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Review

Economic evaluations of pharmacological and non-pharmacological interventions for delirium: A systematic review and meta-analysis

Md Parvez Mosharaf [a,b,*], Khorshed Alam [a], Jeff Gow [a,c], Rashidul Alam Mahumud [d]

[a] School of Business, Faculty of Business, Education, Law and Arts, and Centre for Health Research, University of Southern Queensland, Toowoomba, QLD, 4350, Australia

[b] Bioinformatics Lab, Department of Statistics, University of Rajshahi, Rajshahi, 6205, Bangladesh

[c] School of Accounting, Economics and Finance, University of KwaZulu-Natal, Durban, 4000, South Africa

[d] NHMRC Clinical Trials Centre, Faculty of Medicine and Health, The University of Sydney, Camperdown, NSW, 2006, Australia

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ABSTRACT

Background: Delirium, a prevalent cognitive dysfunction in older adults, particularly in hospital and surgical settings, significantly increases patient morbidity, mortality, and healthcare costs. However, economic evaluations of healthcare interventions aimed at its prevention, management, and treatment are scant. This study synthesized the available economic evaluation evidence on both pharmacological and non-pharmacological interventions.

Methods: A systematic review was conducted on studies published from January 1, 2000, to December 31, 2023, across multiple databases, including PubMed, MEDLINE, Scopus, and EBSCOhost (CINAHL, PsycINFO, and ECOLIT). We adhered to the PICOS framework for inclusion and exclusion criteria and followed PRISMA guidelines for the analysis. The quality of the studies included was assessed using the CHEERS checklist. The meta-analysis of the cost-effectiveness of multicomponent non-pharmacological intervention was evaluated using incremental net benefits (INB).

Results: Sixteen eligible studies met the inclusion criteria including four cost-effectiveness analyses (CEA), two cost-benefit analyses (CBA), three cost-consequence analyses (CCA), and seven cost-saving/minimization analyses. The majority (14/16 studies) evaluated non-pharmacological interventions, while only two studies assessed the cost-effectiveness of drug interventions (i.e. dexmedetomidine). Besides the cost-effective multicomponent interventions, pharmacological intervention was also associated with a cost reduction of a maximum of US$4370 per patient by decreasing the length of ICU stays. The studies predominantly originated from high-income countries. The meta-analysis included four studies and pooled INB of multicomponent non-pharmacological intervention was estimated at US$8014 (95% CI=US$1,060, US$14,969; p-value<0.05) with significant heterogeneity among the studies ($I^2 = 100\%$; p-value<0.01). The pooled INB was US$2657 higher for the model-based economic evaluation studies compared to within-trial evaluation.

Conclusion: The estimated INB indicated that multicomponent non-pharmacological intervention was a cost-effective strategy to prevent and manage delirium cases which indicates improved patient outcomes and potential cost savings. Future research should focus on low-resource settings and direct comparisons of pharmacological and non-pharmacological approaches to further enhance delirium management practices.

1. Introduction

Delirium, a prevalent neuropsychiatric syndrome, disproportionately impacts older adults in hospital settings, especially those requiring mechanical ventilation. Notably, incidence rates reach up to 80% in specialized intensive care units (ICUs) and around 45% in general ICUs (Bannon et al., 2019; Marcantonio, 2017; Poulsen et al., 2021). Despite its high prevalence, delirium often remains underdiagnosed and overlooked, contributing to a significantly increased mortality risk ranging from 25 to 33% among hospitalized patients (Schnorr et al., 2022). Over

* Corresponding author School of Business, Faculty of Business, Education, Law and Arts, and Centre for Health Research, University of Southern Queensland, Toowoomba, QLD, 4350, Australia.

E-mail address: Parvez.Mosharaf@unisq.edu.au (M.P. Mosharaf).

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recent decades, the growing prevalence of delirium has emerged as a formidable challenge in delivering safe (Bruce et al., 2007), and high-quality healthcare (The Australian Commission on Safety and Quality in Health Care, 2019), accentuating the need for cost-effective management strategies within constrained healthcare resources (Mart et al., 2021).

The clinical and economic burdens of delirium are profound; it impedes patient recovery, extends hospital stays, escalates healthcare costs, and increases mortality rates (Gleason et al., 2015; Mosharaf et al., 2022). For instance, the financial toll of inpatient delirium patients in the United States was estimated at approximately US$82.4 billion annually as of 2019 (Kinchin et al., 2021). Particularly, patients with pre-existing dementia who develop delirium incur healthcare costs that are 37%–50% higher than those without delirium (Fick et al., 2005), underscoring its complex and multifactorial nature.

Recent advancements in delirium epidemiology have significantly enhanced our understanding of its clinical factors, leading to the development of targeted screening tools and diagnostic protocols (Khachaturian et al., 2020; Wilson et al., 2020a), and both preventive and therapeutic interventions (Kinchin et al., 2023). Despite these advancements, the application of these strategies remains inconsistent across healthcare settings, with current medical guidelines offering varied recommendations. There is often lack consensus on the efficacy of pharmacological and non-pharmacological interventions (De Asteasu et al., 2022; Lozano-Vicario et al., 2024; Nikooie et al., 2019; Oh et al., 2019), especially those involving multiple components (Abraha et al., 2015; Hshieh et al., 2018; Siddiqi et al., 2016; Wilson et al., 2020a).

Moreover, while considerable research has focused on the clinical aspects of delirium, a palpable gap persists in our understanding of the economic implications related to healthcare resource use and the cost-effectiveness of interventions. Differences in healthcare systems, resource availability, lack of a standardized framework, and cost structures mean the existing outcomes and interventions are not to be generalized (Kinchin et al., 2021, 2023). In addition, caregiver burden, productivity loss, lack of long-term economic evaluation, and the economic impact of long-term functional and cognitive impairment following delirium have not been studied yet (Gou et al., 2021). Addressing these gaps is crucial for gaining a thorough understanding of the economic impact of delirium management and prevention strategies, enabling better-informed policy decisions and more effective allocation of healthcare resources. Given these backdrops, this review aims to systematically examine and synthesize previous economic evaluations of both pharmacological and non-pharmacological interventions for delirium. By doing so, it seeks to provide a comprehensive overview of resource allocation and cost distribution among these interventions. These will help in the development of cost-effective delirium management strategies that might reduce the incidence and severity of delirium episodes in hospitalized patients as well as provide additional benefits for policymakers or decision-makers in the management, prevention, and treatment of delirium.

