 6 items are given different weighted scores based on their estimated contribution to suicide risk. The aggregated score ranges between 0 and 33 points, with higher scores indicating greater risk of suicide (Sheehan et al., 2003). In the analysis we used this "MINI suicide risk weighted score", in addition to "MINI suicide risk raw score" as indexed by the simple total number of positive items ranging between 0 and 6.

2.4. *Measurement of inflammatory markers*

Of the total 93 patients, 83 also participated in the blood sampling. Reasons for the attrition of 10 patients were: informed consent to blood testing was not given, and blood sampling was technically difficult. Additionally, 109 controls participated in the blood sampling.

Details of the measurement of blood inflammatory markers were described in our previous papers (Imai et al., 2018; Otsuka et al., 2021). Briefly, blood samples were collected from each participant for the measurement of high-sensitivity CRP (hsCRP), IL-6, and hsTNF-α levels. Blood sampling was conducted around noon before lunch (between 11:30 a.m. and 12:30 p.m.) on the same day as the psychological assessments. Serum concentrations of these markers were measured at a clinical laboratory (SRL Inc. Tokyo, Japan). hsCRP levels were measured by nephelometry, IL-6 levels were measured by chemiluminescent enzyme immunoassay, and hsTNF-α levels were measured by enzyme-linked immunosorbent assay. Intra- and inter-assay coefficients of variation for hsCRP, IL-6, and hsTNF-α were <2.1%, <2.6%, and <6.0%, respectively. There were no participants who showed hsCRP levels >10,000 ng/ml (i.e., 10 mg/l), an objective feature of acute infection (Chu et al., 2019).

2.5. *Genotyping*

Of the total sample, genotyping was performed for 82 patients and 100 controls. Genomic DNA was extracted using the Maxwell 16 Blood DNA Purification Kit (Promega, Madison, WI, USA) from buffy coat smears as part of centrifuged venous blood. *CRP* rs2794520 (assay ID: C___177486_10) and *IL6* rs1800796 (C__11326893_10) were genotyped using the TaqMan SNP Genotyping Assays. The polymerase chain reaction was carried out using GeneAce Probe qPCR Mixα (Nippon Gene, Toyama City, JPN) under following conditions: 1 cycle at 95 °C for 10 min followed by 45 cycles of 95 °C for 15 s and 60 °C for 1 min. The allele-specific fluorescence was measured with ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems, Foster City, CA). All samples had a genotyping call rate of 97% or greater. Numbers of patients and controls with the *CRP* rs2794520 CC, CT, and TT genotypes and those with the *IL6* rs1800796 CC, CG, and GG genotypes are reported in Supplementary Table S1. For both SNPs, genotype frequencies did not deviate from Hardy-Weinberg equilibrium either in patients or in controls (all $p > 0.05$).

2.6. *Statistical analysis*

Averages are reported as "means ± standard deviation (SD)", or "median (interquartile range: IQR)" where appropriate. Group comparisons and correlations were examined by nonparametric tests, given that suicide scores, CTQ scores, and inflammatory markers all deviated from the normal distribution. Specifically, comparisons between 2 groups were made by the Mann-Whitney *U* test. Comparisons of suicide scores between the 3 genotype groups of *CRP/IL6* were made using the Jonckheere-Terpstra nonparametric trend test, based on the assumption of the additive model of allele effect (or allele dosage effect). The Jonckheere-Terpstra trend test was used because a nonnormally distributed trait (i.e., suicidality) is compared between 3 (i.e., more than 2) groups with a putative trend (i.e., increasing number of minor allele). The Jonckheere-Terpstra trend test has also been used in previous studies including ours that compare nonnormally distributed traits between 3 genotype groups (e.g., Kerb et al., 2001; Schirmer et al., 2008; Hori et al., 2020; Hori et al., 2021). Correlations were calculated using Spearman's rank order correlation (rho). Further, a stepwise multiple regression analysis, with inclusion and exclusion p value thresholds of 0.05 and 0.1, respectively, was used to predict suicidal ideation/risk in patients from inflammatory gene SNPs and inflammatory protein levels, as well as potential confounders; specifically, we first controlled for age, body mass index (BMI), and smoking (Model 1) and then age, BMI, smoking, PTSD severity (as indexed by the PDS total score), comorbid major depressive disorder (MDD), and comorbid anxiety disorders (Model 2). In these regression models, BDI-II item-9 score, MINI suicide risk weighted score, and protein levels of CRP and IL-6 were included after log-transformation (the BDI-II item-9 score and MINI suicide risk weighted score were log-transformed after adding "1" in order to avoid

taking log of 0).

Statistical significance was set at 2-tailed $p < 0.05$. Statistical analyses were performed using the SPSS version 28.0 (IBM Corp., Tokyo, Japan) unless otherwise specified.

3. Results

3.1. Sample characteristics

Demographic characteristics, clinical/psychological variables, and inflammatory marker levels in patients with PTSD are summarized in Table 1. Most patients developed PTSD after experiencing interpersonal violence such as physical and/or sexual violence during adulthood, and had been ill for more than 6 months at the time of study participation. A majority of them had psychiatric comorbidities, and were receiving psychotropic medications. They were on average moderately to severely ill, as indexed by the mean PDS total score.

