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Comparative efficacy of dexmedetomidine versus propofol for sedation in mechanically ventilated adult patients with sepsis: a systematic review and meta-analysis

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Abstract

Current clinical guidelines recommend dexmedetomidine and propofol as first-line sedatives for mechanically ventilated patients. This systematic review and meta-analysis aimed to compare the efficacy and safety of dexmedetomidine versus propofol in mechanically ventilated adults with sepsis or septic shock. PubMed, Embase, CENTRAL, Scopus, Web of Science, and clinical registries were searched for randomized controlled trials (RCTs) and comparative observational studies published in English up to May 2026. The primary outcome was 28/30-day all-cause mortality. Secondary outcomes included duration of mechanical ventilation (MV), ICU length of stay (LOS), delirium incidence, and bradycardia. Random-effects meta-analyses utilized the Restricted Maximum Likelihood (REML) estimator with Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustments. Trial Sequential Analysis (TSA) was performed to assess information size and statistical power. Certainty of evidence was appraised using the GRADE framework. Ten studies (7 RCTs and 3 comparative observational cohorts) comprising 54,430 patients were included. Meta-analysis revealed no statistically significant difference in 28/30-day mortality between dexmedetomidine and propofol (RR, 0.90; 95% CI 0.67–1.21; p=0.435; I2=54.5%). TSA confirmed that the accrued sample size exceeded the Required Information Size (4,036 patients), validating the null finding. There were no significant differences in the duration of MV (MD, -1.13 days; 95% CI -3.46-1.20), ICU LOS (MD -1.54 days; 95% CI -3.59-0.52), or the incidence of delirium (RR 0.87; 95% CI 0.14–5.21). Dexmedetomidine was associated with a statistically non-significant trend toward an increased risk of bradycardia (RR 2.46; 95% CI 0.73–8.31). The overall certainty of evidence was rated as low to very low due to open-label designs, clinical inconsistency, and imprecision. Based on evidence of low to very low certainty, dexmedetomidine does not appear to significantly improve short-term mortality, mechanical ventilation duration, or ICU length of stay compared to propofol. The choice of sedative agent should be highly individualized based on patient-specific hemodynamic profiles and critical care goals, as evidence does not support a survival advantage for either agent.

Keywords: sepsis, septic shock, mechanical ventilation, conscious sedation, dexmedetomidine, propofol, intensive care units, meta-analysis, mortality

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Introduction

Sepsis and septic shock are life-threatening organ dysfunctions caused by a dysregulated host response to infection, and remain a leading cause of morbidity and mortality in intensive care units (ICUs) worldwide [1,2]. A substantial proportion of these patients develop acute respiratory failure, requiring invasive mechanical ventilation [3]. While the administration of sedatives is a fundamental component of ICU care to ensure patient-ventilator synchrony, reduce metabolic demand, and alleviate physical and psychological distress, the choice of sedative agent impacts the clinical trajectory [4,5]. Deep sedation and the accumulation of certain sedatives are independently associated with prolonged mechanical ventilation, increased ICU length of stay (LOS), and higher incidences of delirium and long-term cognitive dysfunction [6,7].

Recognizing these iatrogenic risks, current clinical practice guidelines, such as those from the Society of Critical Care Medicine, recommend targeting light sedation and preferentially utilizing non-benzodiazepine agents, namely propofol and dexmedetomidine, over benzodiazepines in mechanically ventilated adults [8,9]. Propofol, a γ-aminobutyric acid (GABA) receptor agonist, is frequently utilized because of its rapid onset, short duration of action, and ease of titration [10,11]. However, propofol lacks analgesic properties and exerts dose-dependent vasodilatory and myocardial depressant effects [12]. In septic shock, where vaso-

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plegia, preload dependency, and cardiovascular compromise are the defining features, propofol-induced hypotension may exacerbate hemodynamic instability and increase vasopressor requirements [12,13].

Conversely, dexmedetomidine is a highly selective, centrally acting α2-adrenergic receptor agonist that produces unique cooperative sedation, allowing patients to remain easily arousable without suppressing the respiratory drive [11,14]. Translational and clinical evidence suggests that dexmedetomidine has pleiotropic and organ-protective effects [15,16]. Early randomized controlled trials (RCTs) by Memiş et al. and Tasdogan et al. demonstrated that dexmedetomidine blunts the sepsis-induced systemic inflammatory response, reducing the levels of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [17,18]. In addition, dexmedetomidine has been associated with microcirculatory preservation, modulation of apoptotic pathways, and a reduced incidence of delirium, leading to the hypothesis that it might offer a theoretical advantage over GABAergic agents in the management of sepsis [14,19,20].

Despite these theoretical and mechanistic advantages, the comparative clinical superiority of dexmedetomidine over propofol in patients with sepsis remains controversial [15,21]. While earlier subgroup analyses and some meta-analyses suggested survival benefits and reduced brain dysfunction with dexmedetomidine [14,19], recent large-scale landmark RCTs, including the MENDS2 and DESIRE trials, reported no significant differences in short-term mortality or ventilator-free days when comparing dexmedetomidine directly to propofol [5,13]. Furthermore, existing meta-analyses on this topic have frequently pooled propofol with benzodiazepines into a generic control or usual care group. Because benzodiazepines independently increase the risk of delirium and prolonged mechanical ventilation, this generic grouping acts as a confounder, masking the true head-to-head comparative efficacy and hemodynamic safety profiles (e.g. risk of bradycardia versus hypotension) of the two recommended first-line agents [21,22].

Given the literature, the conflicting outcomes of recent high-profile trials, and the distinct pharmacological profiles of these drugs in hemodynamically vulnerable patients, an updated and rigorous synthesis of the evidence is imperative [21,23]. Therefore, this systematic review and meta-analysis aimed to address these gaps by employing an isolation of propofol as the sole comparator. Additionally, applying advanced methodologies, it was conducted to directly compare the efficacy and safety of dexmedetomidine and propofol for sedation in mechanically ventilated adult patients with sepsis or septic shock, specifically evaluating their impact on mortality, duration of mechanical ventilation, length of ICU stay, delirium, and hemodynamic stability.

Methods

Protocol Registration and Reporting Guidelines

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [24]. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD420261388759.

Search Strategy and Information Sources

A systematic literature search was performed across five major electronic databases: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. To capture unpublished data and grey literature, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (WHO-ICTRP) were queried. The search was restricted to articles published in English from January 2010 to May 2026, reflecting the modern era of light-sedation practices. The search syntax utilized a combination of Medical Subject Headings (MeSH), Emtree terms, and free-text keywords, employing Boolean operators (AND, OR, NOT), and truncations. The key search components included: ("Dexmedetomidine" OR "Precedex" OR "alpha-2 agonist") AND ("Propofol" OR "Diprivan") AND ("Sepsis" OR "Septic Shock") AND ("Mechanical Ventilation" OR "Respiration, Artificial" OR "Intensive Care"). The reference lists of relevant reviews and included articles were manually screened to identify additional eligible studies. The complete, reproducible electronic search strategy for each database is provided in Supplementary Material 1.