2. Methods

The systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard flow diagram and PRISMA checklist (Supplementary File 1) (Page et al., 2021). The screening and review processes were conducted using the systematic literature review tool, Covidence (https://app.covidence.org). This review has been registered with the PROSPERO database (PROSPERO ID: CRD42023480379).

2.1. Search strategy

A comprehensive search strategy was utilized to retrieve relevant peer-reviewed studies from electronic databases. To ensure the selection of the most pertinent studies, the literature search was conducted within the timeframe of January 1, 2000, to December 31, 2023, across the electronic bibliographic databases PubMed, MEDLINE, Scopus, and EBSCOhost (CINAHL, PsycINFO, and ECOLIT). The search terms incorporated the Boolean operators "AND" and "OR" in combination with the previously defined terms (Table 1). Before the final search, a pilot study was performed using the PubMed and Scopus databases to identify relevant articles and additional keywords pertinent to the current study. The search strategies are outlined in Table 1. The details of search lines and database outcomes are provided in Supplementary File 2.

The widely utilized search method for economic evaluations of interventions, known as the PICOS (Population, Intervention, Comparators, Outcomes, and Study Design) method, has been employed for the comparative analysis of costs and outcomes in both full and partial economic evaluations (Schardt et al., 2007).

Population – The study population consisted of patients with clinically diagnosed delirium.

Interventions and Comparators – This research encompassed trials including pharmacological or non-pharmacological interventions aimed at preventing, reducing, treating, or managing delirium cases. This includes both pharmacological (clinical) and non-pharmacological (non-clinical) interventions. The cost-effectiveness of these interventions was assessed in comparison to standard practice, and full and partial economic evaluations from trials were considered.

Context – Studies that demonstrated the economic evaluations (see Table 1) of pharmacological and non-pharmacological interventions for delirium.

Outcome – The primary outcome focused on the incremental cost-effectiveness ratio related to the prevention, treatment, and management of delirium, as well as reported composite and natural health outcomes. The incremental health benefits and/or costs of pharmacological and non-pharmacological interventions for delirium were evaluated.

Study Design – The initial search included economic evaluations and evaluation-based quantitative studies, such as randomized controlled trials, cohort studies, and case-control studies.

2.2. Eligibility/selection criteria

Based on the PICOS framework, articles that fulfilled the following inclusion criteria were finally selected: (i) original peer-reviewed research articles that are publicly available and written in English, (ii) reports on any full or partial economic evaluation of pharmacological or non-pharmacological interventions for delirium, (iii) published within the timeframe of January 1, 2000, to December 31, 2023, and (iv) studies that include only human cases of delirium as the study population. Exclusions applied to editorials, letters, perspectives,

Table 1
The search strategies and keywords.

Search keywords	Search operator	Search keywords	Search operator	Search keywords
"Delirium"	AND	"Cost-effectiveness analysis" OR "Cost-utility analysis" OR "Cost benefit analysis" OR "Cost consequences analysis" OR "Cost minimizing analysis"	AND	"Clinical Intervention" OR "Non-clinical Intervention" OR "Pharmacological Intervention" OR "Non-pharmacological Intervention" OR "Drug intervention"

commentaries, reports, reviews, meta-analyses, study protocols, publications in languages other than English, and studies with insufficient relevant data.

2.3. Study screening and selection

A three-stage screening process was implemented to determine the eligibility of articles for inclusion. After removing duplicates, studies were screened based on their titles and abstracts to evaluate their suitability. The final step involved reviewing the complete texts of the studies following the inclusion criteria. Studies that met the criteria were examined and included in this study. Two independent reviewers (MPM and RAM) conducted the screening at each stage. Any discrepancies encountered were discussed among the team (KA and JG), reviewed, and resolved by consensus.

2.4. Quality appraisal

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al., 2013) was utilized to evaluate the quality of the included articles. Each article was scored according to the checklist criteria, with points awarded as follows: one point for fully met particular criteria, half a point for partially or somewhat met criteria, and zero points for criteria not met. The average scores for each paper were calculated based only on applicable fields and expressed as percentages. Articles scoring over 75% are classified as good quality, those scoring between 50% and 75% as moderate quality, and those scoring below 50% as low quality (Zakiyah et al., 2016).

2.5. Data extraction and qualitative synthesis

Data related to the review were extracted from the final selection of studies to create a comprehensive data matrix. This matrix was shared with the team for review, and any discrepancies were discussed and resolved by consensus. The matrix includes various elements, such as the first author, publication year, country of origin, demographic characteristics of the target population, study design and setting, sample size, delirium assessment tools, types of interventions, types of economic analyses, time horizon, cost perspectives (including different types of costs and outcomes), discount rate, currency, intervention costs, results of the main comparator, economic context of each country, and incremental net benefits associated with the intervention (Supplementary Table 1). A narrative presentation of the collected findings including the descriptive analysis outcomes from the included articles were tabulated. The comparative analysis on incremental net benefits of the interventions was also reported.

2.6. Meta-analysis data curation

To assess the economic values of the multicomponent non-pharmacological interventions, only the cost-effectiveness or cost-utility analysis studies were considered for meta-analysis among the included studies. Based on these criteria, the incremental cost (ΔC), incremental effectiveness outcomes (ΔE) (The effectiveness outcomes were measured by QALYs), Incremental cost-effectiveness ratio (ICER) with their variance, and country-specific willingness-to-pay (WTP) were collected as reported by the included studies. If the ΔC or ΔE were presented in a cost-effectiveness plane scatterplot of a probabilistic sensitivity analysis, the data were extracted by using the Web-Plot-Digitizer (Rohatgi, 2024), and hence their variance was calculated. All the costs and country-specific WTP data were converted to USD 2024 values using purchasing power parity (PPP) methodology (Shemilt et al., 2010).

To assess cost-effectiveness, the INB was considered as the primary outcome of interest to measure the economic effect following the COMER method (Bagepally et al., 2022) as it provides a simple but straightforward interpretation of the cost-effectiveness compared to the ICER. If the INB values become positive, then it is cost-effective and otherwise not cost-effective compared with the comparator intervention (Bagepally et al., 2022; Crespo et al., 2014). The INB was calculated using the following formula:

$$\text{INB} = (\lambda \times \Delta E) - \Delta C \quad \text{(i)}$$

$$\text{INB} = \Delta E \times (\lambda - \text{ICER}) \quad \text{(ii)}$$

Where λ represents the WTP, ΔE is incremental effectiveness outcome and ΔC is incremental cost respectively.