Comparisons of the main demographic, biological, and genetic data between patients and controls are provided in Supplementary Table S1. Demographic characteristics including age, educational level, smoking status, and BMI did not significantly differ between patients and controls (Supplementary Table S1).

Table 1
Demographic, clinical, psychological variables and inflammatory markers in PTSD patients.

	PTSD patients (n = 93)
Age, years: mean ± SD	37.1 ± 10.6
Education level[a]: median (IQR)	3.0 (3.0–4.0)
Smoking: yes, n (%)	12 (12.9)
Body mass index[b]: mean ± SD	21.6 ± 3.3
Outpatients/inpatients: n/n	92/1
Duration of illness[b], less than 6 months/6 months or more: n/n	5/87
Type of index trauma[b]	
Interpersonal violence: yes, n (%)	75 (81.5)
Accident: yes, n (%)	4 (4.3)
Other: yes, n (%)	13 (14.1)
Comorbid psychiatric disorder, any: yes, n (%)	78 (87.6)
Major depressive disorder[b]: yes, n (%)	55 (59.8)
Bipolar disorder[c]: yes, n (%)	6 (6.6)
Anxiety disorders[b]: yes, n (%)	41 (44.6)
Alcohol/substance abuse or dependence[c]: yes, n (%)	10 (11.0)
Hyperlipidemia: yes, n (%)	5 (5.4)
Psychotropic medication, any: yes, n (%)	77 (82.8)
Antidepressant: yes, n (%)	53 (57.0)
Anxiolytic: yes, n (%)	46 (49.5)
Hypnotic: yes, n (%)	41 (44.1)
Antipsychotic: yes, n (%)	29 (31.2)
Mood stabilizer: yes, n (%)	11 (11.8)
Regular intake of non-steroidal anti-inflammatory drugs: yes, n (%)	9 (9.7)
Suicidal ideation (BDI-II item-9)[b]: median (IQR)	1.0 (1.0–2.0)
MINI suicide risk raw score[d]: median (IQR)	2.0 (2.0–4.0)
MINI suicide risk weighted score[d]: median (IQR)	7.0 (4.0–13.0)
CTQ, total score[c]: mean ± SD	60.3 ± 21.7
Emotional abuse[c]: mean ± SD	14.9 ± 7.0
Physical abuse[c]: mean ± SD	9.0 ± 5.0
Sexual abuse[c]: mean ± SD	8.3 ± 5.5
Emotional neglect[c]: mean ± SD	17.8 ± 5.7
Physical neglect[c]: mean ± SD	10.3 ± 4.1
PDS, total score[b]: mean ± SD	30.9 ± 10.2
Intrusion: mean ± SD	8.0 ± 3.6
Avoidance: mean ± SD	13.5 ± 4.8
Hyperarousal: mean ± SD	9.6 ± 3.4
hsCRP (ng/ml)[e]: median (IQR)	185.0 (101.0–442.0)
IL-6 (pg/ml)[e]: median (IQR)	0.90 (0.70–1.20)
hsTNF-α (pg/ml)[f]: median (IQR)	0.66 (0.45–0.90)

Abbreviations: PTSD posttraumatic stress disorder, *BDI* Beck Depression Inventory, *MINI* Mini International Neuropsychiatric Interview, *CTQ* Childhood Trauma Questionnaire, *PDS* Posttraumatic Diagnostic Scale, *hsCRP* high-sensitivity C-reactive protein, *IL-6* interleukin-6, *hsTNF-α* high-sensitivity tumor necrosis factor-α.

Notes.

[a] Coded as follows: 1, junior high school graduate; 2, high school graduate; 3, some college graduate/partial university; 4, university graduate; 5, graduate school graduate.

[b] n = 92.

[c] n = 91.

[d] n = 79 (participants with 1 or more missing value for the 6 questions of the MINI suicidality module were excluded).

[e] n = 83.

[f] n = 82.

3.2. Suicidal ideation and risk

Suicidal ideation scores assessed by the BDI-II item-9 for PTSD patients and healthy controls are shown in Fig. 1A. Of the 92 patients, 77 had at least some extent of suicidal ideation assessed by the BDI-II item-9 (defined as a score of 1 or greater). Of the 79 patients whose MINI suicidality data were available, 70 had at least low suicide risk assessed by the MINI suicidality module (defined as a score of 1 or greater). Compared with controls, patients showed significantly higher suicidal ideation ($U = 9642.5$, $p < 0.001$; Supplementary Table S1). None of the controls scored 2 or higher whereas about 35% of patients did. Similarly, a substantial proportion of patients exhibited high suicide risk as assessed with the MINI (Fig. 1B and C).

