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Systematic Review

Melatoninergic Agents for Delirium Prevention in Hospitalized Patients: A Systematic Review

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ABSTRACT

Background: Delirium is a common and serious neuropsychiatric syndrome among hospitalized patients, particularly in elderly and critically ill populations. Circadian rhythm disruption and sleep–wake cycle abnormalities are key pathophysiological contributors. Melatonin and its receptor agonist ramelteon have been proposed as potential preventive and therapeutic agents due to their role in circadian regulation.
Objective: To systematically review and synthesize evidence on the effectiveness of melatonin and ramelteon in the prevention of delirium in hospitalized patients.
Methods: A systematic review was conducted following PRISMA 2020 guidelines. Electronic databases (PubMed/MEDLINE, Scopus, and Google Scholar) were searched up to 2025 using predefined keywords related to melatonin, ramelteon, and delirium. Randomized controlled trials and observational studies involving hospitalized adult patients were included. Studies without delirium-related outcomes or those involving antipsychotic comparisons were excluded. A total of 302 records were identified, of which 18 studies met inclusion criteria (13 melatonin, 5 ramelteon). A qualitative synthesis was performed due to heterogeneity in study design and outcomes.
Results: Melatonin demonstrated a modest but inconsistent preventive effect, with the strongest evidence observed in elderly perioperative populations. Several randomized trials reported reduced postoperative delirium incidence, particularly in orthopaedic and cardiac surgical settings. However, large trials in ICU and general medical populations failed to show significant benefit. Ramelteon showed promising results in early studies, including a landmark trial demonstrating a substantial reduction in delirium incidence, but subsequent studies yielded mixed findings, particularly in ICU and postoperative settings.
Conclusions: Melatonin and ramelteon may have a role in delirium prevention, particularly in selected high-risk populations such as elderly perioperative patients. However, current evidence remains heterogeneous and insufficient to support routine use across all hospitalized populations. Future large-scale, well-designed trials are needed to clarify optimal dosing, timing, and target populations.

Keywords: *Delirium; Melatonin; Ramelteon; Circadian rhythm; ICU delirium; Postoperative delirium.*

INTRODUCTION

Delirium is an acute neuropsychiatric syndrome characterized by disturbances in attention, awareness, and cognition, with a fluctuating course[1]. It is highly prevalent among hospitalized patients, particularly in elderly individuals, intensive care unit (ICU) populations[2], and those undergoing major surgery. The reported incidence ranges from 10–30% in general medical wards[3] to over 50% in high-risk surgical and critically ill[2] populations. Delirium is associated with increased mortality, prolonged hospital stays, functional decline, and long-term cognitive impairment, making its prevention and management a major clinical priority[3].

The pathophysiology of delirium is multifactorial and incompletely understood, involving neurotransmitter imbalance, neuroinflammation, oxidative stress[1], and disruptions in circadian rhythms[4]. Among these, sleep–wake cycle disturbances and circadian dysregulation have emerged as key modifiable contributors. Hospital environments, particularly ICUs, are associated with factors such as noise, light exposure, frequent interventions, and sedation, all of which can impair normal circadian rhythms and precipitate delirium.

Melatonin, an endogenous hormone secreted by the pineal gland, plays a central role in regulating circadian rhythms and sleep–wake cycles. Reduced melatonin levels and altered secretion patterns have been observed in patients with delirium[4], suggesting a potential therapeutic role. Ramelteon, a selective melatonin receptor agonist (MT1 and MT2), mimics the action of endogenous melatonin with greater receptor specificity and a favourable safety profile.

Given their pharmacological properties, melatonin and ramelteon have been increasingly investigated as potential agents for delirium prevention[5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22]. Unlike antipsychotics, which have limited evidence and potential adverse effects[23], these agents offer a biologically plausible and potentially safer alternative targeting circadian dysfunction. Also melatonergic drugs may prevent emergent delirium by targeting the circadian rhythm.

However, despite growing interest, the clinical evidence remains inconsistent. While several studies report a reduction in delirium incidence[5][6][7][8][9][10][11][12][13], particularly in perioperative elderly populations[5][6][7][9], others—especially in ICU and heterogeneous medical settings—have failed to demonstrate significant benefit[14][15][16][17][18][19][20][21][22]. Variability in study design, patient populations, dosing regimens, and outcome measures has contributed to this inconsistency.