The variance of INB was calculated using the following equation:

$$\text{Var (INB)} = \left(\lambda^2 \times \sigma^2_{\Delta E}\right) + \sigma^2_{\text{ICER}} \quad \text{(iii)}$$

$$\text{Var (INB)} = \left(\lambda^2 \times \sigma^2_{\Delta C}\right) - 2\lambda\rho_{\Delta C \Delta E} \quad \text{(iv)}$$

Where $\sigma^2_{\Delta E}$ denotes the variance of incremental effectiveness outcome, $\sigma^2_{\Delta C}$ represents the variance of the incremental cost, $\rho_{\Delta C\Delta E}$ is the covariance of ΔC and ΔE. The variance of ICER is denoted by σ^2_{ICER}.

During the data extraction for meta-analysis, we considered the five scenarios for data harmonization and overcame the methodological issues as described by Bagepally and colleagues (Bagepally et al., 2022). The meta-analysis was conducted to estimate the pooled INB across the included studies with its 95% CI. Based on the heterogeneity index I^2>50%, the random effect model was used, otherwise the fixed effect model was utilized. The subgroup analysis was conducted based on the type of economic evaluation (such as model-based, or within-trial evaluation) to check the sources of heterogeneity. Moreover, the WTP threshold was oscillated to check the effect on overall heterogeneity since the WTP threshold might play an influential role in heterogeneity (Veettil et al., 2022). Based on different WTP thresholds, the INB and the Var(INB) were calculated accordingly. The meta-analysis was conducted based on the datasets considering different WTP thresholds. The Egger's publication bias test was utilized to identify the small study effect and if existed, the Trim-and-Fill analysis was imposed to check the publication bias effect on the overall effect size. All the statistical tests were considered at a 5% level of significance, and the analysis was conducted in STATA/SE Version 17 for Windows (STATA Corp College Station, TX).

3. Results

3.1. Literature search outcome

The review retrieved 325 relevant studies from the selected databases through a comprehensive search using the keywords. After excluding 39 duplicate records, a total of 286 studies were screened against the inclusion and exclusion criteria. A search of the title and abstract excluded 253 studies that were irrelevant to the study. The remaining 33 studies underwent a full-text review, and finally, 16 studies met all of the inclusion criteria. Fig. 1 demonstrates the PRISMA flowchart describing the screening process for this study.

3.2. Characteristics of the included studies

Among the included studies, pharmacological and non-pharmacological interventions were implemented including prevention interventions (Akunne et al., 2012, 2013; Caplan and Harper, 2007; Lee and Kim, 2014; Leslie et al., 2005; Rizzo et al., 2001) (6 studies), delirium management strategies (Awissi et al., 2012; Collinsworth et al., 2020; Otusanya et al., 2022; Tanajewski et al., 2015) (4 studies), drug treatments (Carrasco et al., 2016; Lachaine and Beauchemin, 2012; Pitkala et al., 2008) (3 studies), quality improvement initiatives (Rubin et al., 2006; Rudolph et al., 2014) (2 studies), and one study that covered both prevention and management strategies (Schubert et al., 2020). Based on intervention type, three were pharmacological (Carrasco et al.,

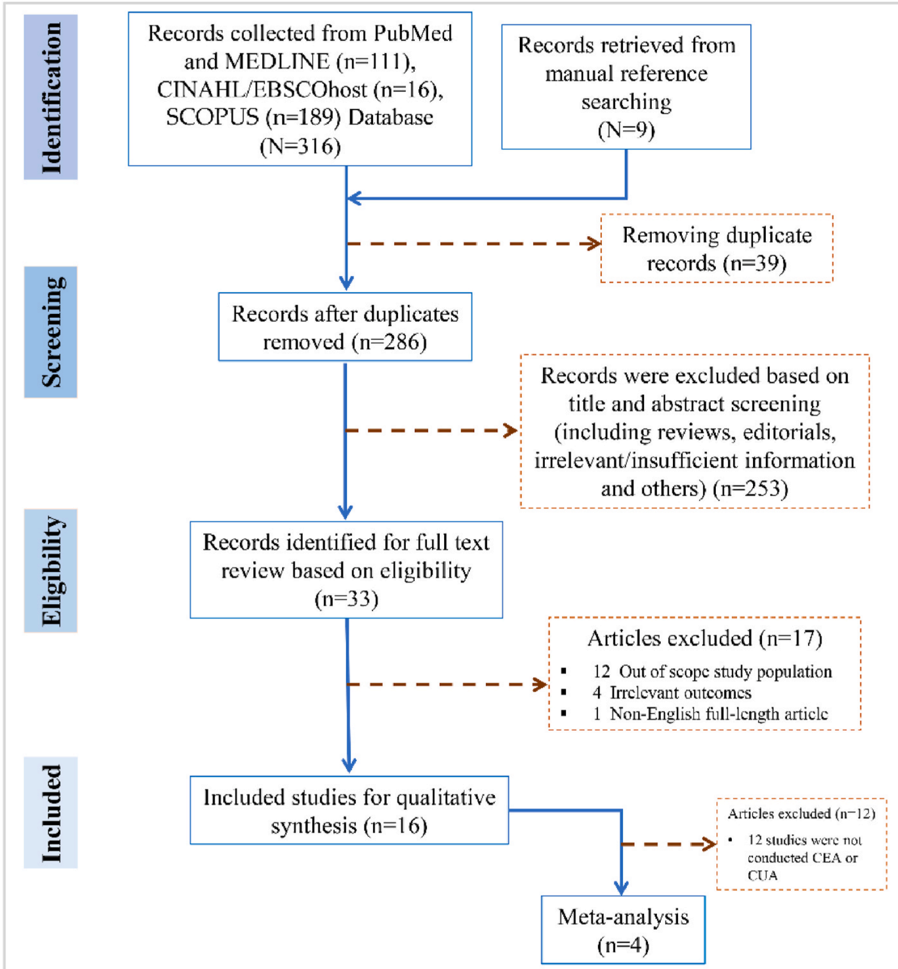

Fig. 1. The PRISMA flowchart.

2016; Lachaine and Beauchemin, 2012; Pitkala et al., 2008), while the remainder were non-pharmacological. The type of economic evaluation included four cost-effectiveness analyses (CEA), two cost-benefit analyses (CBA), three cost-consequence analyses (CCA), and seven cost-saving/minimization analyses (Table 3).