3.3. Association of suicidal ideation/risk with proinflammatory markers

Correlations between the 3 suicide indices and 3 inflammatory marker levels in patients are shown in Fig. 2A. The BDI-II item-9 score was significantly positively correlated with hsCRP levels (rho = 0.33, $p = 0.002$); for the distribution of hsCRP levels, see Fig. 2B. The MINI suicide risk weighted score was significantly positively correlated with hsCRP levels (rho = 0.29, $p = 0.016$; see also Fig. 2C). The distribution of IL-6 levels is shown in Fig. 2D. The BDI-II item-9 score was significantly positively correlated with IL-6 levels (rho = 0.27, $p = 0.015$; Fig. 2E). No significant correlation was observed between MINI suicide risk raw score and 3 inflammatory markers (all $p > 0.05$). In addition, 43 patients (61.4%) had a history of lifetime suicide attempt assessed by the question-6 of the MINI suicidality module; however, no significant difference was observed in the 3 inflammatory markers between patients with the history of lifetime suicide attempt and those without (all $p > 0.1$).

For potentially confounding variables, age was not significantly correlated with any of the 3 inflammatory markers, namely hsCRP (rho = −0.05, $p = 0.69$), IL-6 (rho = 0.07, $p = 0.52$), or hsTNF-α (rho = 0.09, $p = 0.44$) levels, in patients. BMI was significantly positively correlated with hsCRP (rho = 0.47, $p < 0.001$), IL-6 (rho = 0.46, $p < 0.001$), and hsTNF-α (rho = 0.32, $p = 0.004$) levels in patients. The presence vs. absence of smoking habit was not significantly associated with hsCRP ($U = 380.0$, $p = 0.83$), IL-6 ($U = 346.5$, $p = 0.80$), or hsTNF-α ($U = 490.0$, $p = 0.07$) levels in patients. The presence vs. absence of comorbid MDD was not significantly associated with hsCRP ($U = 953.0$, $p = 0.15$), IL-6 ($U = 774.5$, $p = 0.81$), or hsTNF-α ($U = 723.0$, $p = 0.56$) levels. The use vs. non-use of antidepressants was not significantly associated with hsCRP ($U = 856.5$, $p = 0.54$), IL-6 ($U = 822.5$, $p = 0.77$), or hsTNF-α ($U = 791.5$, $p = 0.82$) levels.

3.4. Association of childhood maltreatment with suicidal ideation/risk and inflammatory markers

Fig. 3A shows correlations between childhood maltreatment history assessed by the CTQ scores and the 3 suicide indices in PTSD patients. The CTQ total score was significantly positively correlated with 3 suicide indices: BDI-II item-9 (rho = 0.30, $p = 0.005$; Fig. 3B), MINI suicide risk raw scores (rho = 0.43, $p < 0.001$; Fig. 3C), and MINI suicide risk

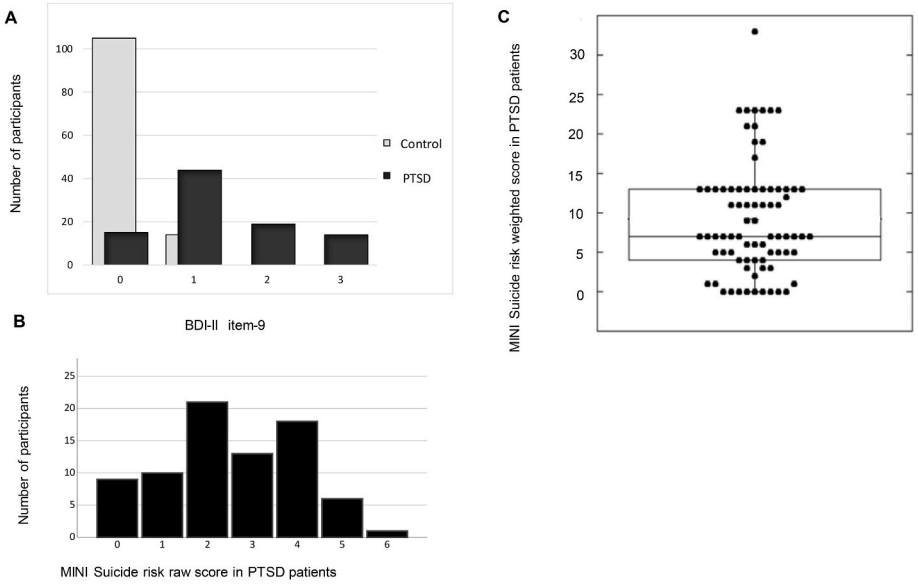

Fig. 1. Suicidal ideation and risk assessed by the BDI-II and MINI. **A,** Histogram of suicidal ideation assessed by the BDI-II item-9 in PTSD patients (n = 93) and healthy controls (n = 119). **B,** Histogram of MINI suicide risk raw scores in patients (n = 79). **C,** Combined dot- and box-plot showing MINI suicide risk weighted score in patients (n = 79).