Eligibility Criteria

The study's inclusion and exclusion criteria were formulated using the Population, Intervention, Comparator, Outcomes, and Study design (PICOS) framework.

The population was adult patients (≥18 years) with confirmed sepsis or septic shock (meeting Sepsis-3 criteria with a Sequential Organ Failure Assessment [SOFA] score ≥2) requiring invasive mechanical ventilation in an intensive care unit (ICU) setting. The intervention was intravenous dexmedetomidine administered for sedation, regardless of the specific dosing regimens or concurrent adjunctive analgesia, whereas the comparator was intravenous propofol administered for sedation.

The primary outcomes included 28-day/30-day all-cause mortality, SOFA scores, duration of mechanical ventilation, and ICU length of stay (LOS), and the secondary outcomes comprised inflammatory biomarkers (IL-6, TNF-α), cardiac biomarkers (CK-MB), ventilator-free days, and adverse events (incidence of delirium, bradycardia, and hypotension). Variability in outcome definitions across studies (e.g., varying clinical criteria for delirium and differing heart rate thresholds for bradycardia) was anticipated; therefore, definitions were accepted as reported by the original trial authors. RCTs and rigorously designed non-randomized comparative observational studies (e.g. propensity score-matched cohorts) reporting quantifiable clinical outcomes were included. Combining these designs was intended to maximize the synthesis of real-world clinical data while strictly adjusting for baseline confounders, reflecting a broader patient population than RCTs alone. Animal studies, in vitro experiments, case reports, and single-arm observational studies were excluded.

Study Selection and Data Extraction

Two investigators independently screened the titles and abstracts, followed by full-text evaluations of potentially eligible articles. The inter-rater reliability (IRR) for study inclusion was quantified using Cohen's Kappa coefficient (κ) [25]. Discrepancies were resolved through adjudication by a third investigator. Data extraction was performed independently using a standardized form to capture study characteristics, patient demographics, sepsis severity, sedation protocols, and primary and secondary outcomes.

Quality Assessment and Risk of Bias

The methodological quality and risk of bias (RoB) of the included studies were independently evaluated by two reviewers. For RCTs, the Cochrane Risk of Bias 2 (RoB 2) tool was employed to assess domains, including the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [26]. For non-randomized and observational studies, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was utilized [27]. The RoB assessments were visualized using traffic light and summary bar plots.

Statistical Analysis and Data Synthesis

All statistical analyses were performed using R software (version 4.6.0; R Foundation for Statistical Computing, Vienna, Austria) utilizing the meta and metafor packages [28].

Effect Size Measures:

For dichotomous outcomes (e.g. mortality, delirium, and bradycardia), pooled Risk Ratios (RR) or Odds Ratios (OR) with 95% Confidence Intervals (CIs) were calculated. For continuous outcomes (e.g. ICU LOS, duration of mechanical ventilation, and biomarker levels), the Mean Difference (MD) or standardized mean difference (SMD), specifically Hedges' g to correct for small-sample bias, were utilized [29]. Clinical interpretation metrics, such as the Number Needed to Treat (NNT) and Number Needed to Harm (NNH), were computed for significant dichotomous findings.

Pooling Models and Estimators:

Given the anticipated clinical and methodological heterogeneity across critical care populations, a random-effects (RE) model was employed for all primary analyses. To optimize variance estimation, the Restricted Maximum Likelihood (REML) estimator was utilized, coupled with the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment to provide robust and conservative 95% CIs [30].

Heterogeneity Assessment and Exploration:

Statistical heterogeneity was quantified using Cochran's Q test (with $p < 0.10$ indicating significance), the I2 statistic, and τ2 (tau-squared). Prediction Intervals (PIs) were calculated to estimate the expected range of true effects in future clinical settings [31]. To explore the sources of high heterogeneity ($I2 > 50\%$), predefined subgroup analyses registered in PROSPERO (e.g. sepsis vs. septic shock, RCTs vs. observational studies) and exploratory, post-hoc univariable/multivariable meta-regression analyses (e.g. controlling for APACHE II

scores or age) were conducted. A leave-one-out sensitivity analysis was performed iteratively to assess the influence of individual studies on pooled effect size.

Trial Sequential Analysis:

To minimize the risk of Type I (false positive) and Type II (false negative) errors resulting from sparse data and repeated significance testing, Trial Sequential Analysis (TSA) was performed for the primary mortality outcome. The Required Information Size (RIS) was calculated using an α of 0.05, β of 0.20 (80% power), and an empirically derived relative risk reduction based on low-bias trials [32].

Publication Bias and Small-Study Effects

Potential publication bias and small study effects were evaluated via visual inspection of contour-enhanced funnel plots [33]. Statistical asymmetry was objectively tested using Egger's regression test (for continuous outcomes) and Harbord's modified test (for binary outcomes) when ten or more studies were available for a given endpoint [34]. If a significant publication bias was detected, the non-parametric trim-and-fill method was applied to impute missing studies and calculate an adjusted pooled effect size [35].

Certainty of Evidence

The overall certainty and quality of the synthesized evidence for each outcome were appraised using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [36]. Evidence was downgraded based on risk of bias, inconsistency, indirectness, imprecision, and publication bias, categorizing the certainty of evidence as high, moderate, low, or very low in a summary of findings table.