The included studies were all conducted in high-income countries, with five studies from England, four from the USA, and two from Canada. Additionally, single studies were conducted in Australia, Finland, Switzerland, Spain, and the Republic of Korea (Table 2). Most of the included study population was general medical/hospital patients (Akunne et al., 2012; Caplan and Harper, 2007; Leslie et al., 2005; Pitkala et al., 2008; Rizzo et al., 2001; Rubin et al., 2006; Rudolph et al., 2014; Tanajewski et al., 2015) (8 studies), hospital ICU settings (Awissi et al., 2012; Carrasco et al., 2016; Collinsworth et al., 2020; Lachaine and Beauchemin, 2012) (4 studies), hospital surgical patients (Akunne et al., 2013; Lee and Kim, 2014; Schubert et al., 2020) (3 studies) and a single study (Otusanya et al., 2022) was conducted among mechanically ventilated patients in ICU. The number of study patients varied from 37 to 3,292, where the number of patients in the intervention group varied from 16 to 1,710, and the number of patients in the comparator group varied from 21 to 1684. Two studies (Akunne et al., 2012, 2013) did not mention the sample size in the intervention and comparator groups as they used a model-based evaluation technique whereas one had a total number of 852 patients (Akunne et al., 2012) and another reported 5000 simulation samples (Akunne et al., 2013). The mean age of the patients varied from 50 years to a maximum of 85 years where most of the study sample units were older patients, except two studies which included young patients (>18 years) (Collinsworth et al., 2020; Schubert et al., 2020). The selected studies utilized different delirium identification methods including the confusion assessment method (CAM, CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), and Mini-Mental State Examination (MMSE). The included studies were conducted from societal and/or healthcare system perspectives. The synthesized characteristics are presented in Tables 2 and 3

3.3. Delirium prevention interventions

Among the included studies, seven studies implemented delirium prevention interventions, and five studies were multicomponent interventions to prevent and manage delirium (Table 3). Two multicomponent delirium prevention intervention studies with usual care using a model based on decision tree analysis were conducted (Akunne et al., 2012, 2013). The first study (Akunne et al., 2012) showed the intervention was cost-effective when compared with usual care and associated with an incremental net monetary benefit (INMB) of £2200 using a cost-effectiveness threshold of £20,000 per quality-adjusted life year (QALY). It remained cost-effective in most of the deterministic sensitivity analyses and 96.8% of the simulations carried out in the probabilistic sensitivity analysis. The second study (Akunne et al., 2013) was implemented among older adults undergoing hip fracture surgery which yielded an INMB of £8180 and remained cost-effective in 96.4% of simulations, surpassing the £20,000 per QALY threshold.

Pitkala (Pitkala et al., 2008) examined the impact of a multicomponent geriatric treatment program on healthcare costs and

Table 2
Characteristics of the included studies (n = 16).

Author	Study Type and Design	Total Sample (n); Intervention/ Comparator (n)	Age in Years [mean (SD)] (Intervention/ Comparator)	Gender [Male; n (%)] (Intervention/ Comparator)	Time Horizon; Price year; Discount adjusted	Study Settings/ Population	Perspective	Delirium Identification Method
Akunne et al. (2012)	Model-based evaluation; the initial study was an RCT	852; NR/NR	Overall: 79 years	NR	3 y; NR; 0.035	Medical/ Hospital patients (General)	Societal	NR
Akunne et al. (2013)	Model-based evaluation; the initial study was an RCT	5000 simulation data; NR/NR	Overall: 79 years	NR	3 y; NR; 0.035	Hospital setting (Surgical)	Societal	CAM; MMSE
Awissi et al. (2012)	NR	1214; 610/604	63.3 (15.2)/63.3 (14.9)	360 (59.0%)/355 (58.8%)	NR; 2004; Yes	Hospital setting (ICU)	Societal	ICDSE
Caplan and Harper (2007)	NR	37; 16/21	85.6 (7.4)/83.8 (4.7)	4 (25.0%)/4 (19.0%)	10 m; NR; NR	Medical/ Hospital patients (General)	Societal	CAM; MMSE
Carrasco et al. (2016)	Nonrandomized controlled trial (quasi-experimental)	132; 46/86	70.3 (±12.5)/71.3 (±11.3)	37 (80.0%)/77 (89.0%)	1 y; 2015; NR	Hospital setting (ICU)	Healthcare system	CAM-ICU; ICDSC
Collinsworth et al. (2020)	Prospective, quasi-experimental design	2953; 1710/ 1243	61.7 (15.6)/61.1 (15.1)	971 (56.8%)/696 (56.0%)	2 y; 2013; NR	Hospital setting (ICU)	Healthcare system	NR
Lachaine and Beauchemin (2012)	Prospective randomized, double-blind trial	366; 244/122	NR	NR	2 y 5 m; 2010; NR	Hospital setting (ICU)	Healthcare system	CAM-ICU; RASS
Lee and Kim (2014)	Retrospective study	130; 68/62	50.7 (±9.1)/52.2 (±8.7)	49 (72.1%)/41 (66.1%)	1 y 8 m; NR; NR	Hospital setting (Surgical)	Societal	APACHE II Score
Leslie et al. (2005)	Longitudinal follow-up from a randomized trial	801; 400/401	81.5 (6.9)/81.9 (6.6)	NA	3 y; NR; NR	Medical/ Hospital patients (General)	Healthcare system	NR
Otusanya et al. (2022)	Retrospective cohort study	215; 123/92	Med (IQR): 60 (51,72)/67 (57,77)	66 (54%)/44 (48%)	1 y; 2013; NR	Hospital setting (ICU)	Healthcare system	NR
Pitkala et al. (2008)	Randomized Control Trial	194; 87/87	84 (5.6)/83 (6.2)	11 (12.7%)/16 (18.4%)	1 y; 2007; NR	Medical/ Hospital patients (General)	Societal	CAM; MMSE; DSM-IV
Rizzo et al. (2001)	Randomized Control Trial	852; 426/426	79.64 (±6.09)/ 79.80 (±6.23)	NR	3 y; 1999; NR	Medical/ Hospital patients (General)	Healthcare system	CAM
Rubin et al. (2006)	A pretest/post-test quality-improvement study	1929; 704/1225	80.9 (6.7)/80.6 (6.2)	257 (36.5%)/443 (36.2%)	2 y; NR; NR	Medical/ Hospital patients (General)	Societal perspective	NR
Rudolph et al. (2014)	NR	1132; 566/566	78.3 (8.0)/78.4 (8.2)	560 (98.9%)/563 (99.5%)	NR; NR; NR	Medical/ Hospital patients (General)	Societal and Healthcare system	DOWB or MOYB or CIB test
Schubert et al. (2020)	Retrospective pre and post-design study	3292; 1684/ 1608	61.8 (±14.5)/61.8 (±14.4)	1158 (69.0%)/ 1109 (69.0%)	2 y; 2011 and 2013; NR	Hospital setting (Surgical)	Societal	CAM; ICDSC; RASS
Tanajewski et al. (2015)	Randomized Control Trial	600; 310/290	≥65 years of age	NR	2 y 8 m; 2007-08; NR	Medical/ Hospital patients (General)	Societal and Healthcare system	MMSE; DRS-R-98

