Response to the Letter to the Editor Entitled "Cystatin C-based AKI Staging in Critically Ill Patients: Methodological Concerns and Clinical Caveats From a Nephrology Perspective"

The Author Replies: We thank Drs. Li and Zhining for their thoughtful comments[1] on our study of cystatin C–based acute kidney injury (AKI) staging in critically ill patients.[2] They raise the following 3 issues:

1. Potential selection bias because of exclusion of patients with declining creatinine or cystatin C.

We respectfully disagree that this may have overestimated risk. Rather, it identifies the population in which AKI staging is a meaningful clinical question. AKI, as defined by the Kidney Disease: Improving Global Outcomes, is characterized by a rise in functional markers. For patients whose biomarkers are declining, there is no clinical equipoise to resolve. Including such patients would not make the cohort more "real-world," instead, it would conflate the grading of evolving injury and recovery, which a single staging scale is not designed to capture.

2. The effect of corticosteroids on cystatin C leading to false upstaging.

We agree that corticosteroids raise cystatin C production independently of glomerular filtration rate, potentially leading to false upstaging of AKI without additional renal injury or increased mortality risk. Such an effect would be expected to attenuate the association between cystatin C stage and mortality, worsening discrimination and calibration. However, we observed the opposite. Cystatin C–based reclassification improved long-term mortality prediction, patients who were upstaged had higher mortality, whereas those who were down-staged had lower mortality. A purely pharmacological artefact would not produce bidirectional reclassification and prognostically coherent reclassification.

3. Concerns regarding overmonitoring and premature initiation of renal replacement therapy.

This argument rests on the assumption that reclassification occurs in 1 direction. Yet, we show bidirectional reclassification—patients shift to higher or lower risk, including reclassification from AKI to no AKI. The net effect is improved accuracy of classification and enhanced prediction of mortality. Moreover, Kidney Disease: Improving Global Outcomes stage alone is not an indication to start renal replacement therapy,[3,4] which is based on clinical complications of AKI.

Finally, we agree that the definitive test of clinical utility would be a prospective interventional study demonstrating that management guided by cystatin C staging improves patient-centered outcomes. Importantly, such trials require clearly defined intervention thresholds, which this study helps to establish.

DISCLOSURES

The authors have no sconflicts of interest to disclose.

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