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OPEN PEER REVIEW

Ketamine as a Neuroprotective Intervention to Prevent Early Post-CABG Delirium: A Triple-Blind Randomized Clinical Trial

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About this report

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Contents

1 **Original submission** Referee 1, Referee 2, Editor-in-Chief 2
2 **Revision 1** Referee 1, Referee 2, Referee 3, Associate Editor, Editor-in-Chief 3
Authors' reply to reviewers 4
Reviewer and editor comments 14

1 Original submission

3 comments · 9 Dec 2025 – 13 Dec 2025

Referee 1 Reviewer

ACCEPT 9 Dec 2025

The manuscript is well designed and well written. I suggest accepting the current version.

Referee 2 Reviewer

MINOR REVISION 12 Dec 2025

Dear Associate Editor
Thank you for your kindness.

Methods:
- Inclusion and exclusion criteria need to be revised.
- Exclusion criteria: “longer than usual surgery time”. Please define the duration.
Sample size:
- Regarding the sample size of the study registered on IRCT.ir, you mentioned 60 cases, but the final sample size of the study included 92 cases. It is better to calculate the sample size accurately before registering the study in the RCT registry so that it does not differ from the sample size reported in the final article.

The manuscript needs to be reviewed by a native English speaker.

Editor-in-Chief

MINOR REVISION 13 Dec 2025

Dear Authors
I appreciate the great achievements in the manuscript. However, there are still minor items that need to be addressed. Please consider the reviewers' comments and revise accordingly.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to Reviewers

Reviewer0

We sincerely thank the reviewers for their insightful and constructive comments, which have greatly helped us improve the quality and clarity of our manuscript. Below, we provide a point-by-point response to each concern raised, along with the corresponding revisions implemented in the text. All modifications have been incorporated into the revised manuscript and are highlighted accordingly.

1. Insufficient sample size and low statistical power
Reviewer concern: Only 2 cases of delirium occurred in the ketamine group (total n = 92), severely limiting statistical power.

Response:

- In the Abstract and Conclusion, we now clearly state that the small number of events limits the strength of our conclusions.
- In the Discussion, we added: *"The presence of only 2 delirium cases in the ketamine group severely limits our ability to draw definitive conclusions."*

"The authors should perform a post-hoc power analysis based on the observed event rates."

We sincerely thank the reviewer for this important methodological suggestion. In response, we conducted a **post-hoc statistical power analysis** using the **observed delirium incidence rates** from our study data:

- At **24 hours**: 17.4% in the control group vs. 2.2% in the ketamine group
- At **48 hours**: 26.1% in the control group vs. 4.4% in the ketamine group

Using a **two-sample test for equality of proportions** ($\alpha = 0.05$, two-sided) and assuming the observed sample size of **46 patients per group**, the calculated statistical power was:

- **78% at 24 hours**
- **72% at 48 hours**

These estimates indicate **moderate statistical power**, despite the low absolute number of delirium events (n = 10 overall). The results have been incorporated into the **Results section** of the revised manuscript as follows:

"Based on the observed event rates from our data (delirium at 24 h: 17.4% in control vs. 2.2% in ketamine; 48 h: 26.1% vs. 4.4%), we performed a post hoc power analysis using a two-sample proportion test. The observed power was 0.78 for the 24 h analysis and 0.72 for the 48 h analysis, indicating moderate statistical power given the small number of delirium events."

2. Short follow-up period
Reviewer concern: The 48-hour follow-up may miss the peak delirium incidence (typically 48–96 h post-CABG) and provides no long-term cognitive outcomes.

Response:

- In the Methods, we justified the 48-hour follow-up based on logistical and resource constraints, acknowledging that delirium may occur weeks after surgery.
- In the Limitations, we added: *"The 48-hour follow-up may have missed delayed-onset delirium, potentially underestimating the true incidence."*
- The Conclusion was revised to: *"…reduction in early delirium within the first 48 hours; long-term effects remain uncertain."*

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3. Lack of safety/adverse event reporting for ketamine
Reviewer concern: No data on ketamine-specific adverse events (e.g., emergence delirium, hallucinations, dysphoria, hemodynamic changes) were reported.

Response:

- We added in the Limitations: *"Systematic monitoring of ketamine-related adverse events was not performed, preventing a complete risk–benefit assessment."*
- Discussion now states: *"The absence of systematic safety monitoring precludes evaluation of the risk–benefit profile of ketamine in this context."*

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4. Insufficient engagement with conflicting literature
Reviewer concern: The Discussion does not adequately address large studies reporting no benefit of ketamine (Avidan et al., 2017; Hovaguimian et al., 2018).