A

Correlations between proinflammatory marker levels and suicide indices in PTSD patients (n = 83)

	hsCRP	IL-6	hsTNF-α
BDI-II item-9: suicidal ideation [a]	0.33**	0.27*	0.16
MINI suicide risk raw score [b]	0.22	0.16	0.19
MINI suicide risk weighted score [b]	0.29*	0.17	0.17

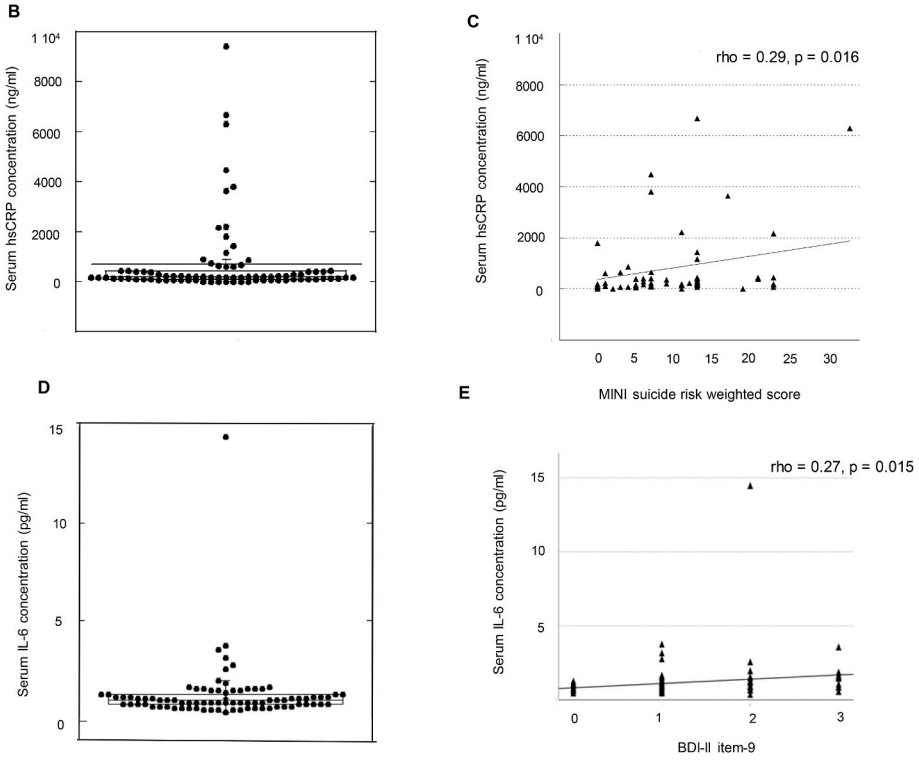

Fig. 2. Relationship between proinflammatory marker levels and suicidal ideation/risk in PTSD patients. **A,** Correlations between proinflammatory marker levels and suicidal ideation/risk calculated using Spearman's rho. [a] n = 83, [b] n = 70. *p < 0.05, **p < 0.01. **B,** Combined dot- and box-plot showing serum hsCRP concentration (n = 83). **C,** Scatterplot showing the relationship between MINI suicide risk weighted score and serum hsCRP concentration (rho = 0.29, p = 0.016) (n = 70). **D,** Combined dot- and box-plot showing serum IL-6 concentration (n = 83). E, Scatterplot showing the relationship between BDI-II item 9 score and serum IL-6 concentration (rho = 0.27, p = 0.015) (n = 83).

weighted scores (rho = 0.44, p < 0.001; Fig. 3D). All the CTQ subscale scores were significantly positively correlated with the 3 suicide indices (all p < 0.05), except for the absence of significant correlation between physical abuse and BDI-II item-9. However, no significant correlations were seen between the CTQ scores including total and 5 subscale scores and the 3 inflammatory marker levels (all p > 0.05; data not shown).

A

Correlations between childhood maltreatment and suicide indices in PTSD patients

	CTQ total score	Emotional abuse	Physical abuse	Sexual abuse	Emotional neglect	Physical neglect
BDI-II item-9: suicidal ideation [a]	0.30**	0.21*	0.17	0.31**	0.21*	0.33**
MINI suicide risk raw score [b]	0.43**	0.38**	0.35**	0.35**	0.38**	0.32**
MINI suicide risk weighted score [b]	0.44**	0.38**	0.39**	0.38**	0.33**	0.32**

