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Letter to the Editor

Comment on "Relationship between macrophage phenotype and kidney survival in patients with lupus nephritis"

Comentario sobre "Relación entre el fenotipo de macrófagos y la supervivencia renal en pacientes con nefritis lúpica"

Dear Editor,

I eagerly read the most recent paper about the role of macrophages in lupus nephritis (LN). I appreciate that the authors addressed this important yet understudied topic and provided new insights into the distribution of $CD68^+$ and $CD163^+$ macrophages. However, I would want to bring up a few points for discussion and clarification.

First, the study included only 21 participants, with 90% of them being female. The validity of statistical analysis is limited by the small and irregular sample size, which also makes it difficult to generalize the results to the larger LN population. It may be more appropriate to confirm these associations using larger, multi-center investigations.

Second, the primary methods used to identify macrophage subtypes were CD68 and CD163 immunostaining. The complicated activation spectrum of macrophages in LN may be oversimplified by this binary classification into M1 and M2, despite its usefulness. Cutting-edge methodologies like transcriptome profiling, flow cytometry, or multiplex immunostaining could provide a more precise understanding of their roles.

Third, the authors found no significant correlation between the adjusted NIH activity/chronicity indices and macrophage numbers. This contrasts with earlier research that found a strong correlation between negative renal outcomes and a decreased response to immunosuppressive medication and a high density of interstitial $CD68^+$ macrophages.[1] The disparity could be the result of different methodology or a small sample size.

Fourth, endocapillary hypercellularity was linked to ≥7 $CD68^+$ cells per glomerulus ($p = 0.031$); however, it is yet unknown if this marker has any predictive value beyond standard clinical indicators like proteinuria, complement levels, and anti-dsDNA titers. Furthermore, although this correlation is in line with earlier findings that connected M1-like macrophages to glomerular damage and active inflammation,[2] it would be crucial to determine whether these markers also predict treatment response. Recent studies suggest that high $CD68^+$ density is associated with poor response to immunosuppressive therapy.[1]

Fifth, since DN is caused by metabolic processes rather than autoimmune ones, using it as a control group is interesting but might not be the best option. It would be more appropriate to include other immune-mediated nephropathies, such as IgA nephropathy and ANCA-associated glomerulonephritis, which would have provided a relevant context. Nevertheless, the fact that LN displayed more glomerular $CD68^+/CD163^+$ infiltration and DN displayed more interstitial $CD163^+$ cells does emphasize the importance of macrophage location in differentiating disease-specific damage patterns.[3] Moreover, non-invasive indicators like urine soluble CD163 can enhance predictive value and supplement histological evaluation.[3,4]

Finally, although the authors suggested a cutoff of 2.7 $CD163^+$ cells per high-power field for survival analysis, such levels are currently impractical for normal pathology reporting. Before being implemented in clinical settings, these cutoffs will need to be validated in larger, independent patient groups.

In conclusion, this work supports the growing evidence showing that macrophages play a role in the pathophysiology and outcome of LN. However, the small sample size, simplified macrophage classification, and limited correlation with clinical indices restrict its generalizability. Future studies that combine molecular profiling, urine biomarkers, and histological macrophage markers ($CD68^+$, $CD163^+$) are encouraged as this could eventually enable more precise risk categorization and personalized treatment in LN.[3–5]

Ethics approval

Not applicable.

Informed consent

Not applicable.

Consent for publication

Not applicable.

Declaration of AI use

During the preparation of this work the author used ChatGPT for language refinement, manuscript structuring and clarity enhancement. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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Conflict of interest

Not applicable.

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Data availability

There is no new data generated.

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