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Letters to the editor

Beyond the epidemiological link: Targeting the gut-liver-kidney axis in hepatorenal disease

To the Editor,

Yuan He et al. [1] demonstrated a robust bidirectional association between CLD and CKD by using CHARLS data. To elucidate this macro-level interplay, we emphasize the gut–liver–kidney axis: disrupted intestinal barrier integrity and microbial-metabolite dysregulation interact via the portal vein and systemic inflammation, collectively promoting hepatorenal damage, with potential for intervention [2–3].

In CLD, particularly MAFLD and cirrhosis, disruption of the intestinal barrier increases permeability, allowing bacterial products such as lipopolysaccharide and toxic metabolites to enter the portal and systemic circulation. This triggers low-grade inflammation and oxidative stress, which directly damage glomeruli and tubules, thereby accelerating CKD onset and progression [4–6].

In CKD, the accumulation of uremic toxins such as indoxyl sulfate and p-cresyl sulfate disrupts the gut microbiota, termed "uremic dysbiosis." These altered microbes produce more harmful metabolites and further compromise the intestinal barrier. Subsequently, these substances enter the liver via the portal circulation, acting as a "second hit" that exacerbates hepatic inflammation, steatosis, and fibrosis, thereby accelerating the progression of CLD [7–9].

This suggests that the gut may serve as a common therapeutic target for both CLD and CKD. Beyond conventional microbiota-directed strategies such as rifaximin, probiotics, or fecal microbiota transplantation, emerging metabolic agents including GLP-1 receptor agonists and SGLT2 inhibitors have shown protective effects on both liver and kidney by improving metabolism, attenuating inflammation, and potentially modulating gut microbiota [10–11]. Evaluating their “dual-benefit” efficacy in patients with combined hepatic and renal disease represents a highly promising research direction.

Moreover, the limitations of existing studies indicate future directions for exploring the gut–liver–kidney axis. First, this work relied on the CHARLS longitudinal survey, and its observational design cannot fully exclude temporal ambiguity, reverse causality, or preclinical effects. These concerns can be partly addressed by applying statistical approaches such as introducing lag periods (e.g., excluding incident cases within 1–2 years after exposure), conducting landmark analyses, and performing sensitivity tests to validate the robustness of findings.

Second, time-dependent risk factors such as BMI, blood pressure, diabetes status, and lifestyle habits challenge models using only baseline values, introducing confounding and biased estimates. Therapies including RAAS and SGLT2 inhibitors, antihypertensives, lipid-lowering agents, and antivirals also influence CLD and CKD risk and may act within causal pathways. Inadequate handling of these treatments risks residual confounding or overadjustment, obscuring true associations. Applying time-updated covariates, MSM/IPTW methods, and complementary sensitivity and stratified analyses can mitigate bias and improve validity.

Third, important modifiers of the CLD–CKD bidirectional association, such as liver disease etiology, disease severity, metabolic status, urban–rural differences, and socioeconomic level, were insufficiently addressed. Limited sample size in some subgroups further reduced statistical power, increased uncertainty, and restricted understanding of heterogeneity. Expanding key subgroup analyses, testing interactions, and applying multicenter or Bayesian approaches may better clarify population-specific variations in the CLD–CKD relationship.

In summary, the study by Yuan He et al. clearly depicts, at the epidemiological level, the hazardous link between liver and kidney diseases. Focusing this macro-level finding on the gut–liver–kidney axis provides an integrated framework and a promising new target for understanding, diagnosing, and treating this increasingly common clinical challenge.

Declaration of competing interest

None.

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