In this context, the present systematic review aims to critically evaluate and synthesize available evidence on the role of melatonin and ramelteon in the prevention of delirium in hospitalized patients, with a focus on identifying patterns of efficacy across different clinical settings and populations. The studies used conventional tools for delirium assessment like Intensive Care Delirium Screening Checklist(ICDSC)[24],Confusion assessment method(CAM)[25] and its modification CAM-ICU[26]

OBJECTIVE:
To systematically review and synthesize evidence on the effectiveness of melatonin and ramelteon in the prevention of delirium in hospitalized patients.

METHODOLOGY

Study Design
This study was conducted as a **systematic review** following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines[27] to evaluate the effectiveness of melatonin and ramelteon in the prevention or management of delirium in hospitalized patients.

Search Strategy
A systematic literature search was performed across multiple electronic databases including:

- PubMed/MEDLINE
- Scopus

The search included studies published up to **2025**.

The following keywords and Boolean operators were used:
(melatonin OR ramelteon OR melatonin receptor agonist)
AND
(delirium OR postoperative delirium OR ICU delirium OR hospital delirium)
AND
(prevention OR treatment OR prophylaxis)
Additional articles were identified by screening reference lists of relevant publications.

Study Selection Process
The study selection process followed the PRISMA framework.

- A total of 302 records were identified through database searching.
- After removal of 18 duplicate records, 284 articles remained for title and abstract screening.
- Following the initial screening, 236 articles were excluded because they were review articles, editorials, narrative reviews, or were not relevant to the study objective.
- The remaining 48 full-text articles were assessed for eligibility.

Among these:

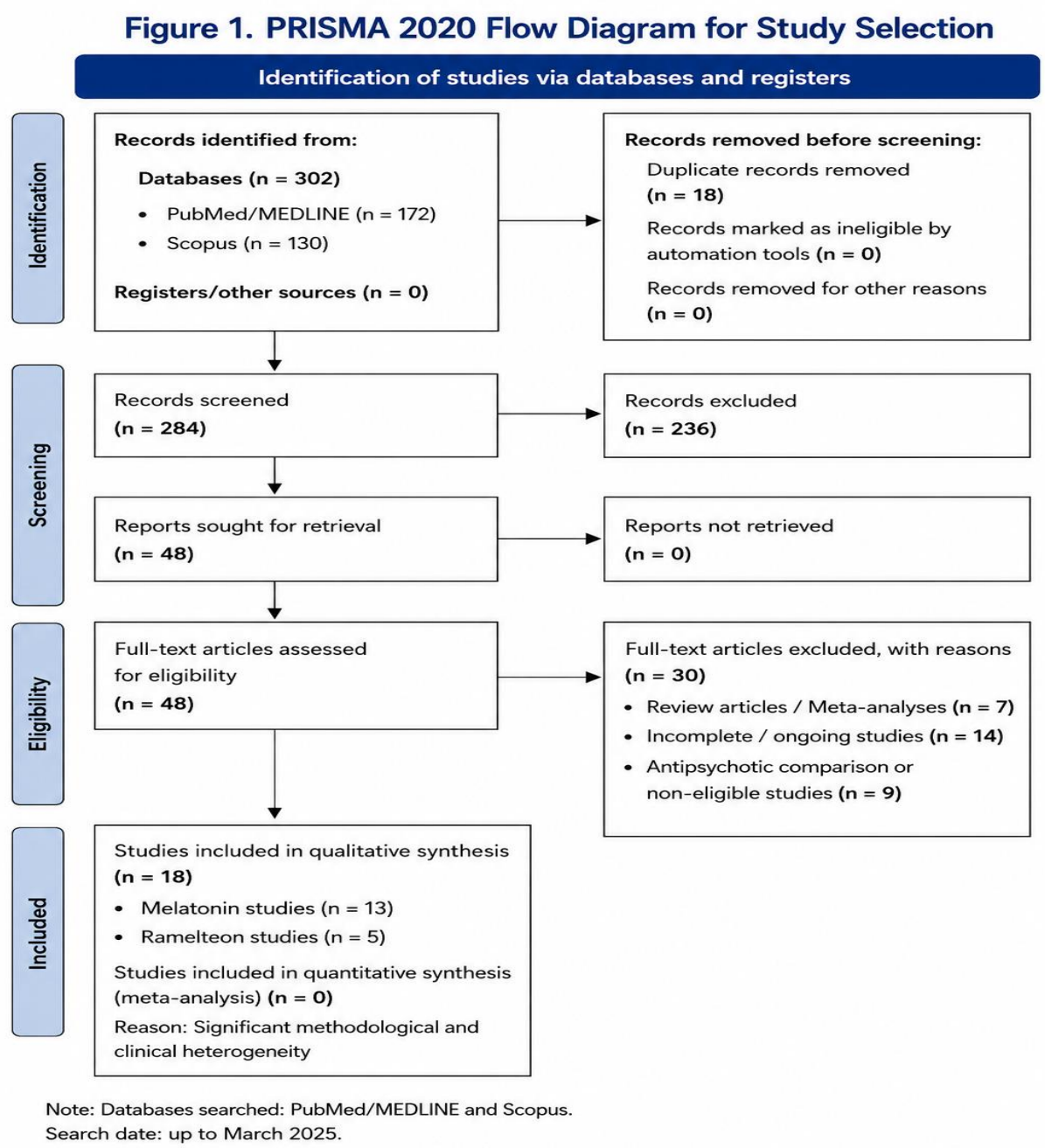
- 7 studies were review articles or meta-analyses[28][29][30][31][32][33]