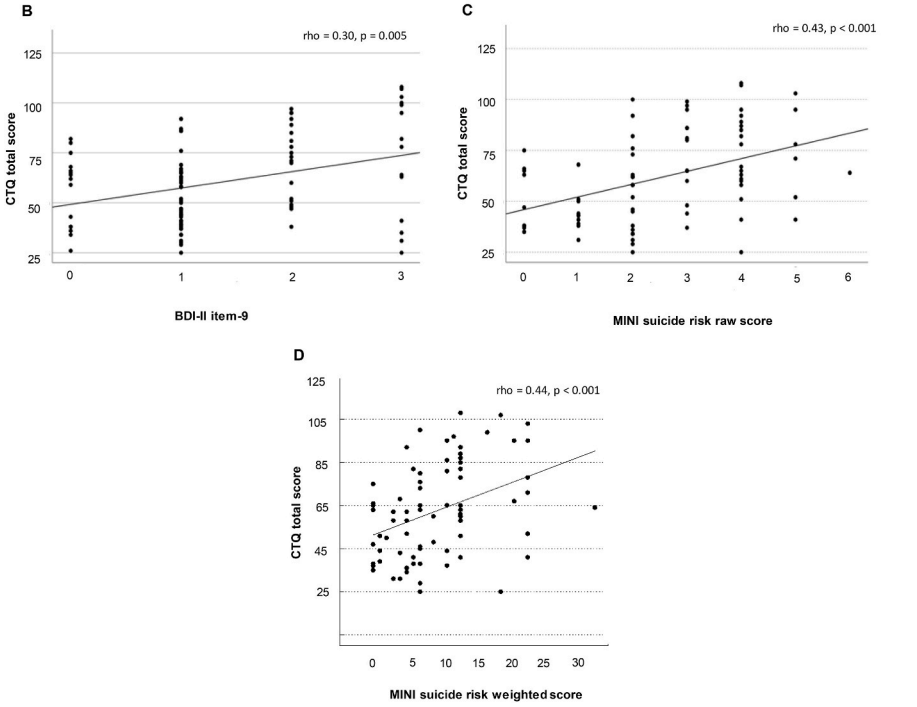

Fig. 3. Relationship of childhood maltreatment with suicidal ideation/risk in PTSD patients. **A,** Correlations between CTQ total/subscale scores and suicidal ideation/risk calculated using Spearman's rho. [a] n = 89, [b] n = 76. *p < 0.05, **p < 0.01. **B,** Scatterplot showing the relationship between BDI-II item 9 score and CTQ total score (n = 89). **C,** Scatterplot showing the relationship between MINI suicide risk raw score and CTQ total score (n = 76). **D,** Scatterplot showing the relationship between MINI suicide risk weighted score and CTQ total score (n = 76).

3.5. Relationship of CRP and IL6 genotypes with suicidal ideation/risk

Comparisons of the suicidal ideation/risk scores as a function of the *CRP* rs2794520 and *IL6* rs1800796 genotypes are shown in Fig. 4.

For the comparisons of suicidal scores between the *CRP* rs2794520 genotype groups, the Jonckheere-Terpstra trend test revealed significantly higher BDI-II suicidal ideation scores (JT = 553.0, p < 0.001), marginally significantly higher MINI suicide risk raw scores (JT = 486.0, p = 0.061), and significantly higher MINI suicide risk weighted scores (JT = 415.0, p = 0.007), with increasing number of the C-allele (Fig. 4A, B, and 4C, respectively). In addition, serum CRP levels were significantly different between the 3 *CRP* genotype groups, with the C-allele being associated with higher CRP levels (JT = 479.5, p < 0.001; data not shown).

For the *IL6* rs1800796 genotype groups, the trend test revealed no significant association for BDI-II suicidal ideation (JT = 859.0, p = 0.447), significantly higher MINI suicide risk raw scores (JT = 439.0, p = 0.007), and significantly higher MINI suicide risk weighted scores (JT = 481.0, p = 0.029), with increasing number of the C-allele (Fig. 4D, E, and 4F, respectively). Serum IL-6 levels were different between the 3 *IL6* genotype groups at a trend level, with the C-allele being associated with higher IL-6 levels (JT = 673.5, p = 0.099; data not shown).

Considering the small number of patients with *CRP* rs2794520 CC genotype and those with *IL6* rs1800796 GG genotype, additional analyses were performed to confirm the results obtained in the comparison between 3 groups by the Jonckheere-Terpstra trend test. Specifically, we combined the minor allele carriers (i.e., minor allele homozygotes and heterozygotes) into a single group for each SNP, and compared suicidality between major allele homozygotes and minor allele carriers by the Mann-Whitney U test (i.e., for rs2794520, TT [n = 39] vs. CC/CT [n = 43]; and for rs1800796, CC [n = 45] vs. CG/GG [n = 37]). For the rs2794520 genotype groups, this test revealed higher BDI-II suicidal ideation (U = 476.0, p < 0.001), marginally significantly higher MINI suicide risk raw scores (U = 446.5, p = 0.10), and significantly higher MINI suicide risk weighted scores (U = 376.5, p = 0.014) in the CC/CT group than in the TT group. For the rs1800796 genotype groups, this test revealed no significant association for BDI-II suicidal ideation (U = 748.0, p = 0.40), significantly higher MINI suicide risk raw scores (U = 368.0, p = 0.009), and significantly higher MINI suicide risk weighted scores (U = 410.5, p = 0.041), in the CC group than in the CG/GG group.

To examine the power of this genetic effect, a post-hoc power analysis was performed using G*Power 3 (Faul et al., 2007). For simplicity, this analysis was applied to the comparison of BDI-II item-9 scores between rs2794520 CC/CT (n = 43) and TT (n = 39) genotypes using the *t*-test (p < 0.001, d = 0.86). It revealed that the present sample (n = 82) had a power of 0.97 to detect the observed effect size for the comparison (i.e., d = 0.86) at a 2-tailed α = 0.05.