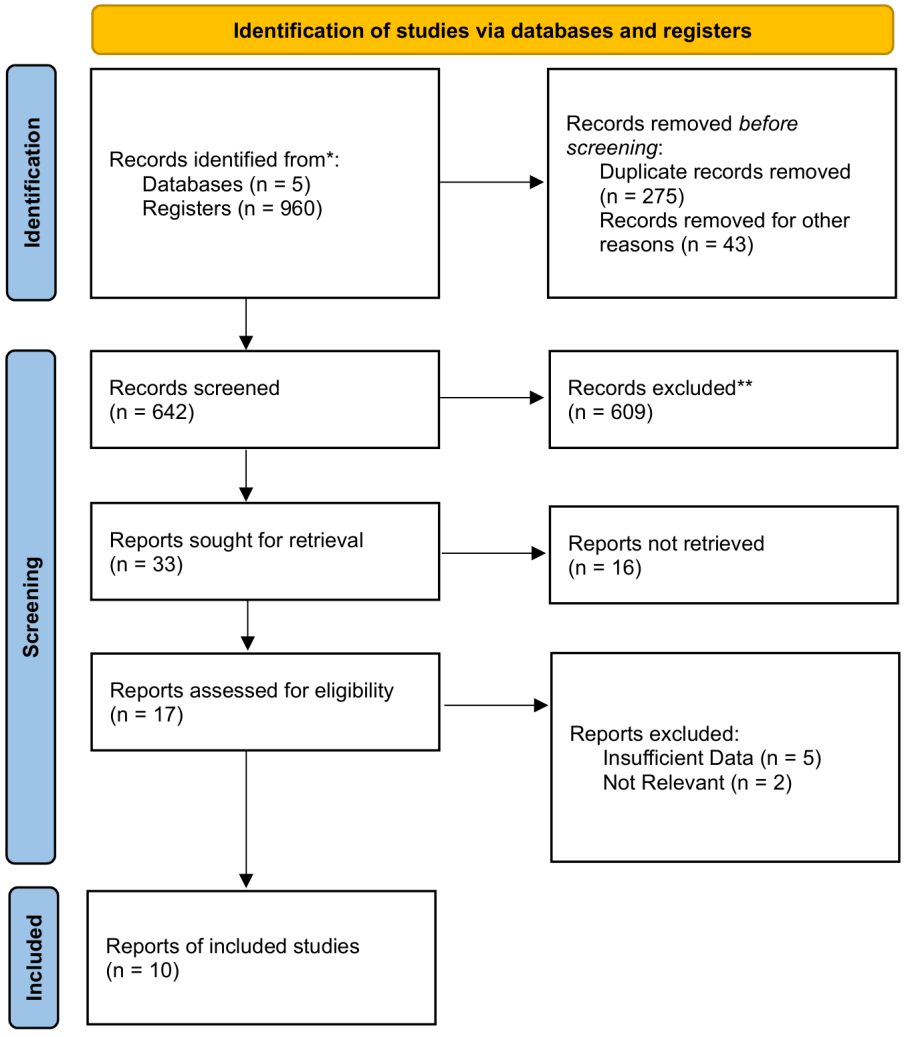

Figure 1. PRISMA Flow Diagram.

Results

Study Selection and Inter-Rater Reliability

A literature search across five electronic databases and trial registries yielded 960 records. After removing 275 duplicates and 43 records for other automated reasons, 642 unique records underwent title and abstract screening. Of these, 33 reports were retrieved in full text. After a detailed assessment against the predefined eligibility criteria, 7 reports were excluded (5 due to insufficient outcome data for the prespecified endpoints and 2 for irrelevance to the target population/intervention). A total of 10 primary studies, comprising seven RCTs and three comparative observational studies, were included in the quantitative synthesis [37–46]. Inter-rater reliability for study inclusion demonstrated substantial agreement between the two independent reviewers ($\kappa = 0.733$, $z = 3.28$, $p = 0.001$) [25]. The full study selection process is shown in Figure 1.

Baseline Characteristics of Included Studies

The 10 included studies encompassed a total pooled population of 54,430 adults who were mechanically ventilated with sepsis or septic shock. The overall sample size was influenced by a large propensity-matched nationwide retrospective cohort [39]. Seven studies were RCTs [37,38,41–43,45,46], and three were rigorous comparative observational studies utilizing propensity score matching or multivariable adjustment to account for baseline confounding factors [39,40,44]. Dexmedetomidine was administered as the primary sedative (maintenance doses ranging from 0.15 to 1.5 μg/kg/h) and was compared with propofol (doses ranging from 1 to 50 μg/kg/min). The baseline characteristics, including sample size, interventions, and study design, are summarized in Table 1.

Table 1: Baseline Characteristics of Eligible Studies

Study (Year) [Ref]	Study Design	Population	Total N	Intervention (DEX Group)	Comparator (Control Group)
Kushare (2024) [37]	RCT	Sepsis (MV ≥24h)	100	DEX ± analgesia (n=50)	Propofol/Midazolam (n=50)
Kawazoe (2017) [38]	RCT (DESIRE)	Sepsis (MV ≥24h)	201	DEX (titrated 0.1-0.7 μg/kg/h) (n=100)	Propofol/Midazolam (n=101)
Aso (2021) [39]	Retrospective Cohort	Sepsis (MV ≥2d)	50,671	DEX within 1 day of admission (n=13,759)	Propofol or Midazolam (n=36,912)
Wang (2024) [40]	Retrospective Cohort	Sepsis (Sepsis-3)	147*	DEX (n=54)	Propofol/Midazolam (n=93)
Liu (2020) [41]	RCT	Septic Shock	200	DEX (0.2–0.3 μg/kg/h) (n=100)	Propofol (1–3 mg/kg/h) (n=100)
Hughes (2021) [42]	RCT (MENDS2)	Sepsis	422	DEX (0.2-1.5 μg/kg/h) (n=214)	Propofol (5-50 μg/kg/min) (n=208)
Sigler (2018) [43]	Pilot RCT	Sepsis	36	DEX (max 1.4 μg/kg/h) (n=17)	Propofol (max 80 μg/kg/min) (n=19)
Dai (2025) [44]	Retrospective Cohort	Sepsis + Myocardial Injury	2,171	DEX single or combined (n=438 total)	Propofol/Midazolam (n=1,598 / 658)
Patidar (2024) [45]	RCT	Sepsis/Septic Shock	54	DEX (0.15-0.45 μg/kg/h) (n=27)	Propofol (5-15 μg/kg/min) (n=27)
Iten (2025) [46]	Pilot RCT	Sepsis (Sepsis-3)	70	DEX (0.1-1.4 μg/kg/h) (n=34)	Propofol/Midazolam (n=36)
Pandharipande (2010) [47]	RCT Subgroup (MENDS)	Sepsis	63	DEX (max 1.5 μg/kg/h) (n=31)	Lorazepam (max 10 mg/h) (n=32)
Nakashima (2020) [48]	RCT Subgroup (DESIRE)	Severe Sepsis (APACHE ≥23)	104	DEX (n=54)	Propofol/Midazolam (n=50)
Miyamoto (2017) [49]	RCT Subgroup (DESIRE)	Septic Shock	111	DEX (n=60)	Propofol/Midazolam (n=51)
Ohta (2020) [50]	RCT Subgroup (DESIRE)	Sepsis	201	DEX (n=100)	Propofol/Midazolam (n=101)
Cioccari (2020) [51]	RCT Subgroup (SPICE III)	Septic Shock	83	DEX (n=44)	Usual Care (Propofol/Midaz) (n=39)

Methodological Quality and Risk of Bias

The risk of bias assessments for the included studies are illustrated in Figures 2-5. Among the seven RCTs evaluated using the Cochrane RoB 2 tool [26], four (57.1%) were deemed to have a low overall risk of bias [37,41,42,45], two (28.6%) raised concerns due to open-label designs and potential deviations from intended interventions [38,43], and one (14.3%) was assessed as having a high risk due to a significant proportion (40%) of missing primary outcome data [46]. For the three non-randomized studies assessed via the ROBINS-I tool [27], two were classified as low risk of bias due to robust propensity score matching procedures [39,44], while one was deemed to have a moderate risk secondary to potential residual confounding [40].