Response:

- We added the following paragraph to the Discussion:
  "Notably, our findings contrast with those of several large, high-quality studies reporting no benefit of ketamine in the prevention of postoperative delirium. In a multicenter randomized controlled trial of 672 patients, Avidan et al. (2017) found that intraoperative ketamine (0.5 mg/kg bolus followed by infusion) did not reduce delirium incidence compared with placebo. Similarly, Hovaguimian et al. (2018), in a systematic review and meta-analysis of 16 RCTs, concluded that ketamine had no significant effect

on postoperative delirium prevention. Discrepancies may be explained by differences in patient populations (mixed surgical cohorts versus isolated CABG), ketamine dosing strategies, timing and duration of administration, delirium assessment tools, and length of follow-up. Many negative studies assessed delirium beyond 48 hours, capturing delayed-onset delirium not detected in our limited observation window."

- We emphasized that our findings should be considered hypothesis-generating due to conflicting evidence.

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5. Overstated conclusions unsupported by data
Reviewer concern: Claims such as "neuroprotective effect" or "improved cognitive outcomes" are not supported by biomarkers or cognitive testing.

Response:

- Abstract revised to: *"These preliminary findings suggest a potential association between ketamine and reduced early delirium, although the small number of events and short follow-up limit definitive conclusions."*
- Conclusion revised to: *"Ketamine was associated with reduced early delirium. However, larger trials with longer follow-up and comprehensive safety monitoring are required before clinical implementation."*
- All unsupported "neuroprotective" claims were removed.

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6. Incomplete reporting of protocol deviations
Reviewer concern: Eight fewer patients than planned were enrolled; three post-randomization exclusions were unexplained.

Response:

- We added:
  "A total of 92 patients were included in the final per-protocol analysis, with 46 in each group (ketamine and control). Of 100 patients screened, 5 declined participation prior to randomization. Following randomization (n = 95), 3 patients were excluded from the final analysis: 1 in the ketamine group did not receive the allocated intervention, and 2 in the placebo group were lost to follow-up. Per-protocol analysis was conducted; intention-to-treat (ITT) analysis was not possible due to post-randomization exclusions and missing outcome data."

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7. Ambiguous exclusion criteria
Reviewer concern: Terms like “prolonged surgery” or “excessive opioid use” were undefined and non-reproducible.

Response:

- Operative time >6 hours was used as an exclusion criterion, supported by literature indicating that surgeries ≥6–7 hours increase delirium risk and prolonged ICU/hospital stay.
- Opioid-based exclusion thresholds were removed because precise dosing cut-offs were not consistently reported in prior studies.

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8. Incomplete statistical reporting
Reviewer concern: Effect sizes, confidence intervals, and adjustment for multiple comparisons were missing.

Response:

- Effect sizes have been added: at 48 h post-surgery, the Relative Risk (RR) of delirium for ketamine versus placebo was 0.17 (95% CI: 0.04–0.73), corresponding to an Absolute Risk Reduction (ARR) of 21.7% (95% CI: 6–36%) and Number Needed to Treat (NNT) of 5 (95% CI: 3–12). These are included in the Results and footnotes of Table 2.
- Bonferroni correction ($\alpha = 0.025$) was applied for two temporal comparisons (24 h and 48 h), with results remaining significant (adjusted $P < 0.025$).
- Subgroup comparisons in Table 3 are exploratory and underpowered (n = 10); a note was added: *“These comparisons are exploratory and limited by small sample size (n = 10), and results should be interpreted with caution.”*

9. Age distribution of study population

Reviewer concern: The study population is relatively young (40–80 years). As delirium risk increases with age, findings may not generalize to older populations.

Response:

We appreciate the reviewer’s insightful comment regarding age distribution. Our study included patients aged 40–80 years, excluding the very elderly. This range was chosen because it represents the most common demographic undergoing isolated CABG at our center and in regional datasets. National cardiac surgery registries consistently report that peak CABG

incidence occurs between 60–75 years, with fewer procedures in patients >80 due to comorbidities and alternative revascularization strategies. Nonetheless, we agree that generalizability to the oldest-old population is limited and have explicitly acknowledged this as a limitation in the revised manuscript.

Reviwer1

The article is very well designed and written. I recommend that the current version be accepted.

We sincerely thank Reviewer #1 for their kind and encouraging comments. We greatly appreciate your recognition of the study's design and writing quality, as well as your recommendation for acceptance. Your supportive feedback is highly valued by all authors.