Note: SD: Standard Deviation; NR: Not Reported; Med: Median; IQR: Inter Quartile Range; ICU: Intensive Care Unit; CAM/CAM-ICU: Confusion Assessment Method (ICU), ICDSC: Intensive Care Delirium Screening Checklist; MMSE: Mini-Mental State Examination; RASS: Richmond Agitation Sedation Scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Version-IV); APACHE-II: Acute Physiology And Chronic Health Evaluation; DRS-R-98: Delirium Rating Scale-Revised-98; DOWB: Days of the Week Backward; MOYB: Months of the Year Backward; CIB: Clock-in-the-Box.

health-related quality of life (HRQoL) for delirious inpatients. Over a year after the delirium episode, the cost difference between the intervention and control groups was not significant, with a difference of €180. Rizzo (Rizzo et al., 2001) used a multicomponent intervention (MTI) to assess the net costs of preventing delirium in hospitalized patients. By linking hospital charge data with a database of 852 patients and using regression methods, the study found that MTI reduced non-intervention costs for those at intermediate risk but not for high-risk patients. A study in Australia used volunteer-mediated delirium prevention programs in geriatric wards to evaluate their efficacy, cost-effectiveness, and sustainability (Caplan and Harper, 2007). In the first phase of the study, they found a lower incidence rate and lower severity of delirium. The overall duration of delirium episodes was also decreased. The second phase of the study demonstrated that the implication of this delirium prevention program was reduced by 314 h of nursing assistance per month which led to annual cost savings of A$129,

Table 3
Summary of interventions, economic evaluation method, and outcomes (n = 16).

Author	Health Economic Evaluation	Intervention Type	Intervention (Comparator)	Sensitivity Analysis	Country; Currency; Funding	Units of Effectiveness Measurement	Conclusion or Recommendation
Akunne et al. (2012)	Cost-effectiveness Analysis (CEA Model based)	Prevention (non-pharmacological)	Multi-component prevention intervention (Usual Care)	NR	UK; British Pound; Yes	Cost per QALY gained	Cost-effective; INMB of £2200 using a cost-effectiveness WTP threshold of £20,000 per QALY gained.
Akunne et al. (2013)	Cost-effectiveness Analysis (CEA Model based)	Prevention (non-pharmacological)	Multi-component prevention interventions (Usual Care)	Deterministic	UK; British Pound; Yes	Cost per QALY gained	Cost-effective; INMB of £8180 using a cost-effectiveness WTP threshold of £20,000 per QALY gained.
Awissi et al. (2012)	Cost saving analysis	Management (non-pharmacological)	A protocol for delirium management (Pre-protocol)	Deterministic	Canada; Canadian Dollar; No	Difference in cost and effectiveness measurement	Cost-effective practice; Average savings of CA $932 per hospitalization
Caplan and Harper (2007)	Rudimentary Cost-effectiveness Analysis; (Cost savings Analysis)	Prevention (non-pharmacological)	Volunteer-mediated delirium prevention program (Usual Care)	NR	Australia; Australian Dollar; Yes	Cost per reduction in nursing assistant hours	Reduced 314 nursing hours per month equivalent to a total annual saving of A $129,186; continuation of the program; extension to other service (geriatric) units.
Carrasco et al. (2016)	Cost-benefit Analysis (CBA)	Treatment (Pharmacological)	Dexmedetomidine for treatment (Haloperidol)	NR	Spain; USD; Yes	Cost per reduction in ICU length of stay (day)	The direct medical cost of dexmedetomidine was 17 times greater than haloperidol but mean savings of US$4370 per patient arose due to lower ICU stay.
Collinsworth et al. (2020)	Cost-effectiveness Analysis (CEA)	Management (non-pharmacological)	Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility (ABCDE) bundle processes (Low adherence vs High adherence)	One way	USA; USD; Yes	Cost per QALY gained	Cost-effective; Significantly decreased odds of inpatient mortality; ICER of US $42,120 per QALY gained.
Lachaine and Beauchemin (2012)	Cost–consequences Analysis (CCA)	Treatment (Pharmacological)	Dexmedetomidine for treatment (Midazolam)	Deterministic	Canada; Canadian Dollar; Yes	Efficacy and safety of drugs; level of sedation and delirium	The overall cost per patient was lower with dexmedetomidine than with midazolam (CA $7022 versus CA$7680).
Lee and Kim (2014)	Cost-benefit Analysis (CBA)	Prevention (non-pharmacological)	Delirium prevention-care group (Usual Care)	Probabilistic	Republic of Korea; USD; No	The costs and benefits of the prevention strategy	The prevalence rate of delirium was 35.3% in the prevention-care group and 51.6% in the usual-care group. The net benefit was US$5539 with a benefit ratio of 145.3
Leslie et al. (2005)	Cost saving analysis	Prevention (non-pharmacological)	Multicomponent Treatment Intervention (MTI) in long-term nursing home (NH) care (Usual Hospital Care)	NR	USA; USD; Yes	Total cost per patient	Adjusted total costs were US$50,881 per long-term NH patient in the MTI group and US$60,327 in the control group, a saving of 15.7%
Otusanya et al. (2022)	Cost saving analysis	Management (non-pharmacological)	Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility (ABCDE) bundle implementation (Portion of the ABCDE bundle (ABD))	NR	USA; British Pound; Yes	Total hospital cost, total ICU, and average daily ICU cost	Full ABCDE bundle implementation resulted in a decrease in total hospital laboratory costs and diagnostic resource utilization while leading to an increase in physical therapy costs.
Pitkala et al. (2008)	Cost-consequences Analysis (CCA)	Treatment (Pharmacological)	Multicomponent geriatric treatment (Usual Care)	NR	Finland; Euro; Yes	Health care costs; and the use and costs of health services	The total cost difference was insignificant (180 €); The intervention improved HRQoL without increasing overall costs of care.
Rizzo et al. (2001)	Cost-consequences Analysis (CCA)	Prevention (non-pharmacological)	Multicomponent targeted risk factor intervention (MTI) strategy (Usual Care)	Deterministic	USA; USD; Yes	Cost per risk reduction	MTI is a cost-effective treatment option for patients at intermediate risk, but not for high risk.