3.6. Prediction of suicidality from inflammatory gene SNPs and their protein levels

Lastly, stepwise multiple regression analyses were used to predict suicidal ideation (BDI-II item-9) and risk (MINI suicide risk weighted score) from *CRP* rs2794520 and *IL6* rs1800796, hsCRP and IL-6 protein levels, age, BMI, smoking (Model 1), PTSD severity, comorbid MDD, and comorbid anxiety disorders (Model 2). The results are summarized in Table 2. These analyses explained 14–25% of variance for both suicidal ideation and risk in both models. In Model 1, rs2794520 was the sole significant predictor for suicidal ideation (β = −0.40, p < 0.001), with its C-allele being associated with greater suicidal ideation; while rs1800796 (β = −0.31, p = 0.009) and rs2794520 (β = −0.29, p = 0.017) were significant predictors for suicide risk, with C-allele of

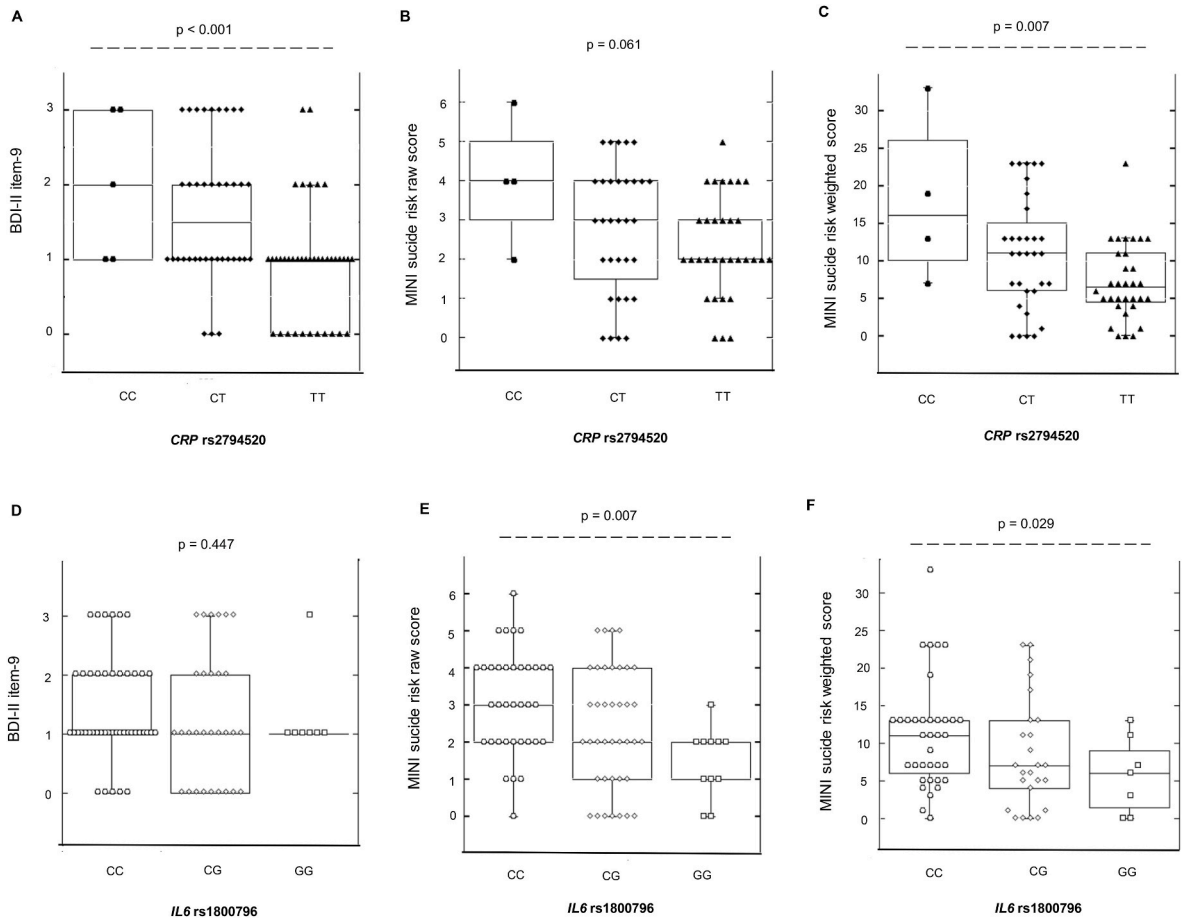

Fig. 4. Suicidal ideation and risk as a function of the *CRP* rs2794520 and *IL6* rs1800796 genotype groups in PTSD patients.
Combined dot- and box-plot showing suicidal ideation/risk between the 3 genotype groups by *CRP* rs2794520, i.e., CC (n = 5), CT (n = 38) and TT (n = 39) (top row: **A**, **B**, **C**) and *IL6* rs1800796, i.e., CC (n = 45), CG (n = 30) and GG (n = 7) (bottom row: **D**, **E**, **F**). **A,** BDI-II item-9. **B,** MINI suicide risk raw score. **C,** MINI suicide risk weighted score. **D,** BDI-II item-9. **E,** MINI suicide risk raw score. **F,** MINI suicide risk weighted score. Broken lines indicate significant trend toward greater suicidality with increasing number of the C-allele of *CRP* rs2794520 and C-allele of *IL6* rs1800796, as revealed by the Jonckheere-Terpstra trend test.

Table 2
Stepwise multiple regression analysis predicting suicidal ideation/risk in PTSD patients from *CRP* rs2794520 and *IL6* rs1800796, hsCRP and IL-6 protein levels, age, BMI, and smoking (Model 1), PTSD severity, comorbid MDD, and comorbid anxiety disorders (Model 2).

