Response to Probing the Surrogate Validity of Proteinuria Thresholds in C3G/IC-MPGN: Unresolved Biases and Mechanistic Gaps

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Response to “Probing the Surrogate Validity of Proteinuria Thresholds in C3G/IC-MPGN: Unresolved Biases and Mechanistic Gaps"

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We thank Zhu et al[1]. for their thoughtful commentary on our recent report[2] and welcome the opportunity to respond.

First, they suggest that the observed association between UPCR and kidney failure (KF) could be confounded by treatment intensity rather than reflecting what they term "disease biology." We agree that causal inferences cannot be drawn from retrospective observational data, and we did not attempt to do so. As reported (Table 2), immunosuppression use was not significantly associated with KF in univariable analysis and was therefore, in line with standard statistical practice, not included in the multivariable model. We acknowledge that, in observational studies, the availability of follow-up measurements may correlate with both treatment decisions and outcomes, potentially influencing the observed relationships. However, if reductions in proteinuria were partly driven by treatment and are associated with improved outcomes, this supports – rather than weakens – the case for proteinuria as a surrogate endpoint. It implies that lowering proteinuria (by treatment) is plausibly linked to improved clinical outcomes, reinforcing its utility in prospective controlled trials.

Second, regarding the reported UPCR thresholds, we explicitly stated that these were demonstrative and agree they do not represent treatment targets. Rather, they quantify the clinical implications of achieving a particular level of proteinuria reduction, informing prognostication and aiding interpretation of changes observed in clinical trials. We included multiple thresholds, as well as absolute and percentage changes, and the data clearly indicate that even modest reductions, across a broad range of proteinuria levels, were consistently associated with lower KF risk. In practice, treatment decisions will reflect a balance of the known and suspected risks and benefits of more, or less, intensive treatment in an individual patient.

Third, we agree that linking proteinuria to complement biomarkers would be valuable for establishing mechanistic plausibility. However, as the correspondent implies, this would need to be evaluated for each specific therapy under investigation. As we stated, our observational study was not designed to test the extent to which changes in proteinuria mediate treatment effects on hard outcomes—an important goal for future prospective controlled studies.

Finally, they note that eGFR slope had a more modest association with KF than in large diabetic nephropathy cohorts. We believe this reflects fundamental differences in disease dynamics: C3G and IC-MPGN are relapsing-remitting glomerulopathies characterized by episodic inflammation and variable podocyte injury, rather than the progressive decline typical of chronic diabetic kidney disease. This distinction underscores the importance of validating potential surrogate endpoints in disease-specific contexts, rather than assuming associations generalize across different diseases.

Disclosure: The authors declare no conflict of interest.

References:

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