(*continued on next page*)

Table 3 (*continued*)

Author	Health Economic Evaluation	Intervention Type	Intervention (Comparator)	Sensitivity Analysis	Country; Currency; Funding	Units of Effectiveness Measurement	Conclusion or Recommendation
Rubin et al. (2006)	Cost saving analysis	Quality-improvement model (non-pharmacological)	HELP interventions (Usual Care)	NR	UK; USD; Yes	Cost per delirium risk reduction	Reduction in relative risk of delirium by 35.3%; Total costs were reduced by US$626,261 over 6 months
Rudolph et al. (2014)	Cost Minimizing Analysis	Quality-improvement model (non-pharmacological)	Delirium Toolbox (Usual Care)	Deterministic	New England; USD; Yes	Hospital variable direct costs	There were improvements in patient outcomes and financial savings from this delirium risk mitigation approach. Programs for identifying and modifying delirium risk should be carefully considered.
Schubert et al. (2020)	Cost savings analysis	Prevention and management (non-pharmacological)	Standardized multi-professional, multi-component delirium guideline on eight outcomes (Pre-intervention group)	NR	Switzerland; CHF; Yes	Cost saving per case prevention	Improved early detection and increased awareness, but increased ICU stay, overall cost and could not influence the mortality.
Tanajewski et al. (2015)	Cost-effectiveness Analysis (CEA)	Management (non-pharmacological)	The Medical and Mental Health Unit, (MMHU) (Usual Care)	Probabilistic	UK; Great British Pounds; Yes	Cost per QALY gained	Less cost-effective due to very less and insignificant QALY gained (0.001), worthy of further evaluation. The difference in QALYs gained was 0.001

[Note: NR: Not reported; HELP: Hospital Elderly Life Program; ICER: Incremental Cost-Effectiveness ratio; QALY: Quality Adjusted Life Years; INMB: Incremental Net Monetary Benefit; HRQoL: Health-Related Quality of Life].

186. The cost-effectiveness of a delirium prevention strategy was assessed by Lee and Kim (2014).

It found that the prevention group had a lower delirium rate (35.3%) compared to the usual-care group (51.6%). The cost of the prevention strategy was US$38, while the treatment would have incurred US $5,578, resulting in a net benefit of US$5539 and a benefit-to-cost ratio of 145.3. Another multicomponent targeted intervention (MTI) (Leslie et al., 2005) study showed that the intervention did not affect the likelihood of needing long-term nursing home (NH) care. The patients in the MTI group had significantly lower costs, shorter hospital stays, and lower costs per surviving day, resulting in a 15.7% cost reduction. A delirium prevention and management strategy was implemented among ICU patients focusing on eight outcomes (Schubert et al., 2020). Results showed that among the eight target components, the intervention improved early detection and increased awareness, conversely leading to longer ICU stays and higher costs, but did not affect mortality rates.

3.4. Delirium management interventions

Five articles showcased delirium management interventions. Two studies conducted a CEA (trial-based) (Awissi et al., 2012; Tanajewski et al., 2015), two focused on cost-saving analysis (Otusanya et al., 2022; Schubert et al., 2020), and one conducted a model-based CEA (Collinsworth et al., 2020). Two studies implemented the ABCDE bundle intervention, measuring its impact on inpatient and one-year mortality, QALYs, length of stay, and care costs (Collinsworth et al., 2020) as well as reducing the overall hospital cost (Otusanya et al., 2022). The ABCDE bundle (≥60%) significantly reduced inpatient mortality (odds ratio 0.28) while elevating inpatient costs by US$3920. The incremental cost-effectiveness ratios were US$15,077 per life saved and US$1057 per life-year saved, with a 0.12 increase in QALYs and an additional US $4949 in one-year care costs, leading to an incremental cost-effectiveness ratio of US$42,120 per QALY gained (Collinsworth et al., 2020). Another study found a decrease in total hospital laboratory costs and total hospital laboratory and diagnostic resource use while leading to an increase in physical therapy costs (Otusanya et al., 2022).

A trial-based full economic evaluation (i.e., CEA) was conducted to measure the effectiveness of MMHU intervention for older patients with delirium and dementia against standard care in general hospitals (Tanajewski et al., 2015). A small total cost difference of -£149 was identified and the difference in QALYs gained was minimal (0.001). The MMHU had a 58% chance of being cost-effective and a 39% chance of being cost-saving, albeit a reduction in QALY. At a £20,000 per QALY gained threshold, its cost-effectiveness probability was 94% but dropped to 59% when accounting for cases with QALY loss and cost savings. The author recommended a further evaluation of the effectiveness of the MMHU intervention in the long-term. Awissi (Awissi et al., 2012) implemented a protocol for the management of analgesia, sedation, and delirium in the ICU saving costs. The mean total cost of ICU hospitalization decreased from CA$6212 (SD: CA$7846) in the pre-protocol control group to CA$5279 (SD: CA$6263) in the post-protocol intervention group, with the incidence of delirium remaining constant.

3.5. Patient quality improvement intervention

The Hospital Elder Life Program (HELP) multicomponent intervention was assessed by Rubin (Rubin et al., 2006) for delirium risk. This study evaluated whether a quality improvement project focused on identifying and addressing delirium risk through cognitive stimulation, sensory improvement, and sleep promotion improved patient outcomes and reduced healthcare costs. It reduced delirium rates by 14.4% from baseline, translating to a 35.3% relative risk reduction (*p-value* < 0.01). Over 6 months, it reduced costs by US$626,261 in a 40-bed nursing unit which also demonstrated high satisfaction and lasting benefits. The project led to similar discharge rates to rehabilitation but resulted in shorter hospital stays, reduced restraint use, and a trend towards lower direct costs (Mean-difference of US$1390).

