

Response to Yadav et Katarina's letter to the editor on 'Exploring Discordance in Evidence from Meta-Analyses and Subsequent Large-Scale Randomized Controlled Trials in Perioperative Medicine'

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Dear Editor,

We thank Yadav et Katarina for their thoughtful comments on our article on the discordance between meta-analysis and subsequent large-scale randomized controlled trials (RCTs)¹. We appreciate the opportunity to clarify the intent, scope and methodologic choices underlying our work.

We fully agree with these researchers, that the methodological standards highlighted in their comments – comprehensive database searches, duplicate study selection, transparent reporting of search strategies, formal quality appraisal (e.g. AMSTAR2), and preregistration are essential components of a rigorously conducted systematic review². These practices enhance reproducibility, minimize bias, and strengthen the credibility of evidence synthesis. We acknowledge that our study does not fulfill these criteria, and we agree that this limits the extent to which our findings can be interpreted as providing a precise or unbiased estimate of concordance between meta-analysis and subsequent RCTs.

However, we would like to emphasize that our work was not conceived nor presented as a formal systematic review or meta-analysis. Rather, as reflected in the title and study rationale, it originated as an exploratory investigation aimed at illustrating a specific and well-recognized phenomenon: the apparent discordance between statistically significant findings from meta-analyses and the results of subsequently published large-scale RCTs³. It was intended primarily to stimulate reflection on the interpretation of meta-analytic evidence in perioperative medicine.

In this context, our principal objective was not to establish the exact frequency of agreement or disagreement between meta-analysis and later trials, but to highlight a potential underlying explanation for such discordance – namely, limited statistical power in meta-analyses. We aimed to demonstrate that meta-analyses, particular those based on relatively small cumulative sample sizes or sparse event-rates, may yield apparently definitive conclusions based on conventional significance thresholds, despite being underpowered to detect or refute clinically meaningful effects reliably.

To explore this issue, we applied the framework of Trial Sequential Analysis (TSA), which explicitly incorporates the concept of required information size and adjusts from repeated significance testing. We believe TSA offers a valuable perspective by reframing meta-analytic results in terms of accrued evidence relative to the information needed for robust inference. From this viewpoint, a statistically significant pooled estimate may still represent inconclusive evidence if the cumulative sample size remains insufficient. This perspective is, in our opinion, underappreciated in the anesthesiology literature, where meta-analysis and RCTs alike are often interpreted dichotomously based on p-values^{4,5}.

The concerns raised by the authors regarding the potential bias in our estimate of concordance are well taken. Given the non-systemic nature of our search strategy and study selection process, our reported concordance rates should not be interpreted as precise or generalizable estimates. We acknowledge that these figures may be influenced by selection bias and incomplete retrieval of relevant studies. Importantly, however, our intention was not to provide a definitive epidemiological measure, but rather to offer illustrative examples supporting a broader methodological point. Nevertheless, we recognize that greater transparency in reporting, including provision of the search strategy and cleared documentation of the study selection procedures, would have improved the reproducibility of our work. We appreciate this feedback and agree that even exploratory analyses benefit from enhanced methodological clarity.

In summary, we would like to emphasize that our study should be interpreted as a hypothesis-generating, exploratory analysis rather than a formal systematic review. Its primary contribution lies in drawing attention to the role of statistical power and information size in the interpretation of meta-analytic findings, and in advocating for

wider consideration of approaches such as TSA in perioperative research. We agree that future work addressing this question would benefit from a fully systematic approach, incorporating rigorous methodology and comprehensive reporting standard.

We thank the authors again for their comments, which have allowed us to clarify these important distinctions and limitations.

References

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