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Reply to letter to the editor: “Inflammatory biomarkers in PTSD: A look at the fingerprint”

Dear Editor:

We thank Dr. Sand and Dr. Rössler for their interest in our recent article (Kawanishi et al., 2023) and respond to their comments below.

In the first comment they argue that “neither the criteria used to diagnose PTSD nor the expertise of the respective physicians have been addressed”. This is, however, not the case, since this issue is clearly stated in the Methods section, as follows: “The diagnosis was confirmed by the Posttraumatic Diagnostic Scale (PDS; Foa, 1995), a well-established self-report questionnaire to assess PTSD diagnosis”; “The PDS was created in accordance with the diagnostic criteria of PTSD in DSM-IV”; and “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”. In addition, the use of the DSM-IV-based version of PDS is acknowledged as a study limitation, as follows: “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”.

Concerning the second comment about the analysis of inflammatory proteins and gene polymorphisms, they correctly point out that the genotyping data were not available for 16.0% (19/119) of the total control sample. It is important to note, however, that the main aim of this study was to examine the association between inflammation and suicidality in the *patient group*, and as such, the comparison of genotypes between patients and controls is reported only in Supplementary table, and not mentioned or discussed in the main text at all. Moreover, contrary to what they argue, the significant association between *CRP* rs2794520 and serum CRP levels ($JT = 479.5$, $p < 0.001$) observed in this study is described in the Results (3.5.) section.

The third comment also relates to the analysis of inflammatory gene polymorphisms, and we agree with their suggestion that trend tests are suited to examine the association between genotype data and phenotypes, given the assumption of additive model of allele effect. In the main analysis we compared suicidality/biomarkers between the 3 genotype groups for each polymorphism (i.e., *CRP* rs2794520 and *IL6* rs1800796) using the Jonckheere-Terpstra trend test, which accords with their comment. On the other hand, the association between diagnosis and genotype (i.e., the 2*3 contingency table) was examined by χ^2 test or Fisher’s exact test, but we agree with their comment that the Cochran-Armitage trend test is better suited here; however, this issue does not affect the main finding or discussion since this result is reported only in Supplementary table.

As for the last comment, we agree that there may be a variety of factors that can potentially confound the association between inflammation and suicidality, especially in a clinical sample. We therefore controlled for several important potential confounders, such as age, body mass index, smoking, PTSD severity, and comorbid psychiatric disorders, in the multiple regression analysis. Thus, while there might be other potential confounders, our analysis considered the key variables determined based on the relevant literature and theoretical background. As pointed out, future investigations with larger sample sizes that allow for more detailed analyses can further clarify the role of inflammatory genes and molecules in suicidality of individuals with PTSD, which will ultimately lead to the development of biomarkers useful in detecting those at high risk of suicide.

CRediT authorship contribution statement

Hiroaki Hori: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Hitomi Kawanishi:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Yoshiharu Kim:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

There is no conflict of interest for all authors.

Data availability

Data will be made available on request.

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