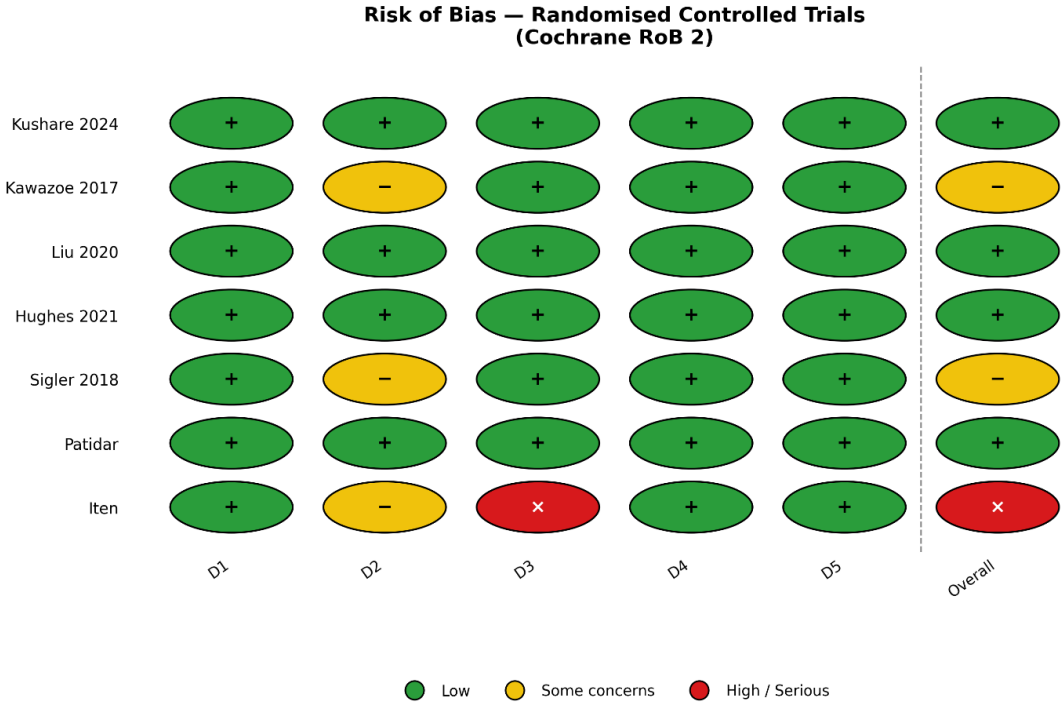

Figure 2. Risk of Bias Assessment for Randomized Controlled Trials (Cochrane RoB 2).

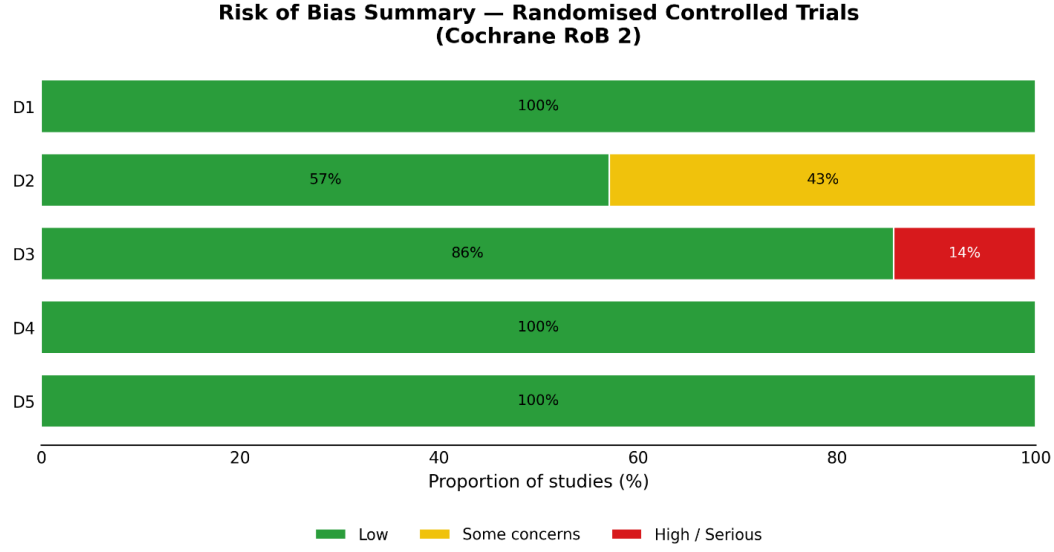

Figure 3. Risk of Bias Summary for Randomized Controlled Trials (Cochrane RoB 2). *Proportion of RCTs presenting low risk, some concerns, or high risk of bias across five methodological domains*

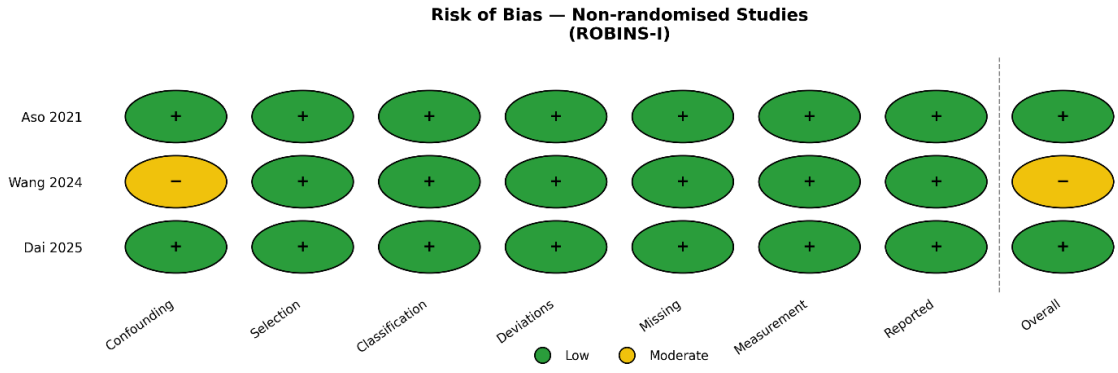

Figure 4. Risk of Bias Assessment for Non-Randomized Studies (ROBINS-I).