- 14 studies had incomplete or ongoing results
- 9 studies compared melatonin with antipsychotics or did not meet the inclusion criteria[34][35]

After applying the eligibility criteria, 18 studies were included in the qualitative synthesis, consisting of:

- 13 melatonin studies
- 5 ramelteon studies

Of these 18 ,16 are randomised clinical trials and 2 are observation cohort studies
The study selection process is summarized in the PRISMA flow diagram (Figure 1).



Inclusion Criteria

Studies were included if they met the following criteria:

1. Original primary research studies
2. Randomized controlled trials or observational studies(Case control, cohort)
3. Studies evaluating melatonin or ramelteon
4. Studies assessing delirium prevention
5. Studies conducted in hospitalized adult patients
6. Studies published in English language

Exclusion Criteria
The following studies were excluded:

1. Narrative reviews, systematic reviews, or meta-analyses
2. Study protocols or ongoing trials without published results
3. Animal studies
4. Studies without delirium-related outcome measures

Data Extraction
Data from the included studies were extracted independently and summarized in tabular form. The following variables were recorded:

- Author name
- Year of publication
- Study design
- Sample size
- Study population
- Intervention and dosage
- Outcome related to delirium incidence or severity

Risk of Bias Assessment
The methodological quality of included studies was assessed independently by two reviewers. The following tools were used:
1)Randomized controlled trials: evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool[36]
2)Observational studies: assessed using the Newcastle–Ottawa Scale (NOS)[37]
Studies were categorized as having low, moderate, or high risk of bias. Any disagreements were resolved through discussion

Data Synthesis
A qualitative synthesis of the included studies was performed. Studies were categorized based on:

1. Type of intervention (melatonin vs ramelteon)
2. Clinical setting (perioperative, ICU, medical wards)

Due to heterogeneity in study design, population characteristics, and intervention protocols, a meta-analysis was not performed, and the findings were summarized narratively.

The overall certainty of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach[38], considering**:**

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

RESULTS
Study Selection:
The literature search identified 302 records, of which 18 duplicates were removed, leaving 284 articles for screening. Following title and abstract review, 236 studies were excluded. Of the 48 full-text articles assessed, 18studies met inclusion criteria and were included in the qualitative synthesis, comprising 13 melatonin studies and 5 ramelteon studies.

Study Characteristics:
The included studies encompassed randomized controlled trials and observational designs conducted across heterogeneous clinical settings, including perioperative surgical populations, intensive care units (ICUs), and general medical wards. Most studies enrolled older or high-risk hospitalized patients, with interventions administered either prophylactically to prevent delirium. Substantial heterogeneity was observed across studies with respect to patient populations and baseline delirium risk, timing and duration of intervention, dosing regimens, and outcome definitions and assessment tools. This heterogeneity precluded quantitative synthesis. The table(Table 1) shows the studies in detail:

Author	Year	Study design	Sample size	Population	Dose	Outcome
Sultan[6]	2010	Randomized comparative perioperative study	222 completed	Elderly hip arthroplasty under spinal anaesthesia	Melatonin 5 mg preop and postop regimen	Postoperative delirium lower in melatonin group

