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LETTER

Methodological Considerations on the Longitudinal Analysis of Polymyxin B-Induced Kidney Injury [Letter]

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Dear editor

We read with interest the retrospective cohort study by Zhang et al[1] investigating polymyxin B (PMB)-associated acute kidney injury (AKI) and renal recovery in 325 Chinese patients. The authors report an AKI incidence of 34.5% and identify several independent risk factors, including concomitant nephrotoxic agents and PMB loading dose. While the study addresses a clinically important question, we wish to raise several methodological concerns that may affect the interpretation of the findings.

First, AKI was defined and staged solely based on serum creatinine (SCr) changes according to KDIGO criteria,[2] without incorporating urine output data.[1] The authors acknowledge this limitation. However, in critically ill ICU patients—who constituted 87.7% of the cohort—oliguria is often an earlier and more sensitive indicator of renal injury than SCr elevation.[2] Exclusive reliance on SCr may lead to substantial underestimation of AKI incidence, particularly in the early stages. This concern is compounded by the fact that 49.8% of patients had pre-existing AKD or CKD before PMB administration. For patients with elevated baseline SCr, achieving the 1.5-fold threshold required for KDIGO Stage 1 AKI is more difficult than for those with normal baseline renal function—a "ceiling effect" that may systematically misclassify renal injury in patients with pre-existing impairment. The observation that baseline renal function was not associated with AKI risk (P=0.586)[1] is itself unusual and may reflect this diagnostic bias rather than a genuine absence of association; previous work has shown that lower eGFR is a strong predictor of AKI in hospitalized patients.[3]

Second, the statistical approach to handling multicollinearity warrants reconsideration. The authors excluded weight, maintenance dose, cumulative dose, and treatment duration from the multivariable model because variance inflation factor (VIF) exceeded 5.[1] While collinearity among dose-related variables is mathematically expected—cumulative dose is the product of maintenance dose and duration—excluding them collectively may have removed clinically meaningful exposure metrics. Alternative approaches, such as principal component analysis, ridge regression, or retaining daily dose per kilogram as a single composite variable, could have preserved the dose–response relationship while addressing collinearity.[4] The final model retained only loading dose (RR=1.004, 95% CI: 1.000–1.008, P=0.004),[1] an effect size so close to unity that its clinical significance is questionable and may be driven by sample size rather than biological relevance.

Third, there is an inconsistency between the Methods and Results regarding follow-up. The Methods state that SCr for AKI patients was followed "until discharge from hospital",[1] yet the Results report "30-day mortality rate".[1] If patients were discharged before day 30, post-discharge mortality data would not be available unless additional follow-up mechanisms were implemented—but none are described. This discrepancy raises questions about whether the reported 30-day mortality reflects true 30-day outcomes or merely in-hospital mortality, which are not interchangeable.

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Fourth, the analysis of renal recovery did not account for competing risks. Patients who died before recovery could be observed naturally cannot contribute to the recovery outcome, yet the logistic regression treated non-recovery as a simple binary endpoint.[1] In the presence of substantial mortality (27.6% overall),[1] death competes with recovery. Failure to use competing-risk models such as Fine-Gray regression may bias the estimated associations[5]—particularly the finding that vasoactive agent use was associated with lower recovery (OR=0.298, P=0.013).[1] As the authors themselves note, vasoactive agents likely reflect underlying hemodynamic instability rather than a direct effect on recovery; this confounding-by-indication cannot be adequately addressed without adjusting for illness severity scores such as APACHE II or SOFA, which were not included.[1]

Finally, the authors report that renal recovery rates did not differ significantly across KDIGO stages (Stage 1: 37.1%, Stage 2: 42.9%, Stage 3: 42.9%).[1] This absence of a dose–response relationship—more severe AKI showing similar recovery to milder AKI—is counterintuitive and may reflect the limitations of SCr-based staging in this population, or insufficient power to detect differences. A sensitivity analysis using alternative recovery definitions (eg, return to within 1.5× baseline rather than exact baseline) might help clarify whether this finding is robust; long-term outcomes after AKI recovery have been shown to vary substantially depending on the definition used.[6]

We do not question the clinical relevance of PMB nephrotoxicity or the value of identifying modifiable risk factors. However, we suggest that the combination of incomplete AKI ascertainment, exclusion of key dose-related variables due to collinearity, unresolved follow-up inconsistency, and absence of competing-risk adjustment may limit the strength of the conclusions. Re-analysis with these considerations—particularly stratification by baseline renal function and adjustment for illness severity—would substantially strengthen the evidence.

Disclosure

The authors report no conflicts of interest in this communication.

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