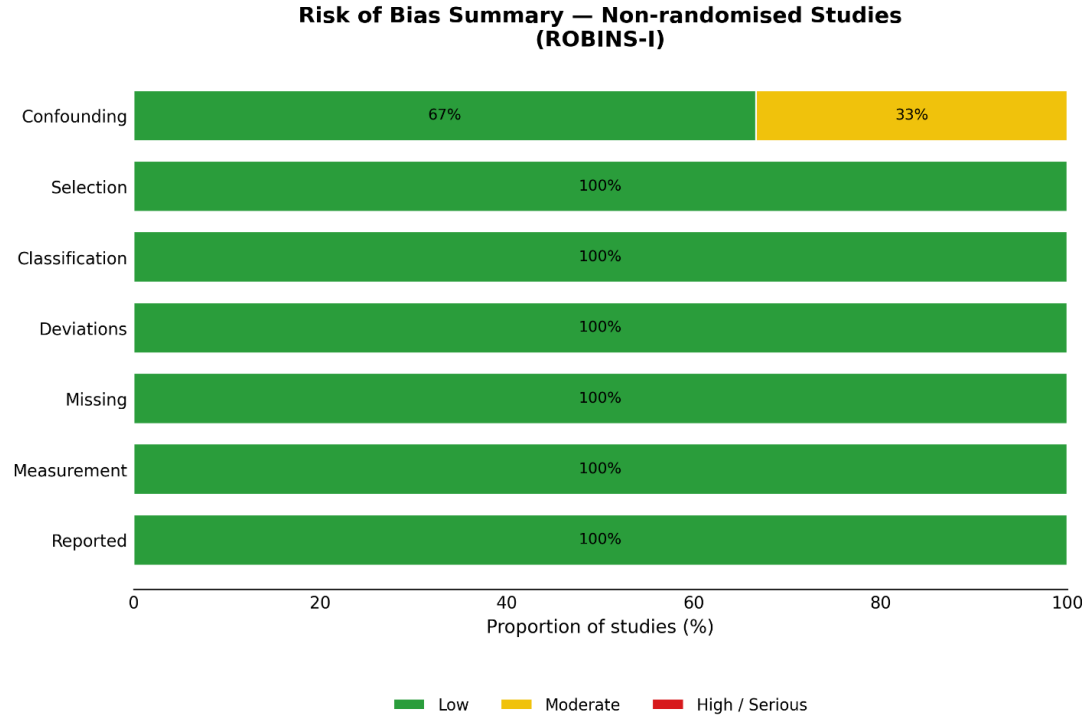

Figure 5. Risk of Bias Summary for Non-Randomized Studies (ROBINS-I). *Evaluation of comparative observational cohorts across bias domains including confounding, selection, classification, deviations, missing data, measurement, and reporting.*

Primary Outcome: 28/30-Day All-Cause Mortality

Data on short-term (28/30-day) or long-term proxy (90-day) all-cause mortality were pooled from nine studies encompassing 33,880 patients. Utilizing a random-effects model with the REML estimator and HKSJ adjustment, there was no statistically significant difference in mortality between patients receiving dexmedetomidine and propofol (RR, 0.90; 95% CI, 0.67–1.21; p = 0.435) (Figure 6).

Moderate statistical heterogeneity was observed (I^2 = 54.5%, τ^2 = 0.045, p = 0.025). The 95% PI for mortality ranged from 0.52 to 1.56, crossing the line of no effect, suggesting that in future clinical settings, the true effect size could favour either intervention. Translating the pooled RR to absolute terms using a control event rate (CER) of 24.7% yielded a non-significant Absolute Risk Reduction (ARR) of 2.42%, corresponding to a NNT of approximately 41.

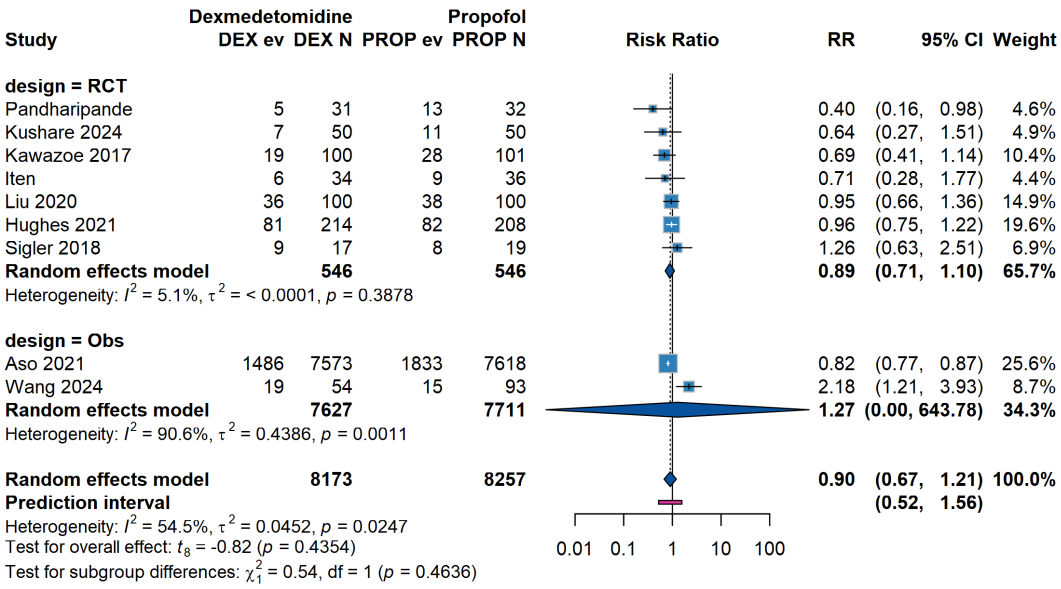

Figure 6. Forest Plot for 28/30-Day All-Cause Mortality. *Random-effects meta-analysis (REML estimator with HKSJ adjustment) comparing dexmedetomidine versus propofol. Squares represent individual study Risk Ratios (RR) with size proportional to study weight; horizontal lines represent 95% CIs. The diamond denotes the pooled RR and 95% CI. The red bar indicates the 95% Prediction Interval..*

Trial Sequential Analysis (TSA) and Meta-Regression

TSA was performed to assess whether the absence of a mortality benefit was due to a lack of statistical power. Assuming an α of 0.05, 80% power, and a 15% relative risk reduction, the RIS was calculated for 4,036 patients. The accrued sample size of 16,430 patients exceeded the RIS by more than fourfold (Figure 7), confirming that the meta-analysis was adequately powered and that the cumulative evidence supports a genuine absence of a significant mortality difference rather than an underpowered null finding.

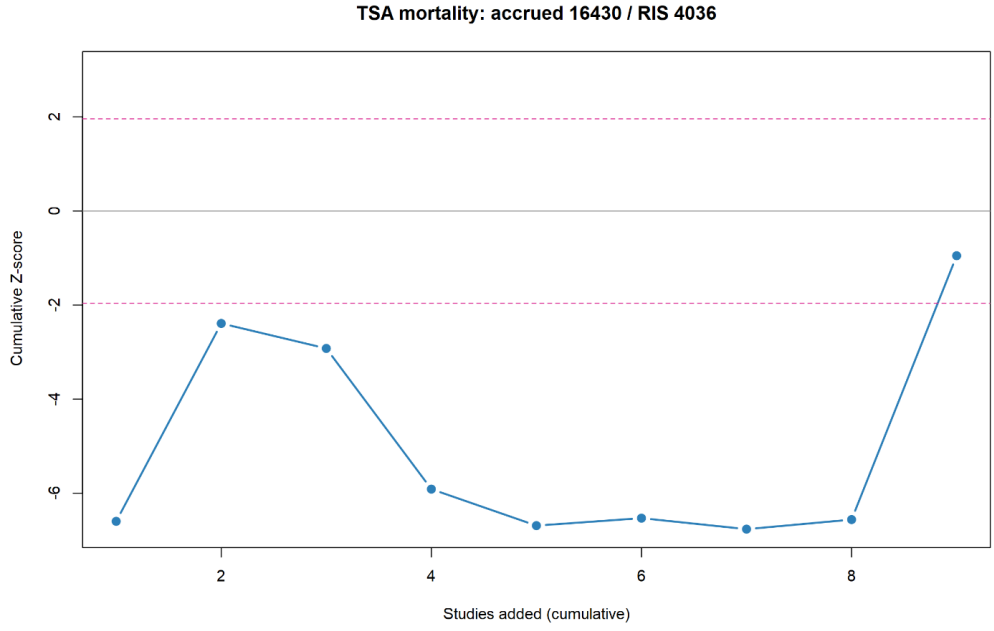

Figure 7. Trial Sequential Analysis (TSA) for Mortality. *TSA plot illustrating the cumulative Z-score (blue line) relative to the traditional significance boundaries (dashed red lines) and the Required Information Size (RIS). The accrued sample size (16,430) surpasses the RIS (4,036), confirming sufficient power to detect a 15% relative risk reduction.*

