Dear Dr. Hoffman and the Editorial Team at *Clinical Toxicology*,

I am pleased to submit our manuscript, titled **“INTOXICATE-US: Validation of the INTOXICATE Model in an American Health Care System”** for consideration in *Clinical Toxicology*. This study externally validates a clinical decision support tool designed to reduce ICU admissions for poisoned patients.

In 2017, *Clin Tox* published the initial derivation of a model that predicted which poisoned patients admitted to the ICU could be safely downgraded. I was motivated by that publication and the subsequent presentation at EAPCCT in 2023, which suggested an automated way to safely reduce ICU admissions by one-third, simultaneously reducing unnecessary procedures and increasing ICU capacity. The study used a Dutch ICU cohort. Our goal was to evaluate the model in the US healthcare system. Mindful of the pitfalls of automating clinical decision making, we also assessed whether the model was getting the right answers for the right reasons by comparing its recommendations to bedside toxicologists.

We conducted a retrospective study in one urban healthcare system with 24/7 bedside toxicology. Our findings suggest that INTOXICATE, if applied as originally designed, could reduce ICU admissions by 31% in adults. However, when used broadly in an ED population, it significantly increased ICU utilization without meaningful agreement with bedside toxicologists. Adjusting the INTOXICATE Risk Score (IRS) threshold improved its performance but introduced inappropriate downgrades, including one death. These results highlight the potential of INTOXICATE while underscoring the need for further refinement before widespread implementation.

We believe our article is a good fit for *Clin Tox* because it demonstrates proof-of-concept in using algorithms to help clinicians reduce unnecessary admissions in the poisoned patients who present to an Emergency Department. Our findings contribute to ongoing discussions about optimizing patient triage in toxicology and could inform future efforts to refine support tools in clinical practice. Our approach of directly comparing algorithm and clinician recommendation also demonstrates a useful criterion to evaluate other models.

**Author Contributions & Ethical Considerations:**

This manuscript has been approved by all co-authors and is not under consideration elsewhere. The study was conducted in accordance with institutional ethical guidelines, and all statistical analyses were performed using open-source code available at https://github.com/mac389/INTOXICATE.

We appreciate your time and consideration of our manuscript. We look forward to your feedback and the opportunity to contribute to *Clinical Toxicology*. Please do not hesitate to contact me if you require any further information.

Sincerely,

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