



Letter to the Editor

Letter to the editor: The impact of ketamine on ICU mortality in patients with sepsis: A retrospective cohort study

ARTICLE INFO

Keywords:

Sepsis
Ketamine
Etomidate
Rapid sequence intubation
Intensive care unit

The recent article by Liu et al., entitled “The impact of ketamine on ICU mortality in patients with sepsis: A retrospective cohort study,” reported that ketamine exposure was associated with lower 7-day intensive care unit (ICU) mortality among patients with sepsis [1]. The authors should be commended for analyzing a large critical care database. Nevertheless, several aspects of the interpretation of these findings warrant discussion.

In their conclusion, the authors suggest that ketamine exposure may reduce short-term ICU mortality [1]. However, the current body of randomized evidence comparing ketamine with other induction agents has not demonstrated a clinically meaningful benefit on organ dysfunction or patient-centered outcomes. Several randomized trials evaluating ketamine versus etomidate for rapid sequence intubation (RSI) in critically ill patients have reported no significant differences in major clinical outcomes.

Randomized studies have shown no significant differences in maximum Sequential Organ Failure Assessment (SOFA) scores or post-intubation hemodynamic instability between critically ill adults receiving ketamine or etomidate for RSI, including patients with sepsis [2]. In the largest and most recent randomized trial, 801 critically ill patients undergoing RSI in the ICU were assigned to receive either ketamine or etomidate [3]. Although seven-day survival was numerically higher in the ketamine group, this difference did not persist at day 28, and no significant differences were observed in secondary outcomes including ICU length of stay, duration of mechanical ventilation, SOFA scores, or vasopressor requirements [3].

Similarly, Jabre et al. conducted a multicenter randomized trial enrolling 655 critically ill adult patients undergoing RSI and found no difference in maximum SOFA score, mortality, or secondary outcomes between ketamine and etomidate [4]. Smischney et al. analyzed 152 adult ICU patients who received either a combination of reduced-dose ketamine and propofol or etomidate and likewise observed no significant difference in post-intubation hemodynamics or vasopressor use between groups [5].

Taken together, available randomized evidence suggests that ketamine and etomidate have broadly comparable clinical effects when used for RSI in critically ill patients. Importantly, these trials have not

demonstrated a clear improvement in organ dysfunction or mortality associated with ketamine. Therefore, the association between ketamine exposure and lower early mortality reported by Liu et al. should be interpreted cautiously, particularly given the inherent limitations of retrospective analyses. Potential confounding by indication, unmeasured sedation strategies, and incomplete information regarding ketamine dosing, timing, and duration of administration may influence the observed associations.

Moreover, the randomized studies cited above primarily evaluated single-dose ketamine administered during RSI, whereas the exposure in the study by Liu et al. largely reflected continuous infusion during the ICU stay. These differences in clinical context and drug exposure make direct comparisons challenging.

From a clinical perspective, existing evidence suggests that both ketamine and etomidate appear to be safe and effective agents for RSI in critically ill patients, including those with sepsis. Clinicians may select either agent based on individual patient characteristics, hemodynamic status, and institutional practice. Further prospective studies specifically designed to evaluate the role of ketamine in sepsis management will be necessary to determine whether the association observed in retrospective analyses reflects a true therapeutic effect.

Author's contribution

CYM, YB & PMH designed the paper. All authors participated in drafting and reviewing. All authors read and approved the final version of the manuscript.

CRediT authorship contribution statement

Catherine Y. Muscato: Writing – original draft, Writing – review & editing. **Yasser Benkaddour:** Writing – original draft, Writing – review & editing. **Nathan De Lissnyder:** Writing – original draft, Writing – review & editing. **Patrick M. Honoré:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

<https://doi.org/10.1016/j.jcrc.2026.155571>

Received 23 March 2026; Accepted 31 March 2026

Available online 9 April 2026

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Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Funding

None.

Declaration of competing interest

The authors declare to have no competing interests.

Acknowledgements

None.

Data availability

Not applicable.

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