3.6. Delirium treatment pharmacological intervention

Two included studies tested the effectiveness of Dexmedetomidine for delirium treatment and used a cost-benefit analysis (Carrasco et al.,

2016) and a cost-consequence analysis (Lachaine and Beauchemin, 2012). The cost-benefit analysis (Carrasco et al., 2016) compared dexmedetomidine and haloperidol for treating agitated delirium in non-intubated critically ill patients. Dexmedetomidine provided better sedation (92.7% vs. 59.3%) and was more riskless, with fewer cases of oversedation and QT prolongation. Although dexmedetomidine was 17 times more expensive than haloperidol, it resulted in US$4370 savings per patient by reducing the length of their ICU stay. Overall, dexmedetomidine proved more effective, safer, and cost-beneficial than haloperidol in these cases. Another study (Lachaine and Beauchemin, 2012) showed that dexmedetomidine had a higher medication cost than midazolam (CA$1929 vs. CA$180 per patient), but it resulted in lower costs for mechanical ventilation (CA$2939 vs. CA$4448) and delirium management (CA$2127 vs. CA$3012). Overall, the cost per patient was lower with dexmedetomidine (CA$7022 vs. CA$7680). A sensitivity analysis confirmed these findings.

3.7. Intervention for delirium in ICU

Of the sixteen included studies, five were conducted in hospital ICU settings. The summary of the included studies revealed that four distinct interventions were introduced for ICU-delirium, including two pharmacological drugs: dexmedetomidine (Lachaine and Beauchemin, 2012) and haloperidol (Carrasco et al., 2016). The other three interventions included the multi-component intervention (Awissi et al., 2012) and ABCDE bundle interventions (Collinsworth et al., 2020; Otusanya et al., 2022) both of the latter are also multi-component. It was shown that the dexmedetomidine drug intervention was effective for patient outcomes, despite their increasing medication costs, and yet this remained cost-effective compared to comparator drugs. Besides the drugs, the multi-component interventions showed cost-effectiveness compared to usual care and other comparators.

3.8. Meta-analysis of cost-effectiveness of non-pharmacological intervention

In this review, four CEA studies of the multicomponent non-pharmacological intervention (Akunne et al., 2012, 2013; Collinsworth et al., 2020; Tanajewski et al., 2015) were selected for meta-analysis. The INB and the Var(INB) were calculated from these four studies. Two studies (Akunne et al., 2012, 2013) directly reported the INB value that have been collected. The mean value, variance, and covariance of ΔC and ΔE were calculated from the cost-effectiveness scatterplot using Web-Plot-Digitizer (Scenario IV) and Var(ICER), and the Var(INB) was calculated using the equation (iv). On the other hand, the other two studies (Collinsworth et al., 2020; Tanajewski et al., 2015) reported the ICER and their 95% CI, by which the Var(ICER) was calculated (Scenario II). Among these two, one study (Collinsworth et al., 2020) reported the point estimation of the ΔE without any dispersion measurement (Scenario III). The Monte Carlo simulation with 1000 replications under the normal distribution was utilized and hence the Var(ΔE) was calculated. Another study (Tanajewski et al., 2015) reported the point estimation of ΔE with 95% CI (Scenario II), and Var(ΔE) was calculated accordingly. Then the INB and Var(INB) were calculated using the equations (ii) and (iv) respectively. The final calculated INB and the Var(INB) have been provided in Table 4 for each of the studies. The details of the collected cost data, incremental cost and outcome data, ICER, descriptive statistics, and measure of dispersion have been provided in Supplementary File 3.

3.9. Cost-effectiveness analysis findings

The meta-analysis revealed a significant pooled INB value of US $8014 (95% CI=US$1060, US$14,969; p-value<0.05) under the random effect model (inverse variance) (Fig. 2). The polled value of INB along with its 95% CI indicated that the non-pharmacological intervention is significantly cost-effective compared to the usual treatment strategy to manage and prevent delirium. Significant heterogeneity was found among the included studies ($I^2 = 100\%$; p-value<0.01) which led to the use of the random effect model for pooled estimation. Subgroup analysis by the type of economic evaluation study showed that the pooled INB estimation was US$2657 higher (US$10,671; p-value<0.01) for the model-based economic evaluation studies compared to the overall estimation (Fig. 2). The WTP threshold-based analysis revealed that the heterogeneity remained the same over the WTP threshold values varied from US$30000 to US$150000 (Supplementary Table 2). This indicates that more studies with similar effective interventions should be incorporated to check their global effectiveness. In general, meta-analysis, the publication biases, and the small study effect were assessed using Egger's test (Z = 7.10; p-value<0.01) since the number of included studies was low. The Egger's test revealed that there might be a small study effect on the overall effect size estimation (Supplementary Table 2). The Trim-and-Fill analysis yielded that the publication bias did not affect the overall effect size estimation (Supplementary Table 2).

In contrast, the leave-one-out analysis revealed that there existed significant heterogeneity in the study which influenced the overall output (Supplementary Fig. 1). The meta-analysis excluding any of these two studies (Akunne et al., 2013; Collinsworth et al., 2020) led to an insignificant overall effect size although it showed cost-effectiveness.

3.10. Quality assessment of the included studies

The quality appraisal of the included studies was evaluated with the CHEERS checklist. The quality appraisal showed an average of 73% positive score (Fig. 3). Most of the articles scored better for the methodological aspects of the studies. Six included articles were of good quality (score>75%) and the remaining articles were of moderate quality (50%<score<75%) based on their CHEERS checklist quality appraisal (Supplementary File 4). No low-quality studies were included in this review and only three studies (25%) reported the discount rate. The results section included most of the checklist items which implies a good quality evaluation was undertaken in the study. It would be better

Table 4
The data and information used for meta-analysis.

Author	Evaluation Type	Intervention type	Price year; Scenario	WTP Threshold (Reported)	Measure of dispersion of INB	INB[#] (USD)	Var (INB)[#] (USD)
Akunne et al. (2012)	Model-based evaluation	Multi-component non-pharmacological	NR*; IV	£20000	No	$4353	$546350
Akunne et al. (2013)	Model-based evaluation	Multi-component non-pharmacological	NR*; IV	£20000	No	$15628	$8994566
Collinsworth et al. (2020)	Model-based evaluation	Multi-component non-pharmacological	2013; II and III	US$50,000	Yes	$12037	$44074578
Tanajewski et al. (2015)	Within-trial evaluation	Multi-component non-pharmacological	2007; II	£20000	Yes	$44	$37817

[Note: NR: Not Reported; [#] The cost values are PPP adjusted in 2024 USD; *when the base cost year was not reported, the publication year was considered as the base cost year for PPP conversion into 2024 USD].