	R-squared	Adjusted R-squared	Analysis of variance for regression	B	Standardized β	t	p
Model 1							
Suicidal ideation	0.16	0.15	F = 14.3, p < 0.001				
(Constant)				(1.1)		(9.8)	**(< 0.001)**
CRP rs2794520				−0.28	−0.40	−3.8	**< 0.001**
Suicide risk	0.17	0.14	F = 6.1, p = 0.004				
(Constant)				(2.9)		(9.8)	**(< 0.001)**
IL6 rs1800796				−0.42	−0.31	−2.7	**0.009**
CRP rs2794520				−0.43	−0.29	−2.4	**0.017**
Model 2							
Suicidal ideation	0.29	0.25	F = 9.4, p < 0.001				
(Constant)				(0.95)		(6.0)	**(< 0.001)**
CRP rs2794520				−0.34	−0.51	−4.0	**< 0.001**
Comorbid MDD				0.41	0.36	2.8	**0.008**
Suicide risk	0.16	0.14	F = 8.0, p = 0.007				
(Constant)				(2.4)		(15.9)	**(< 0.001)**
IL6 rs1800796				−0.47	−0.40	−2.8	**0.007**

Notes: Suicidal ideation and risk were assessed with BDI-II item-9 and MINI suicide risk weighted score, respectively.BDI-II item-9 score, MINI suicide risk weighted score, and protein levels of hsCRP and IL-6 were included in this model after log-transformation. PTSD severity was assessed by the PDS total score.
Rs2794520 was coded as 0: "CC", 1: "CT", and 2: "TT"; rs1800796 was coded as 0: "CC", 1: "CG", and 2: "GG".
Bold p values represent significant results.

rs1800796 and C-allele of rs2794520 being associated with greater suicide risk. In Model 2, rs2794520 (β = −0.51, p < 0.001) and comorbid MDD (β = 0.36, p = 0.008) were significant predictors for suicidal ideation; while rs1800796 (β = −0.40, p = 0.007) was the sole significant predictor for suicide risk. In contrast, suicidal ideation/risk was not significantly predicted by protein levels of hsCRP or IL-6 in

either model.

4. Discussion

In the present study we first confirmed that patients with PTSD exhibited significantly increased suicidal ideation/risk and that childhood maltreatment history was significantly associated with higher suicidality in these patients. Our main findings can be summarized as follows. Serum hsCRP levels were significantly correlated with suicidal ideation and risk, and serum IL-6 levels were significantly correlated with suicidal ideation. Childhood maltreatment was not significantly correlated with the inflammatory markers. *CRP* rs2794520 was significantly associated with suicidal ideation and weighted risk, and *IL6* rs1800796 was significantly associated with raw/weighted risk. This association between the SNPs and suicidality was observed in a dose-dependent fashion regarding the number of risk allele. The multivariate regression analysis controlling for age, BMI, and smoking revealed that rs2794520 significantly predicted suicidal ideation/risk and rs1800796 significantly predicted suicide risk, while serum levels of hsCRP and IL-6 did not. Further, rs2794520 and rs1800796 significantly predicted suicidal ideation and risk (respectively) even after controlling for PTSD severity and comorbid MDD/anxiety disorders in addition to age, BMI, and smoking, suggesting that the effect of these SNPs on suicidality in PTSD is not a mere reflection of their effect on global PTSD severity or comorbid psychopathology.

Our finding of the association of suicidality with hsCRP and IL-6 levels in PTSD accords with previous findings including meta-analytic ones among patients with psychiatric disorders (Black and Miller, 2015; Brundin et al., 2017; Janelidze et al., 2011; Miola et al., 2021; Yan et al., 2021). The relationship between peripheral low-grade inflammation and suicidality might be explained by neuroinflammation, given that the peripheral proinflammatory molecules can affect inflammation in the brain via several mechanisms, e.g., through active transport across leaky regions in the blood-brain barrier (Dantzer et al., 2008). It should also be noted, however, that a recent study of Positron Emission Tomography brain imaging using a microglial marker suggested neuroimmune *suppression* in PTSD patients (Bhatt et al., 2020). Further studies will be needed to investigate whether and to what extent individuals with PTSD show inflammation in the brain as well as in the periphery.

The observed association of childhood maltreatment with suicidality is consistent with the literature (Felitti et al., 1998). On the other hand, contrary to our hypothesis, we did not find a significant relation between childhood maltreatment and inflammatory markers in PTSD. While previous meta-analyses have reported significant association of childhood maltreatment with elevated inflammation, this association is found to be weak (Baumeister et al., 2016; Coelho et al., 2014). These results suggest that there might be other pathways than inflammation that could explain the association between childhood maltreatment and increased suicide risk in PTSD. It would also be important to note that effects of adverse childhood experiences on health outcomes are shown to depend on developmental timing/age (Dunn et al., 2019; Riem and Karreman, 2019). However, such data of time or age of childhood maltreatment was unavailable in the present study since the CTQ does not identify particular time/age of the experiences. It may therefore be that our data of childhood maltreatment was not sufficiently sensitive for detecting any effects of such early adversity on later inflammatory activities.

