In Brief | Critical Care, Anaesthetics & Emergency Medicine |

Critical Care: Etomidate vs Ketamine for RSI in Critically Ill Adults: Mortality and Haemodynamic Outcomes

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Key Takeaway

In critically ill adults undergoing rapid sequence intubation, etomidate was associated with higher in-hospital mortality, while ketamine caused more early post-intubation haemodynamic instability, highlighting a trade-off between short-term physiology and longer-term outcomes.

Context and Purpose

Rapid sequence intubation (RSI) is a high-risk intervention in critically ill adults, and the choice of induction agent may influence short-term outcomes.Etomidate and ketamine are widely used because of their favourable haemodynamic profiles, yet their comparative safety remains controversial.

Observational data and physiological concerns—particularly regarding etomidate-associated adrenal suppression—have led to ongoing debate, with limited contemporary, real-world evidence to guide agent selection in emergency settings.

Study Objective: This recent study, published in JAMA Open Network in December 2025, aimed to compare the safety of etomidate versus ketamine as induction agents for emergency RSI in critically ill adults, focusing primarily on in-hospital mortality.

Methodology

This observational cohort study used a target trial emulation framework.

Data were obtained from the Brazilian Airway Registry Cooperation and included adults who underwent RSI in 18 emergency departments.

Patients received either etomidate or ketamine as the sole hypnotic agent. Those with pre-intubation cardiac arrest or immediate post-intubation transfer were excluded. Inverse probability of treatment weighting was used to adjust for confounding, and outcomes were compared using risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals.

*The primary outcome was **28-day in-hospital mortality**. Secondary outcomes included **7-day in-hospital mortality**, first-attempt intubation success, and major adverse events within 30 minutes of intubation (new haemodynamic instability, severe hypoxaemia, and cardiac arrest).*

Study Findings

Among 1,810 critically ill adults undergoing rapid sequence intubation.

The median age was 64 years (IQR, 50-74 years); and 1048 (57.9%) were men. 514 (28,4%) received ketamine and 1296 (71.6%) received etomidate.

Baseline characteristics suggested that patients in the ketamine group were more haemodynamically compromised before intubation, reflected by a higher median shock index and a greater prevalence of pre-intubation vasopressor use compared with those receiving etomidate.

Weighted 28-day in-hospital mortality was higher in the etomidate group compared with the ketamine group (60.5% vs 54.4%). This difference corresponded to a relative increase in mortality risk of 14% and an absolute risk difference of 7.6%. A similar pattern was observed for 7-day in-hospital mortality, which was also higher among patients who received etomidate.

In contrast, new haemodynamic instability within 30 minutes of intubation occurred more frequently in the ketamine group (24.2% vs 18.9%), despite adjustment for baseline differences.

This outcome included events such as new hypotension requiring intervention, occurring in nearly one quarter of ketamine-treated patients versus under one fifth of those receiving etomidate.
No statistically significant differences were observed between the two groups in first-attempt intubation success, rates of severe hypoxaemia, or peri-intubation cardiac arrest.

28-day in-hospital mortality *was* ***higher in the etomidate group*** *compared with the ketamine group (60.5% vs 54.4%).*

Similarly, the ***7-day mortality rate was 35.2% in the etomidate*** *group compared with 30.1% in the ketamine group*

Discussion

This large, multicentre observational study found that etomidate use during RSI was associated with higher 7-day and 28-day in-hospital mortality compared with ketamine, despite patients in the ketamine group demonstrating markers of greater pre-intubation haemodynamic compromise. This association persisted after adjustment for measured confounders, suggesting that baseline illness severity alone did not account for the observed mortality difference.

In contrast, ketamine use was associated with a higher incidence of early post-intubation haemodynamic instability. No differences were observed in first-attempt intubation success, severe hypoxaemia, or peri-intubation cardiac arrest, indicating comparable airway procedural performance between agents. Collectively, these findings highlight a divergence between early physiological effects and longer-term in-hospital outcomes associated with induction agent choice during RSI.

In their discussion section, the researchers contextualise their findings within the existing literature, noting alignment with some observational studies showing etomidate-associated harm while acknowledging a meta-analysis of 11 RCTs found no mortality difference. The authors prioritise supportive evidence and mechanistic explanations when interpreting this mixed evidence base.

Regarding confounding, the authors calculate an E-value of 1.54 and compare this to single confounders like lactate (OR 1.11), concluding that unmeasured confounding is unlikely to alter their interpretation. They note that ketamine patients were sicker at baseline, framing this as strengthening rather than

undermining their findings since etomidate still showed worse outcomes. The emulated trial design adjusts for measured variables but cannot balance unknown confounders like true randomisation.

The discussion attributes etomidate's apparent harm to adrenal suppression, citing external studies (KETASED[3], CORTICUS[4]), though the current study did not measure adrenal function directly. The authors note their population had higher baseline mortality than North American cohorts, explaining their larger effect size but raising questions about generalisability.

They position their observational findings as conflicting with 2023 SCCM guidelines recommending either agent, advocating for reconsidering routine etomidate use while awaiting ongoing randomised trials. The analysis does not stratify implications by clinical subgroups where immediate haemodynamic stability might be prioritised.

***Key insight**: It is the authors' view that their observational findings, when considered alongside other recent data, warrant reconsideration of current practice recommendations while awaiting definitive randomised evidence.*

The following limitations should be considered on review of these findings.

The selection of ketamine or etomidate may have been influenced by clinical factors not fully captured in the dataset. Patients receiving ketamine were more haemodynamically compromised at baseline, as reflected by higher shock indices and greater pre-intubation vasopressor use, which would be expected to bias results against ketamine.

Despite this, etomidate remained associated with higher in-hospital mortality after inverse probability of treatment weighting and sensitivity analyses. Residual and unmeasured confounding may nonetheless persist and could attenuate the observed associations.

Neurological or functional outcomes at discharge or follow-up were not collected, precluding assessment of disability-free survival.

In addition, 302 patients intubated in urgent care or emergency units without on-site intensive care units were transferred elsewhere, and 28-day outcomes were unavailable for these cases. This logistics-driven exclusion may introduce selection bias and limit generalisability, particularly to centres with on-site intensive care capability. Although sensitivity analyses, including models with hospital-level random effects, yielded consistent findings, residual bias related to inter-facility transfer cannot be excluded.

In Conclusion

While causality cannot be inferred from the above findings, the results contribute contemporary, real-world evidence to ongoing discussions regarding optimal induction strategies in critically ill adults, emphasising the need to balance immediate haemodynamic considerations against potential downstream outcomes.

Original Study

Maia IWA, Decker SRR, Oliveira J. e Silva L, et al. **Ketamine, Etomidate, and Mortality in Emergency Department Intubations.** *JAMA Netw Open.* 2025;8(12):e2548060. doi:10.1001/jamanetworkopen.2025.48060.

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