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RESPONSE TO LETTER

Letter to Editor Regarding: "Serum Pyroptosis-Related Cytokines as Biomarkers for Diagnostic Assessment and Risk Stratification of Ocular Graft-Versus-Host Disease: A Case-Control Study." [Response to Letter]

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Dear editor and Dr. Elsaddig,

We sincerely thank Dr. Elsaddig for his careful reading of our paper entitled "Serum pyroptosis-related cytokines as biomarkers for diagnostic assessment and risk stratification of ocular graft-versus-host disease" and for his thoughtful and constructive comments. We appreciate the opportunity to clarify the rationale of our study and to address the important methodological points he raised.

At present, the diagnosis of ocular graft-versus-host disease (oGVHD) relies largely on clinical signs and patient-reported symptoms, as defined by the NIH consensus criteria[1] and the recommendations of the International Chronic oGVHD Consensus Group.[2] Although these criteria are widely adopted in clinical practice, they lack objective and quantifiable biomarkers, which limits early diagnosis, risk stratification, and longitudinal assessment. The identification of clinically feasible biomarkers was therefore the primary motivation for our exploratory study.

Previous studies have demonstrated that oGVHD frequently coexists with systemic GVHD, and that improvement in systemic immune activity is often accompanied by amelioration of ocular manifestations.[3,4] Consistent with these reports, our clinical experience suggests that the onset and progression of oGVHD are often closely associated with systemic GVHD activity.[5] In particular, patients with concomitant cutaneous GVHD and severe eyelid margin inflammation appear to be at increased risk of rapid ocular disease progression.[6] In addition, our group has previously reported altered inflammatory cytokine profiles in the tears of patients with oGVHD.[7] Taken together, these observations suggest that ocular surface inflammation in oGVHD occurs in the context of broader systemic immune dysregulation. On this basis, we focused our exploratory analysis on inflammasome- and pyroptosis-related inflammatory pathways, which are increasingly implicated in GVHD pathogenesis and closely linked to systemic innate immune activation.

We fully agree with Dr. Elsaddig that elevated circulating levels of IL-1β and IL-18 should not be interpreted as direct evidence of active pyroptotic cell death. As he correctly notes, canonical inflammasome activation is a multistep process involving priming, inflammasome assembly, caspase-1 activation, cytokine maturation, and gasdermin D–mediated membrane pore formation. Moreover, IL-1β and IL-18 may also be generated or released through inflammasome-independent mechanisms under certain inflammatory conditions.

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Accordingly, in our study we did not intend to interpret increased serum IL-1β and IL-18 as proof of ongoing pyroptosis, but rather as markers reflecting inflammasome-associated inflammatory activity. We acknowledge that this conceptual distinction was not sufficiently emphasized in the original manuscript and have clarified this point accordingly. Further mechanistic investigations are planned to directly address pyroptotic signaling in future studies.

Regarding upstream inflammasome components, our exploratory proteomic screening was conducted using a commercially available sandwich-based antibody microarray targeting proteins involved in Toll-like receptor and NOD-like receptor signaling pathways. Caspase-1 was included in this panel; however, no significant difference was observed between patients with non-oGVHD and those with oGVHD. We agree that this finding likely reflects generalized systemic inflammation rather than ocular-specific pathology, which may explain its limited discriminatory value in our cohort.

In contrast, several downstream inflammasome-associated cytokines demonstrated differential expression and diagnostic relevance, forming the basis for our subsequent analyses. We believe that reporting both significant and non-significant findings is important for transparency and may inform future refinement of biomarker panels.

We acknowledge that direct executors of pyroptosis, such as cleaved gasdermin D, were not assessed in the present study, as these targets were not included in the antibody array used for exploratory screening. The selection of this platform was primarily guided by considerations of clinical feasibility and translational applicability, which are critical for biomarker development intended for routine clinical use. In future studies, we plan to employ customized panels and complementary approaches, including multiplex assays and flow cytometry–based methods, to directly assess key executors of pyroptosis and further delineate inflammasome activation pathways.

Several limitations of our study should be acknowledged. The discovery phase was conducted in a relatively small cohort, and validation in larger, independent populations is required. Clinical heterogeneity, including differences in underlying hematologic diseases, systemic GVHD activity, treatment regimens, infections, and immunosuppressive therapies, may have contributed to variability in circulating cytokine levels. In addition, the proposed diagnostic model has not yet undergone external validation, and cutoff values derived from the same dataset should be regarded as preliminary. The cross-sectional design also precludes conclusions regarding causality or temporal relationships.

We agree that disease stage, systemic inflammatory burden, and extra-ocular immune activity may influence circulating cytokine profiles. Ongoing and future studies will therefore focus on longitudinal cohorts and mechanistic investigations to better define the relationship between inflammasome-associated signaling, pyroptosis-related pathways, and ocular surface pathology. From a translational perspective, our goal is to identify biomarkers that balance biological relevance with clinical feasibility and potential utility in routine clinical practice.

We thank Dr. Elsaddig again for his valuable comments, which have helped improve the clarity and balance of our manuscript. We hope that the revisions and clarifications provided above adequately address his concerns.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Jing Lou: Writing – original draft; Writing – review & editing. Yue Xu, Xinyu Zhuang, Ye Zhao, Hui Pan, and Yingjie Chen: Conceptualization; Formal analysis. Xiaofeng Zhang and Peirong Lu: Writing – review & editing; Supervision. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this communication.

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