In terms of genetic factors, the C-allele of *CRP* rs2794520 and C-allele of *IL6* rs1800796 were dose-dependently associated with higher suicidality in PTSD. Moreover, these genetic effects, but not the protein levels, emerged as significant predictors in the regression analysis. Notably and somewhat counterintuitively, the regression analysis revealed that the effect of these SNPs on suicide risk survived even after controlling for PTSD severity. These results are consistent with previous findings showing the association of SNPs in *CRP* (Suchankova et al., 2013) and *IL6* (Bokor et al., 2021; Eftekharian et al., 2018) with suicidality. These results, along with the result that control individuals including those with the risk alleles of rs2794520 and rs1800796 showed virtually no suicidality, suggest that the observed effect of these SNPs on suicidality may be mediated by PTSD illness. This possibility accords with the notion that suicide is a multifactorial phenomenon where complex interaction between biological and environmental factors is likely involved. More needs to be done to elucidate the mechanism(s) by which inflammatory genes confer risk for suicide, but the SNPs of *CRP* (Pankow et al., 2001) and *IL6* (Terry et al., 2000) are known to affect circulating levels of the respective proteins, which was also supported by our results. These findings together suggest that the SNPs of *CRP* and *IL6* can give rise to suicide risk by influencing their protein levels.

It may also be worth noting that the allele frequencies of rs2794520 and rs1876096 differ substantially across ethnicities. Concerning the *CRP* rs2794520, the frequency of C-allele was approximately 0.29 in our sample, which is consistent with a database for Japanese individuals reporting as approximately 0.30 (Cariaso and Lennon, 2012). In contrast, the frequency of this allele is reported to be around 0.65 among many other populations such as Europeans (Cariaso and Lennon, 2012). Still, the C-allele of rs2794520 has been consistently associated with increased inflammation and PTSD symptomatology across ethnicities (Chu et al., 2012; Li et al., 2016; Otsuka et al., 2021). As for the *IL6* rs1800796 polymorphism, the frequency of C-allele was approximately 0.73 in our sample, being consistent with the database for Japanese reporting as approximately 0.75 (Cariaso and Lennon, 2012); while the allele frequency of rs1800796 is quite different across ethnicities. Nonetheless, rs1800796, or rs1800795, has been repeatedly reported to be associated with increased inflammation (Ljungman et al., 2009) and elevated suicide risk (Eftekharian et al., 2018).

There were several limitations to the current study. Firstly, since we only included women, it is unknown whether the present findings might be specific to women or common to both sexes, given the evidence for sex differences in the prevalence (Kessler et al., 1995) and etiology (Yehuda et al., 2015) of PTSD. Secondly, considering that most of our patients had comorbid psychiatric disorders and were taking a variety of medications, potentially confounding effects of these factors cannot be ruled out. Perhaps relatedly, age was not significantly correlated with any of the 3 inflammatory marker levels in the patient group as described above, but in the control group age was significantly correlated with hsTNF-α ($rho = -0.22$, $p = 0.021$) but not with IL-6 ($rho = 0.07$, $p = 0.48$) or hsCRP ($rho = -0.01$, $p = 0.92$) levels. These results indicate that the absence of significant association between age and hsTNF-α levels in patients may be attributable to some PTSD (or patients)-specific factors such as medications. On the other hand, age was not associated with IL-6 or hsCRP levels in controls as well as in patients, which suggests that our finding on the association between IL-6/hsCRP and suicidality was not confounded by such factors. Thirdly, our cross-sectional assessment of suicidality precluded the precise prediction of a future actual event. Longitudinal studies are important, considering that perceived suicidal risk is considered to be different from an actual risk for suicide attempt/completion and that biomarkers and genetic predictors for the latter can be more useful than those for the former. Fourthly, a self-report scale, namely PDS, was used to evaluate the diagnosis and severity of PTSD. Although PDS is a well-established scale, it should also be noted that the diagnosis of PTSD can be more reliably made by clinician-rated measures than self-report measures. Fifthly, the PDS used in the current study was a DSM-IV-based scale but not an updated DSM-5-based one, which was because we were not aware of any Japanese version of DSM-5-based scale for the diagnosis of PTSD at the time of the study initiation. Sixthly, this study adopted a hypothesis-based candidate gene approach, but data-driven genome-wide studies are required to get a bigger picture of genetic effects on suicidality. Lastly, this study had a relatively small sample size, especially for the genetic analysis; still, we observed the significant association of the hypothesis-based, carefully selected SNPs with suicidality as

well as with inflammatory marker levels. Indeed, the post-hoc power calculation revealed a sufficient power to detect the observed genetic effect on suicidal ideation/risk. It may be that our relatively homogeneous sample in terms of sex, trauma type (i.e., mostly interpersonal violence), illness chronicity, and ethnicity led to the significant finding. Still, further studies with larger sample size are required to verify generalizability of the finding and make it suitable for practical/clinical use.

In summary, using a sample of civilian women with PTSD, we show that patients carrying the risk alleles of *CRP* rs2794520 and *IL6* rs1800796 that are associated with increased respective protein levels exhibit greater suicidality. This suggests that SNPs within inflammatory genes may be useful in detecting PTSD patients at high risk of suicide. Future studies that examine the association of suicidality with multiple risk/protective factors, as well as those that investigate the underlying mechanisms, are warranted.

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Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100650.

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