						(9.43%) than control (32.65%).
Al-Aama[5]	2011	Randomized double-blind placebo-controlled trial	145	Elderly medical inpatients	Melatonin 0.5 mg nightly	Reduced incident delirium versus placebo.
de Jonghe[14]	2014	Multicentre double-blind randomized controlled trial	452 planned / large hip-fracture cohort	Elderly hip-fracture surgery patients	Melatonin 3 mg nightly for 5 days	No reduction in incident delirium.
Perkisas[11]	2014	Randomized placebo-controlled trial	67	Acutely ill elderly inpatients	Ramelteon 8 mg nightly	Delirium incidence 3% vs 32%; strongly positive.
Nishikimi[12]	2018	Single-centre randomized placebo-controlled trial	88	ICU patients	Ramelteon 8 mg nightly	Reduced delirium occurrence and duration; trend to shorter ICU stay.
Jaiswal [15]	2018	Randomized clinical trial	69	Non-ICU adults hospitalised	Melatonin 3 mg nightly	Did not prevent delirium or improve sleep.
Abbasi[22]	2018	Single-centre randomized placebo-controlled trial	172	ICU adults hospitalised	Melatonin 3 mg nightly	Did not prevent delirium
Thom[21]	2019	Single-centre retrospective cohort study	322	Critically ill delirious ICU patients	Ramelteon exposure during ICU stay	Not associated with delirium-coma resolution, extubation, or mortality benefit.
Ford (Healthy Heart-Mind)[16]	2020	Randomized double-blind placebo-controlled trial	210	Major cardiac surgery	Melatonin 3 mg for 7 days	No support for prophylactic melatonin after cardiac surgery.
Shi[9]	2021	Randomized single-centre double-blind placebo-controlled trial	297	Elderly patients after PCI	Melatonin 3 mg/day for 7 days	Significant reduction in delirium incidence.
Javaherforoosh Zadeh[10]	2021	Randomized clinical trial	60	On-pump CABG patients	Melatonin 3 mg night before and after surgery	Reduced delirium incidence/severity after CABG.
Fazel[7]	2022	Randomized double-blind clinical trial	72 completed	Elderly lower-limb fracture surgery	Melatonin regimen perioperative; article reports oral melatonin	Significantly lower postoperative delirium in melatonin group.

Wibrow (Pro-MEDIC)[17]	2022	Randomized controlled trial	847	Critically ill ICU adults	Enteral melatonin started within 48 h	Did not reduce delirium prevalence.
Siokas[20]	2023	Observational propensity-matched cohort	339	Intracerebral haemorrhage stroke-unit patients	Melatonin 2 mg daily	No efficacy in preventing post-stroke delirium.
Kinouchi[19]	2023	Double-blind randomized placebo-controlled trial	108	Elderly postoperative general-anaesthesia patients	Ramelteon 8 mg	No significant difference in postoperative delirium incidence.
Elbakry[8]	2024	Randomized placebo-controlled trial	100	Colorectal CA patient's post-operative	Melatonin 5 mg	Reduced incidence of post-operative delirium in Melatonin arm
Dessap (DEMEL)[18]	2025	Multiarmed multistage adaptive randomized clinical trial	355	Mechanically ventilated ICU patients	Melatonin 0.3 mg or 3 mg nightly	May decrease postoperative delirium incidence.
Akhileshwar[13]	2025	Randomized placebo-controlled trial	60	Critically ill ICU patients	Ramelteon(dose not mentioned)	No change in delirium incidence versus placebo.

Effects of Melatonin:
Across included studies, melatonin demonstrated a modest and context-dependent preventive signal. Evidence of benefit was most consistently observed in elderly perioperative populations, where several randomized trials reported reduced incidence of postoperative delirium. These effects were typically seen in settings characterized by predictable circadian disruption and high baseline vulnerability. In contrast, larger and methodologically rigorous trials conducted in ICU and general medical populations did not demonstrate a significant reduction in delirium incidence or improvement in sleep-related outcomes. Collectively, these findings suggest that the efficacy of melatonin is not uniform across clinical settings and may depend on the relative contribution of circadian dysregulation.

Effects of Ramelteon:
The evidence base for ramelteon was limited and less consistent. A landmark randomized trial reported a substantial reduction in delirium incidence in acutely ill elderly patients, establishing early clinical interest. However, subsequent studies, including those conducted in ICU and perioperative settings, yielded heterogeneous and often non-significant results, with limited evidence of benefit on clinically relevant outcomes such as delirium duration or ICU length of stay. Overall, while ramelteon remains biologically plausible, current evidence does not support consistent efficacy across broader hospitalized cohorts.