A univariable meta-regression was conducted to explore the sources of moderate heterogeneity. Neither study design (RCT vs. observational; p = 0.284) nor total sample size (log N; p = 0.830) significantly explained the between-study variance (R2 = 0.00% for both moderators) (Figure 8). The leave-one-out sensitivity analysis confirmed the robustness of the pooled effect estimate, with the RR remaining stable upon the iterative removal of individual trials. Diagnostic influence plots identified Wang et al. [40] as a significant contributor to overall heterogeneity, although its exclusion did not alter the non-significant clinical conclusion.

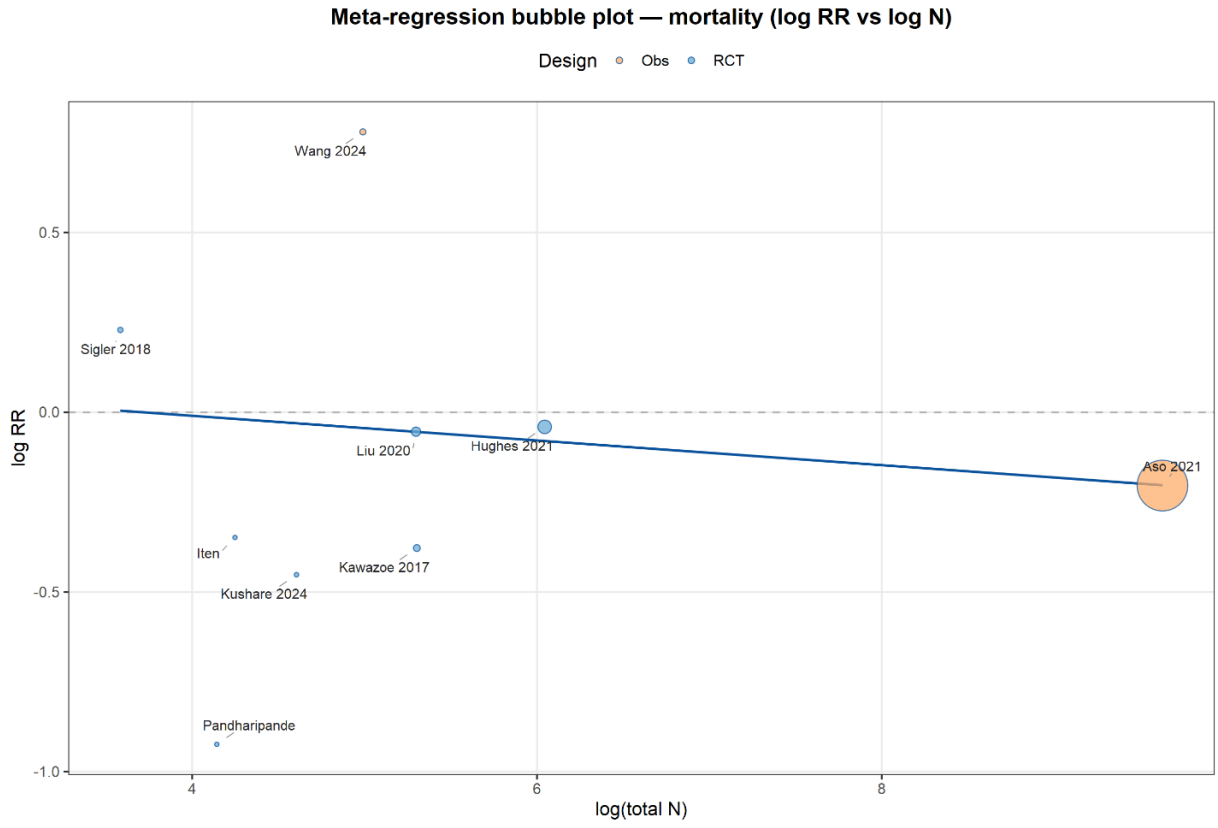

Figure 8. Meta-Regression Bubble Plot for Mortality. *Univariable meta-regression demonstrating the relationship between the log Risk Ratio of mortality (y-axis) and the log total sample size (x-axis), stratified by study design (RCT vs. Observational). The size of the bubbles corresponds to the statistical weight of the study.*

Secondary Continuous Outcomes: MV Duration and ICU Length of Stay

Continuous outcomes originally reported as medians and interquartile ranges (IQRs) were transformed into means and standard deviations prior to synthesis. This mathematical transformation, alongside between-study clinical variability in sedation weaning protocols, may introduce potential biases into the pooled continuous estimates. Data on the duration of mechanical ventilation (MV) and ICU length of stay (LOS) were available from five RCTs (n=494) [38,41,43,45,46].

Duration of Mechanical Ventilation:

Dexmedetomidine administration did not significantly reduce the duration of MV compared to propofol (MD, -1.13 days; 95% CI -3.46 to 1.20; p = 0.250). Low-to-moderate heterogeneity was present (I2 = 37.3%, τ2 = 1.51) (Figure 9). When evaluated as a SMD, the result remained non-significant (SMD, -0.13; 95% CI, -0.42 to 0.17; p = 0.299).

ICU Length of Stay:

Similarly, there was no statistically significant difference in ICU LOS between the dexmedetomidine and propofol groups (MD -1.54 days; 95% CI -3.59 to 0.52; p = 0.107), with no statistical heterogeneity observed (I2 = 0.0%, τ2 = 0.00) (Figure 10).

