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CORRESPONDENCE ON

"Serum caspase-1 is correlated with vasculitis activity at diagnosis and associated with all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis"

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Dear Editor,

We read with interest the article by Jang Woo Ha et al. entitled "Serum caspase-1 is correlated with vasculitis activity at diagnosis and associated with all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis" published online in *ARP Rheumatology*[1]. The authors are to be commended for exploring the potential clinical relevance of inflammasome-related pathways in ANCA-associated vasculitis (AAV), an area where biomarker data remain limited. We would like, however, to highlight several methodological and biological considerations that may help contextualize the findings.

First, the biological interpretation of circulating caspase-1 warrants further clarification. Caspase-1 is predominantly an intracellular cysteine protease, and its detection in serum does not necessarily equate to inflammasome activation or pyroptosis. Importantly, commercially available ELISA assays may detect pro-caspase-1, active caspase-1, or extracellular degradation fragments, depending on antibody specificity[2,3]. Without clarification of the molecular form being measured, the assumption that serum caspase-1 directly reflects inflammasome-mediated pyroptosis remains speculative. This distinction is particularly relevant given that extracellular caspase-1 may arise from non-specific cell injury or apoptosis rather than inflammasome-driven processes[4].

Second, although the authors propose serum caspase-1 as a surrogate marker of inflammasome activation, key downstream products of inflammasome signaling interleukin-1β (IL-1β) and interleukin-18 (IL-18) were not assessed. Prior studies in AAV have shown heterogeneous and sometimes discordant associations between these cytokines and disease activity[5–7]. In the absence of concurrent measurement of IL-1β or IL-18, it remains uncertain whether elevated serum caspase-1 represents inflammasome activation per se or a broader, non-specific inflammatory burden.

Third, the correlations between serum caspase-1 and clinical or laboratory parameters were modest. The association with BVAS was weak (r = 0.241), and all reported correlation coefficients were below 0.4. While statistically significant, such effect sizes suggest limited explanatory power and uncertain clinical relevance. Moreover, multiple correlation analyses were performed without adjustment for multiple testing, increasing the risk of type I error. This is particularly relevant for the BVAS item and sub-item analyses, which appear to be post-hoc and exploratory in nature rather than hypothesis-driven.

Fourth, the specificity of serum caspase-1 as a biomarker for AAV-related inflammation remains unclear. Caspase-1 activity has been implicated in a wide range of inflammatory and metabolic conditions, including infections, cardiovascular disease, and age-related inflammation [8,9]. The absence of a healthy or disease control group limits the ability to determine whether elevated serum caspase-1 is specific to AAV activity or simply reflects systemic inflammation. Consequently, the proposed utility of serum caspase-1 as an AAV-specific biomarker should be interpreted cautiously.

Finally, the clinical applicability of serum caspase-1 measurement remains to be defined. No threshold value or risk stratification framework was proposed, and it is unclear how a single baseline measurement could be integrated into routine clinical decision-making. Before serum caspase-1 can be considered a useful biomarker in clinical practice, prospective studies with longitudinal sampling and clearly defined clinical endpoints will be required.

In conclusion, the study by Jang Woo Ha *et al.* provides interesting preliminary data suggesting an association between serum caspase-1 and disease activity in AAV. However, uncertainties regarding the biological meaning of circulating caspase-1, the modest strength of observed associations, and the lack of specificity

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analyses suggest that the findings should be interpreted as hypothesis-generating. We hope that these comments will contribute to further discussion and refinement of inflammasome-related biomarker research in systemic vasculitis.

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