Risk of Bias:
Risk of bias assessment indicated that the majority of randomized trials were associated with some concerns, primarily due to lack of blinding, potential bias in outcome measurement, and incomplete reporting of prespecified outcomes. Only one trial was judged to be at low risk of bias across all domains, whereas one study was assessed as high risk due to deviations from intended interventions and outcome assessment limitations. Observational studies were of moderate to good quality but were consistently limited by residual confounding, particularly inadequate adjustment for illness severity and comorbidities. Across both study designs, measurement bias and clinical heterogeneity were the dominant methodological limitations.

Table 2. GRADE Certainty of Evidence Assessment for Melatonin and Ramelteon in Delirium Prevention and Management

Clinical Question / Outcome	Study Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty	Summary of Findings

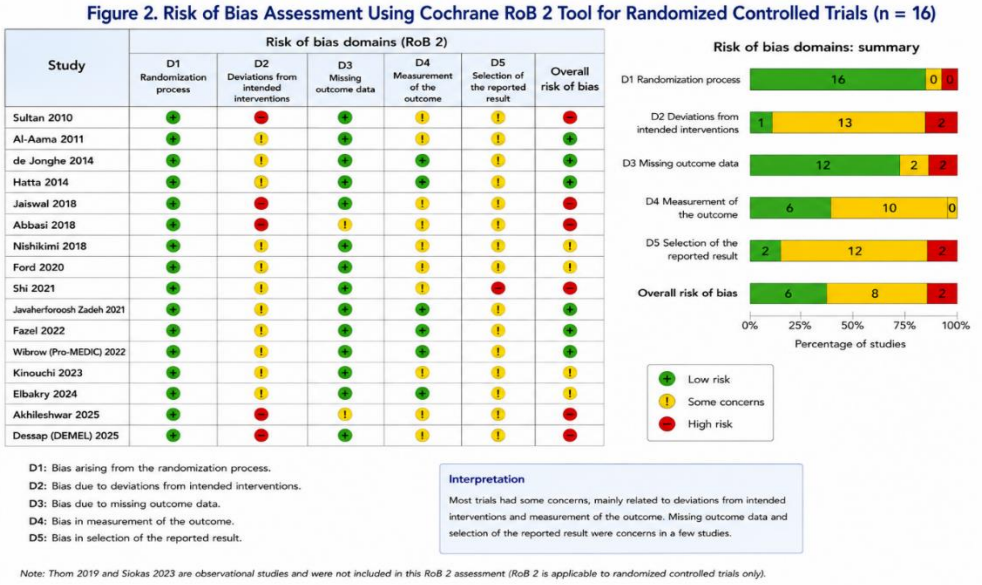
							(GRADE)	
Melatonin for prevention of postoperative delirium in elderly perioperative patients	Primarily RCTs	Serious concerns due to incomplete blinding and missing outcome data	Moderate inconsistency across surgical populations	Mild indirectness	Moderate imprecision	Possible publication bias	Moderate certainty	May reduce postoperative delirium incidence in selected elderly surgical populations.
Melatonin for delirium prevention in ICU patients	RCTs + observational studies	Serious concerns regarding performance bias and missing data	High inconsistency with several negative large trials	Moderate indirectness	Serious imprecision	Suspected publication bias	Low certainty	Current evidence does not consistently support melatonin for ICU delirium prevention.
Melatonin for delirium prevention in general medical inpatients	Mixed RCTs	Moderate risk of bias	Moderate inconsistency	Moderate indirectness	Serious imprecision	Possible publication bias	Low certainty	Evidence remains inconclusive in general hospitalized populations.
Melatonin for treatment of established delirium	Small RCTs and observational studies	Serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Likely publication bias	Very low certainty	Insufficient evidence for treatment efficacy.
Ramelteon for delirium prevention in elderly hospitalized patients	Small RCTs	Moderate risk of bias	Moderate inconsistency	Mild indirectness	Serious imprecision	Possible publication bias	Low to Moderate certainty	May reduce delirium incidence in selected elderly patients.
Ramelteon for ICU delirium prevention	RCTs + retrospective cohorts	Serious risk of bias	High inconsistency	Moderate indirectness	Serious imprecision	Suspected publication bias	Low certainty	Evidence does not consistently support ICU benefit.
Ramelteon for delirium duration/severity reduction	Small heterogeneous studies	Serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Possible publication bias	Very low certainty	Evidence insufficient to determine effect on duration or severity.