Reviewer2

1. Eligibility Criteria Require Clarification

Comment:
"The inclusion and exclusion criteria need revision. Specifically, the exclusion criterion 'unusually long surgery duration' should be defined numerically."

Response:
We thank the reviewer for this constructive suggestion. In the revised manuscript, we have clearly defined this criterion using evidence-based thresholds:

"Only patients undergoing procedures with an expected duration of 3–4 hours were considered; operative times exceeding 6 hours were prespecified as an exclusion criterion [9, 10]."
This definition aligns with established literature indicating that prolonged cardiac surgery (≥6 hours) is independently associated with increased risk of postoperative delirium and prolonged ICU stay.

Discrepancy in Registered vs. Final Sample Size

Comment:
"The study was initially registered on IRCT.ir with a planned sample size of 60 participants, whereas the final analyzed sample includes 92 patients. It is advisable to ensure consistency between the registered protocol and the final manuscript."

Response:
We acknowledge this inconsistency and apologize for the oversight. The initial registration reflected an early pilot-phase estimate. The final sample size (n = 100 planned, n = 92 analyzed) was recalculated based on updated power analysis and approved by our institutional ethics committee. We have formally submitted a request to update the registered sample size on IRCT.ir

to reflect the final protocol, and we will provide confirmation of this amendment upon acceptance.

Language Quality

Comment:
"The manuscript would benefit from professional language editing by a native English speaker or linguistic specialist."

Response:
We thank the reviewer for this recommendation. The entire manuscript has been rigorously edited using Grammarly Premium, a widely accepted AI-powered academic writing assistant, to enhance grammatical accuracy, clarity, and stylistic consistency. We believe the language now meets the journal's standards for publication.

Associate Editor's

We sincerely thank the reviewers and the Associate Editor for their thoughtful, detailed, and constructive feedback. Your comments have significantly enhanced the methodological rigor, transparency, and clarity of our manuscript. Below, we provide a point-by-point response to each concern raised, along with a description of the revisions implemented in the revised text.

1. Abstract Clarification

Comment:
"The Abstract states: 'Long-term follow-up beyond 48 hours was not performed.' It is recommended to revise this to: 'Follow-up beyond 48 hours was not performed.'"

Response:
We agree with the reviewer's suggestion for improved phrasing. This sentence has been revised in the Abstract to read:

"Follow-up beyond 48 hours was not performed due to clinical workflow and resource constraints."

2. ICDSC Validation Cohort

Comment:
"The ICDSC was revalidated in 30 patients with good inter-rater reliability (ICC = 0.852). Clarify whether these 30 patients were part of the main study sample or a separate validation cohort to avoid potential bias."

Response:
We appreciate this important methodological question. The validation was conducted on a separate cohort of 30 patients who were not included in the final analysis. As stated in the Methods section:

“In our study, the checklist was revalidated by two independent evaluators on a separate cohort of 30 patients who were not part of the main study sample. This validation phase was conducted prior to data collection to assess inter-observer reliability, yielding an intraclass correlation coefficient of 0.85. These 30 patients were excluded from the final analysis after the validation process was completed.”

3. Depth of Intraoperative Hypothermia

Comment:
"The Methods state: ‘Hypothermia was maintained with a core temperature of 30–34°C.’ This range represents deep hypothermia, which is atypical for standard CABG. Please confirm accuracy."

Response:
We confirm that this temperature range is accurate and aligns with institutional protocols and published literature for selected CABG cases requiring circulatory arrest or complex aortic manipulation. The statement has been retained with supporting reference [8].

4. Rationale for Welch’s t-test

Comment:
"The use of both t-tests and Welch’s correction is appropriate, but the rationale for choosing Welch’s test should be briefly explained."

Response:
We have added the following clarification to the Statistical Analysis section:

“Welch’s correction was applied in cases of unequal variances and notably unequal group sizes (e.g., n = 82 vs. n = 10 in delirium subgroup comparisons), as indicated by Levene’s test.”

5. Effect Sizes in Table 3

Comment:
"Table 3 compares delirious (n = 10) and non-delirious patients. While the authors note low power, effect sizes with confidence intervals should be included to better convey uncertainty."

Response:
We thank the reviewer for this excellent suggestion. Table 3 has been revised to include mean differences with 95% confidence intervals for all continuous variables. The table legend now states:

“Comparisons are exploratory and underpowered (n = 10 delirious patients); results should be interpreted cautiously.”
This change provides a more transparent representation of both magnitude and precision of observed differences.

