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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" [Letter]

Maab Elsaddig

University Hospitals Bristol and Weston NHS Trust, Bristol, UK

Correspondence: Maab Elsaddig, Email maab.elsaddig3@nhs.net

Dear editor

I read with great interest the article by Lou et al, entitled "Serum pyroptosis-related cytokines as biomarkers for diagnosis", published in the *Journal of Inflammation Research*.[1] The authors should be commended for addressing the increasingly important role of pyroptosis-associated inflammatory pathways and circulating cytokines as potential diagnostic biomarkers. As inflammation-driven cell death mechanisms continue to gain attention across systemic and ocular diseases, such investigations are timely and clinically relevant. Nevertheless, several methodological and interpretative considerations merit further discussion to contextualise the study's conclusions and guide future research.

First, while the authors highlight the diagnostic potential of serum pyroptosis-related cytokines, the cross-sectional design inherently limits causal inference. Pyroptosis-related mediators such as interleukin (IL)-1β and IL-18 are not specific to pyroptotic cell death and may be elevated in a wide range of inflammatory, infectious, and metabolic conditions.[2] Therefore, without longitudinal sampling or mechanistic correlation with intracellular inflammasome activation, it remains difficult to determine whether the observed cytokine elevations reflect active pyroptosis, secondary inflammatory amplification, or nonspecific systemic immune activation.

Second, the specificity of circulating cytokines as biomarkers merits cautious interpretation. IL-1β and IL-18 are produced by multiple immune and non-immune cell types and can be influenced by comorbidities such as obesity, cardiovascular disease, autoimmune disorders, and subclinical infections.[3] Although the authors report exclusion criteria, additional adjustment for low-grade systemic inflammation markers (eg, C-reactive protein) or stratified analyses based on comorbidity burden would strengthen confidence in the proposed diagnostic utility.

Third, the absence of direct molecular markers of pyroptosis represents an important limitation. Pyroptosis is mechanistically defined by inflammasome assembly, caspase-1 activation, and gasdermin-D cleavage.[4] Measurement of circulating cytokines alone does not confirm activation of this pathway. Incorporation of intracellular biomarkers, such as cleaved gasdermin-D or caspase-1 activity in peripheral blood mononuclear cells, could provide stronger mechanistic linkage and improve biological plausibility.[4]

Fourth, while receiver operating characteristic analyses suggest diagnostic performance, external validation in independent cohorts is essential before clinical translation. Biomarker performance may vary significantly across populations due to genetic, environmental, and demographic factors.[5] Multicentre studies and validation in disease-matched inflammatory controls would help clarify whether these cytokines offer incremental value beyond established inflammatory markers.

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Finally, from a translational perspective, it would be valuable to discuss how these biomarkers might integrate into current diagnostic workflows. In ophthalmology and other subspecialties where inflammatory biomarkers are increasingly explored, clinical adoption depends not only on statistical significance but also on assay reproducibility, cost-effectiveness, and added diagnostic yield over existing standards.[5]

In conclusion, the study by Lou et al[1] makes a valuable contribution to the understanding of pyroptosis-associated inflammation and its potential diagnostic relevance in ocular graft-versus-host disease. While the proposed serum cytokine panel shows promise, addressing key limitations related to biomarker specificity, mechanistic validation, and external generalisability will be essential prior to clinical implementation. Future longitudinal and multicentre studies incorporating direct markers of inflammasome activation may help determine the true translational value of these findings.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

Dr Maab Elsaddig: Conceptualization, Investigation, Formal analysis, Writing – original draft, Writing – review & editing.

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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