Overall evidence for melatonin and ramelteon in delirium prevention	Mixed RCTs + observational studies	Serious methodological limitations	High heterogeneity	Moderate indirectness	Moderate-to-serious imprecision	Likely publication bias	Low certainty	Possible benefit in selected high-risk populations but insufficient for routine use.

Overall Synthesis

Taken together, the available evidence suggests that melatonin may confer a modest preventive benefit in selected high-risk populations, particularly in perioperative elderly patients, whereas evidence for ramelteon remains inconclusive. However, the overall certainty of evidence is limited by methodological heterogeneity, risk of bias, and inconsistent reproducibility of findings across clinical settings, precluding definitive conclusions regarding routine use in hospitalized populations.

Figure 2. Risk of Bias Assessment Using Cochrane RoB 2 Tool for Randomized Controlled Trials (n = 16)

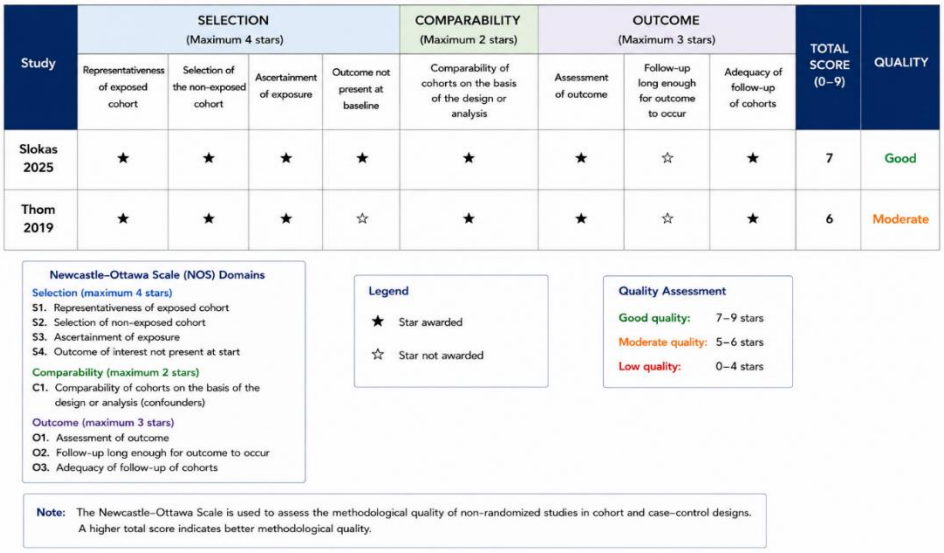


Note: Thom 2019 and Slokas 2023 are observational studies and were not included in this RoB 2 assessment (RoB 2 is applicable to randomized controlled trials only).

This is a summary using Traffic light plot(Figure 2) for assessing the Randomised clinical trials in our study which shows that most of the studies suffered from bias due to deviation from intended interventions.

For Observational Studies we used Newcastle-Ottawa scale. Figure 3 summarises the findings:

Figure 3. Newcastle–Ottawa Scale (NOS) Assessment of Observational Studies (n = 2)



SUMMARY:

Across the included literature, the strongest methodological evidence comes from large randomized placebo-controlled perioperative and ICU trials. Importantly, several of the most rigorous studies reported negative findings, particularly in ICU populations. Positive studies were more frequently smaller, single-centre, or conducted in highly selected perioperative elderly cohorts.

The most consistent methodological limitation across studies was the subjective nature of delirium assessment, introducing potential detection bias even in blinded trials. Additionally, marked clinical heterogeneity in patient populations, intervention timing, and delirium subtype reduced comparability between studies.

CONCLUSIONS:

- The certainty of evidence supporting melatonin in perioperative elderly populations is low-to-moderate.
- The certainty of evidence supporting routine ICU use is low.
- Evidence for ramelteon remains promising but insufficiently reproducible.
- Observational evidence provides supportive but non-definitive findings due to residual confounding.

Consequently, the current literature does not support universal routine use of melatonin or ramelteon for delirium prevention across all hospitalized populations, although selective use in high-risk perioperative settings remains biologically and clinically plausible.

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