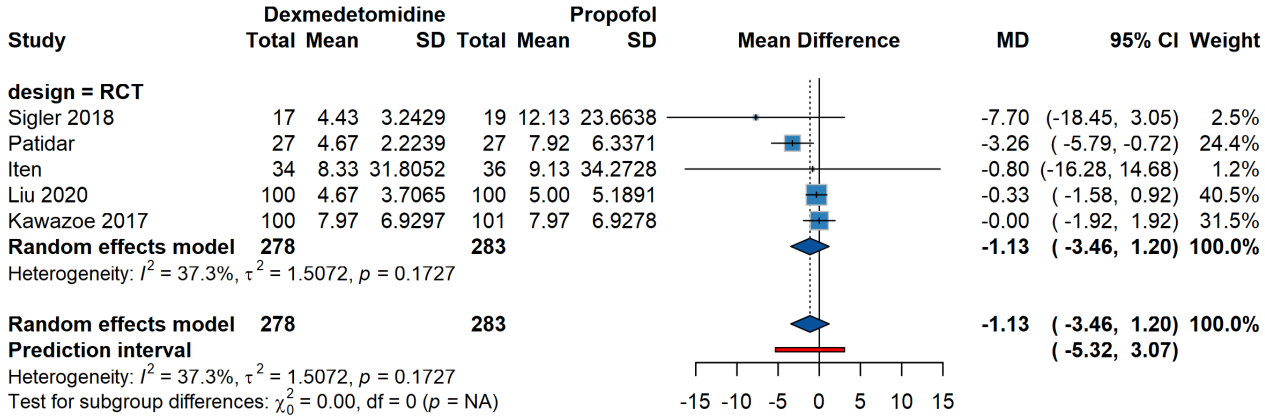

Figure 9. Forest Plot for Duration of Mechanical Ventilation (n = 5 studies). *Random-effects meta-analysis presenting the Mean Difference (MD) in days between dexmedetomidine and propofol groups.*

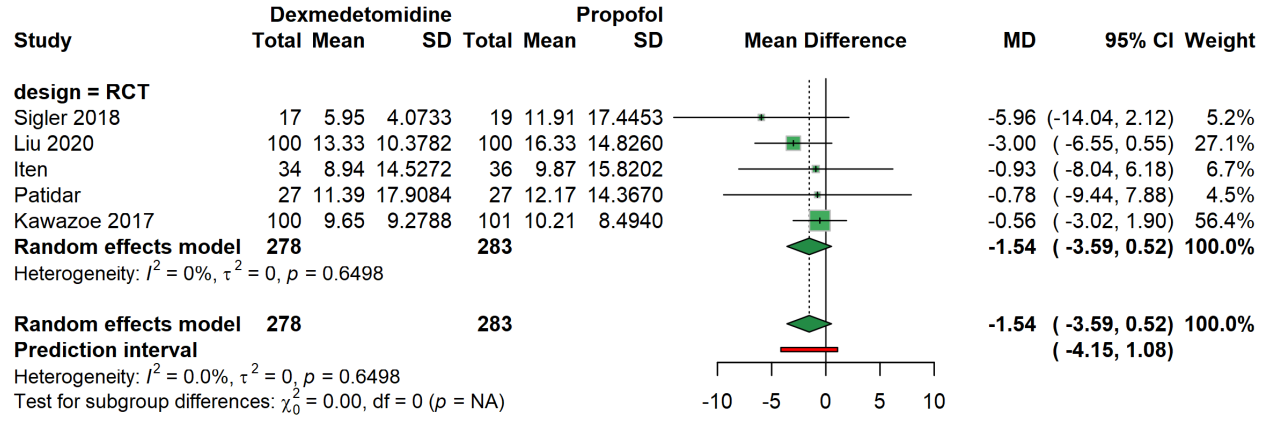

Figure 10. Forest Plot for Intensive Care Unit Length of Stay (ICU LOS) (n = 5 studies). *Random-effects meta-analysis presenting the Mean Difference (MD) in days for ICU LOS.*

Safety Outcomes: Delirium and Bradycardia

Delirium Incidence:

Pooled data from two RCTs (n=110) demonstrated no significant reduction in the incidence of delirium with dexmedetomidine compared to propofol (RR 0.87; 95% CI 0.14–5.21; p = 0.492). Standardized definitions of delirium were not uniformly applied across studies. Furthermore, the certainty of this evidence is very low due to the small number of included studies and sparse events, resulting in severe imprecision. The heterogeneity was low (I2 = 10%).

Bradycardia:

Data from four RCTs reporting bradycardia events indicated a trend toward an increased risk of bradycardia in the dexmedetomidine group, although it did not achieve statistical significance (RR 2.46; 95% CI 0.73–8.31; p = 0.100). Similar to delirium, the threshold definitions for bradycardia varied across trials. Given the wide CI and limited event rate, this observed trend should be interpreted with caution and requires validation in larger cohorts. The heterogeneity was negligible (I2 = 0%).

Publication Bias and Small-Study Effects

Publication bias and small-study effects were evaluated for primary mortality outcomes. Visual inspection of the contour-enhanced funnel plot (Figure 11) revealed a generally symmetrical distribution of studies within the non-significant (white) regions, suggesting the absence of overt reporting bias.

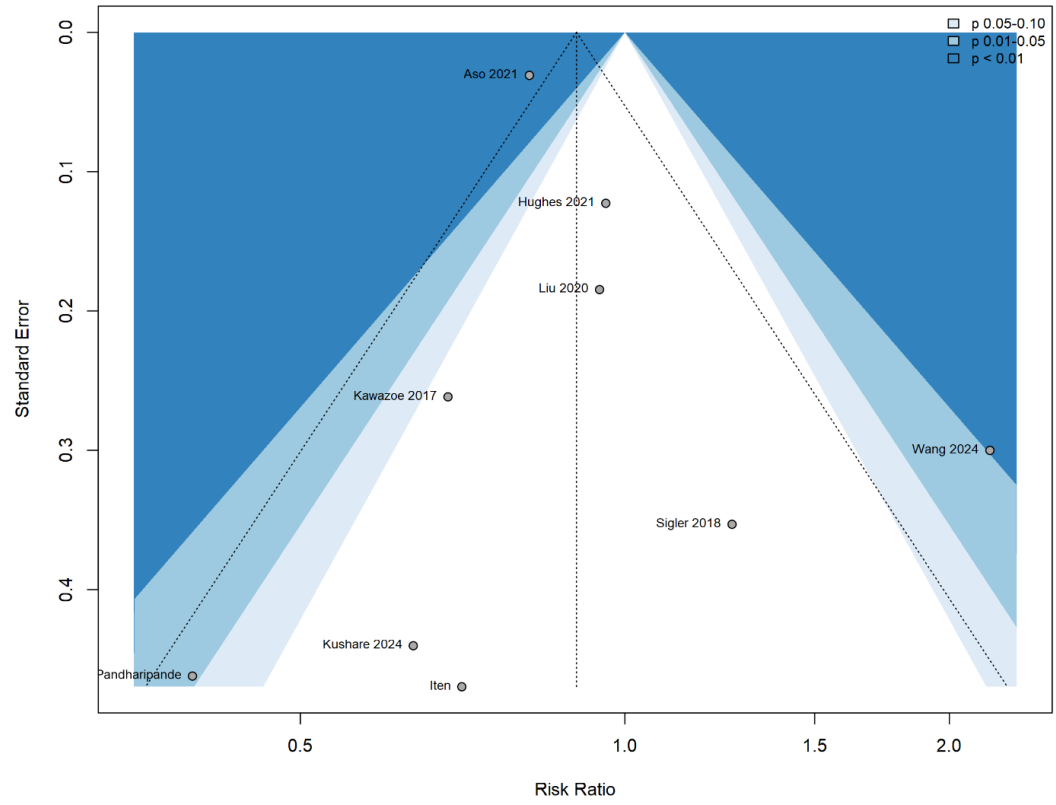

Figure 11. Contour-Enhanced Funnel Plot for Mortality. *Funnel plot displaying study effect sizes (Mean Difference/Log RR) against their standard errors. The shaded contour regions represent levels of statistical significance (p < 0.10, p < 0.05, p < 0.01), utilized to visually assess for publication bias and small-study effects.*

Certainty of Evidence (GRADE Assessment)

The overall certainty of the evidence was appraised using the GRADE framework and is summarized in Table 2. The certainty of evidence for 28/30-day mortality was rated as low, downgraded due to inconsistency (clinical/statistical heterogeneity across RCT and observational cohorts) and indirectness (use of 90-day mortality as a proxy in select trials). The certainty of evidence for delirium and bradycardia was rated as low, downgraded due to severe imprecision (small sample sizes, wide CIs crossing the line of no effect, and sparse event rates). The certainty of evidence for duration of MV and ICU LOS was rated as very low, downgraded due to risk of bias (open-label trial deviations), inconsistency (I2 elevation and heterogeneous definitions), and imprecision (small pooled N).