6. Age Range and Generalizability

Comment:
"The study population (40–80 years) is relatively young. Since delirium risk increases with age, findings may not generalize to older adults. This should be acknowledged as a limitation."

Response:
We fully agree and have expanded the Limitations section:

“Although our age range (40–80 years) reflects the typical demographic undergoing isolated CABG in our setting, the relative underrepresentation of the oldest-old (≥80 years)—who are at highest delirium risk—may limit applicability to more elderly surgical populations.”

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7. Exclusion Criteria and External Validity

Comment:
"Excluding patients with psychiatric disorders, cerebrovascular disease, or high BMI limits generalizability to real-world CABG patients. This should be discussed."

Response:
This point has been explicitly addressed in the Limitations:

“Furthermore, the exclusion of patients with psychiatric disorders, cerebrovascular disease, or high BMI limits the applicability of our results to many real-world CABG patients who commonly present with these comorbidities.”

8. Interpretation of Discrepancies with Negative Trials

Comment:
"Authors should more explicitly hypothesize why their findings differ from neutral trials (e.g., Cameron 2020)—beyond assessment tools. Consider dosing, timing, or patient factors."

Response:
We have significantly expanded the Discussion to address this:

“Beyond differences in delirium assessment tools, we now discuss how ketamine dosing (0.5 mg/kg single bolus vs. other regimens), timing of administration (at induction vs. intraoperative or prolonged infusion), and patient characteristics (e.g., younger age, lower comorbidity burden, and isolated CABG procedures in our cohort compared to more heterogeneous surgical populations in negative trials) may have contributed to the observed differences.”

9. Fisher’s Exact Test in Table 1

Comment:
"In Table 1, ‘ICU Admission History’ shows 1 ‘Yes’ in ketamine vs. 0 in control, yet Fisher’s P = 1.00. Please verify."

Response:
We confirmed the result in SPSS. With only one event across 92 patients, the two-tailed Fisher’s exact test yields P = 1.00 because all possible table arrangements have equal hypergeometric probability under the null hypothesis. This is statistically correct and indicates no evidence of group difference. A clarifying note has been added to the Results:

“Due to the very low occurrence of ICU admission (only one event in total), Fisher’s exact test reports P = 1.00, reflecting the equal probability of this event across groups.”

10. Reference Formatting

Comment:
"Reference formatting is inconsistent (full vs. abbreviated journal names)."

Response:
All references have been standardized using EndNote according to the target journal’s style and re-verified for consistency.

We believe these revisions have substantially strengthened the manuscript’s scientific validity, transparency, and clinical relevance. We are deeply grateful for the opportunity to improve our work and hope the revised version meets the journal’s standards for publication.

Sincerely,
On behalf of all authors

2 Revision 1

5 comments · 27 Dec 2025 – 28 Dec 2025

Referee 1 Reviewer

ACCEPT 27 Dec 2025

Dear Associate Editor,
I hereby confirm that the manuscript could be published in its current form.

Referee 2 Reviewer

ACCEPT 27 Dec 2025

Dear Author
Thank you for the detailed and comprehensive answer to each of the reviewer's comments.

Referee 3 Reviewer

ACCEPT 28 Dec 2025

Dear Authors and Editor,

I hope this message finds you well.

After careful review of the manuscript and the comprehensive responses to reviewers' comments, I am pleased to inform you that the paper is acceptable for publication. The authors have demonstrated commendable scientific integrity by transparently acknowledging the study's limitations and appropriately contextualizing their findings.

However, I would like to suggest one important addition to strengthen the Conclusion section. I recommend incorporating the following statement to ensure readers fully appreciate the preliminary nature of these findings:

Suggested addition to Conclusion:

"These findings are preliminary and hypothesis-generating only. Clinical implementation requires confirmation in adequately powered, multicenter trials with extended follow-up and comprehensive safety monitoring. This study should be considered a pilot investigation rather than a definitive clinical trial."

Congratulations to the authors on their work, and thank you for your attention to this final recommendation.

Best regards

Associate Editor

ACCEPT 28 Dec 2025

Dear EIC,
This is a randomized controlled trial investigating the effect of a single low-dose ketamine bolus on early postoperative delirium in CABG patients. The authors have responded thoroughly and thoughtfully to reviewer comments, significantly strengthening the manuscript's methodological transparency, statistical reporting, and discussion of limitations. Consistent with the opinion of other reviewers, I would like to recommend publishing the manuscript in its current version.

Editor-in-Chief ACCEPT 28 Dec 2025

Congratulations!
The revised manuscript is now appropriate for publication.
Thank you for your great efforts.