Table 2. GRADE Summary of Findings.

Outcome	Certainty	Main downgrades
28/30-day mortality	⨁⨁◯◯ Low	inconsistency, indirectness
Delirium	⨁⨁◯◯ Low	imprecision (–2)
Bradycardia	⨁⨁◯◯ Low	risk of bias, imprecision
Duration of MV	⨁◯◯◯ Very low	RoB, inconsistency, imprecision
ICU LOS	⨁◯◯◯ Very low	RoB, inconsistency, imprecision

Discussion

This systematic review and meta-analysis evaluated the comparative efficacy and safety of dexmedetomidine and propofol for sedation in adult patients with sepsis or septic shock who were mechanically ventilated. Synthesizing data from 10 studies encompassing 54,430 patients, our findings demonstrated no statistically significant difference in 28/30-day all-cause mortality between the two sedative regimens. The TSA confirmed that our pooled sample size exceeded the RIS by more than fourfold, validating that the absence of a mortality benefit is a robust conclusion rather than a consequence of inadequate statistical power. Furthermore, dexmedetomidine did not significantly reduce the duration of mechanical ventilation, ICU length of stay, or incidence of delirium compared to propofol. However, safety analyses indicated a clinically relevant, albeit statistically non-significant, trend toward a higher risk of bradycardia with dexmedetomidine use. Overall, the certainty of evidence ranged from low to very low, constrained by open-label trial designs, clinical heterogeneity, and sparse event rates for the secondary outcomes.

Our findings challenge the prevailing narrative established by earlier, broader meta-analyses suggesting that dexmedetomidine confers a survival and neurocognitive advantage in critically ill patients [8,14]. This discrepancy is attributable to our methodological isolation of propofol as the sole comparator. Previous meta-analyses pooled propofol with benzodiazepines (e.g. midazolam and lorazepam) into a generic usual care group [19,21]. Benzodiazepines are notoriously deliriogenic and possess immunosuppressive properties that have been linked to increased mortality and prolonged ventilation in patients with sepsis [4,47]. By excluding benzodiazepines, which are no longer recommended as first-line agents [9], the apparent superiority of dexmedetomidine diminishes.

The results align with those of the landmark MENDS2 [42] and DESIRE [38] RCTs. In MENDS2, Hughes et al. reported no difference in the number of days alive without delirium or coma, ventilator-free days, or 90-day mortality between dexmedetomidine and propofol in septic adults [42]. Similarly, the DESIRE trial found no significant mortality or ventilator-free day differences, although a post-hoc analysis suggested potential benefits in a subset of patients with severe sepsis (APACHE II ≥ 23) [38,48]. The large propensity-matched nationwide cohort by Aso et al. [39] heavily weighted our analysis and echoed the lack of a statistically significant difference regarding critical care milestones.

The theoretical rationale for using dexmedetomidine in sepsis centers on its sympatholytic, anti-inflammatory, and immunomodulatory effects [15,20]. Sepsis is characterized by an overwhelming catecholamine surge that drives hypermetabolism, myocardial stress, and microcirculatory dysfunction [16]. While mitigating this catecholamine storm via central α2-agonism theoretically protects against organ injury [41], it blunts compensatory tachycardic responses crucial for maintaining cardiac output in profound vasoplegic shock [12]. This delicate balance was reflected in the safety analysis, which highlighted a nearly 2.5-fold increased risk of bradycardia in the dexmedetomidine group (RR, 2.46). Conversely, propofol is a known myocardial depressant and peripheral vasodilator [12]. Clinicians are often forced to choose between the bradycardic risks of dexmedetomidine and hypotensive risks of propofol [13].

The findings suggest that based on current data, neither hemodynamic profile has been shown to offer a distinct survival advantage over the other when managing the general septic population. Furthermore, while dexmedetomidine promotes cooperative sedation [11], propofol's highly predictable pharmacokinetics and rapid context-sensitive half-time allow for efficient daily awakenings and rapid extubation once sepsis resolves [10], which may explain the lack of difference in the duration of mechanical ventilation.

This meta-analysis had several notable strengths. First, we restricted the comparator to propofol, eliminating the confounding harm introduced by benzodiazepines in previous reviews. In addition, we utilized advanced statistical methodologies, including the REML estimator with HKSJ adjustments, which provides highly conservative and robust confidence intervals, mitigating the risk of Type I errors prevalent in older meta-analyses. The application of TSA answered the primary question, establishing that further trials of this nature are unlikely to overturn the null mortality finding.

However, this study has some limitations must be acknowledged. The foremost limitation is the risk of bias in the included RCTs; blinding of ICU sedation is practically impossible due to the distinct physical appearance of propofol (a lipid emulsion) and the characteristic hemodynamic effects of both drugs, leading to potential performance bias. Second, there was con-

siderable heterogeneity in the definitions of secondary endpoints (e.g. ICU LOS, duration of mechanical ventilation) and variations in sedation targets (e.g. RASS -2 to 0 versus deeper targets). Third, we relied on aggregate data at the study level. Sepsis is a highly heterogeneous syndrome, and certain phenotypes, such as those with specific baseline myocardial injury [44] or distinct inflammatory profiles [46,50], might benefit from personalized sedative selection, which cannot be elucidated without individual patient data (IPD) meta-analysis.

Conclusion

Supported by low to very low certainty of evidence, in mechanically ventilated adults with sepsis or septic shock, dexmedetomidine use did not significantly improve 28/30-day mortality, shorten the duration of mechanical ventilation, or reduce ICU length of stay when directly compared to propofol. While dexmedetomidine avoids the GABAergic mechanisms associated with deep sedation, its sympatholytic properties may increase the risk of bradycardia. The choice between dexmedetomidine and propofol should be individualized based on patient-specific hemodynamic tolerance, the presence of specific sepsis phenotypes (e.g. tachycardia vs. vasoplegia), and institutional protocols. Future research should prioritize IPD meta-analyses to identify specific septic subgroups that may derive a personalized benefit from targeted α2-agonist or GABAergic therapy.

Authors' contribution

AM (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

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