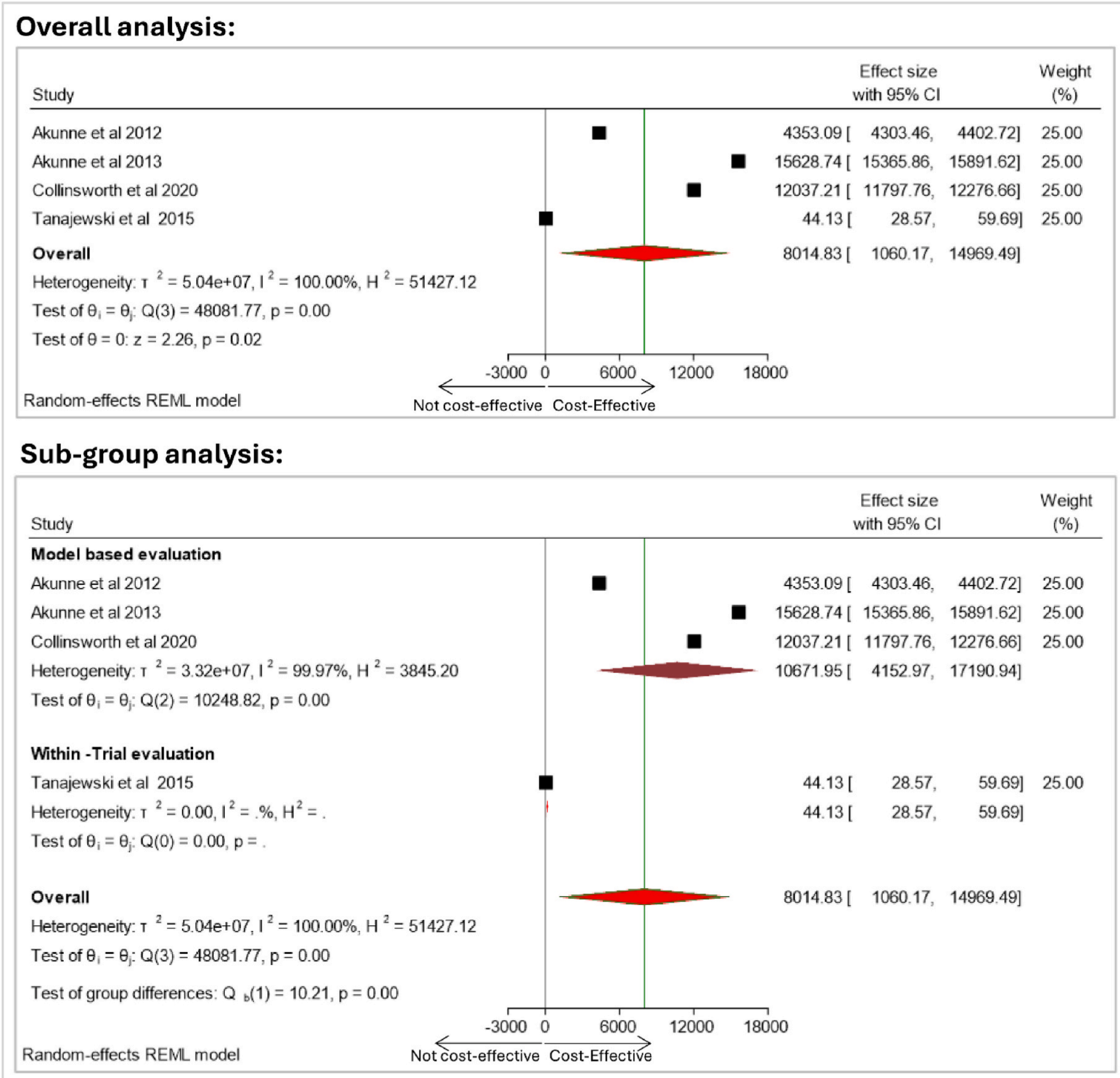

Fig. 2. The forest plot of the meta-analysis evaluating the cost-effectiveness of multicomponent non-pharmacological interventions along with the subgroup-analysis results.

if all the studies demonstrated the rationale and description of their analysis model. On the other hand, half of the studies incorporated sensitivity analysis to check the robustness of their findings, and nine studies included the cost components of their studies. In addition, only three studies adjusted the inflation/discount rate in their analyses (Akunne et al., 2012, 2013; Awissi et al., 2012).

4. Discussion

This systematic review provided a detailed overview of the effectiveness of different pharmacological and non-pharmacological implemented for delirium prevention, management or mitigation, and treatment in different settings. We included 16 distinct studies which used various economic evaluation techniques including CEA (Akunne et al., 2012, 2013; Collinsworth et al., 2020; Tanajewski et al., 2015), CBA (Carrasco et al., 2016; Lee and Kim, 2014), CCA (Lachaine and Beauchemin, 2012; Pitkala et al., 2008; Rizzo et al., 2001), and cost minimization or cost-saving analyses (Awissi et al., 2012; Caplan and Harper, 2007; Leslie et al., 2005; Otusanya et al., 2022; Rubin et al., 2006; Rudolph et al., 2014; Schubert et al., 2020). All the studies were conducted in high-income developed countries. A review study suggested that the pooled prevalence of global emergence delirium was 19.2%, with a higher chance among younger patients. It also noted that there is a scarcity of studies in Africa, and very limited research in the Asia Pacific region and Northern Europe (Chen et al., 2024). Studies suggest that 60–70% of older adults experience undiagnosed delirium in hospital emergency settings and ICUs, with hypoactive delirium and delirium superimposed on dementia being the most common overlooked conditions (Aggar et al., 2022; Han et al., 2009a; Inouye et al., 2014a; Saczynski et al., 2014; Shrestha and Fick, 2023; Steis et al., 2012). The current review also emphasizes more research about delirium in these regions since there might be a greater chance of undiagnostic delirium in hospital settings. The nature of the condition being treated, the training of health professionals, the faculty's competencies in care units, and, in particular, the use of pharmacological and anesthetic agents can all have an impact on the occurrence of delirium (Sudhakar et al., 2022; Tripathi et al., 2015). The lack of study among these regions raises a high demand for more rigorous studies focusing on delirium diagnosis, prevention, management, and treatment. The healthcare professionals and the policy implications should focus on developing strategies to enable the healthcare system to focus on delirium and improve the patient experience during hospitalization.

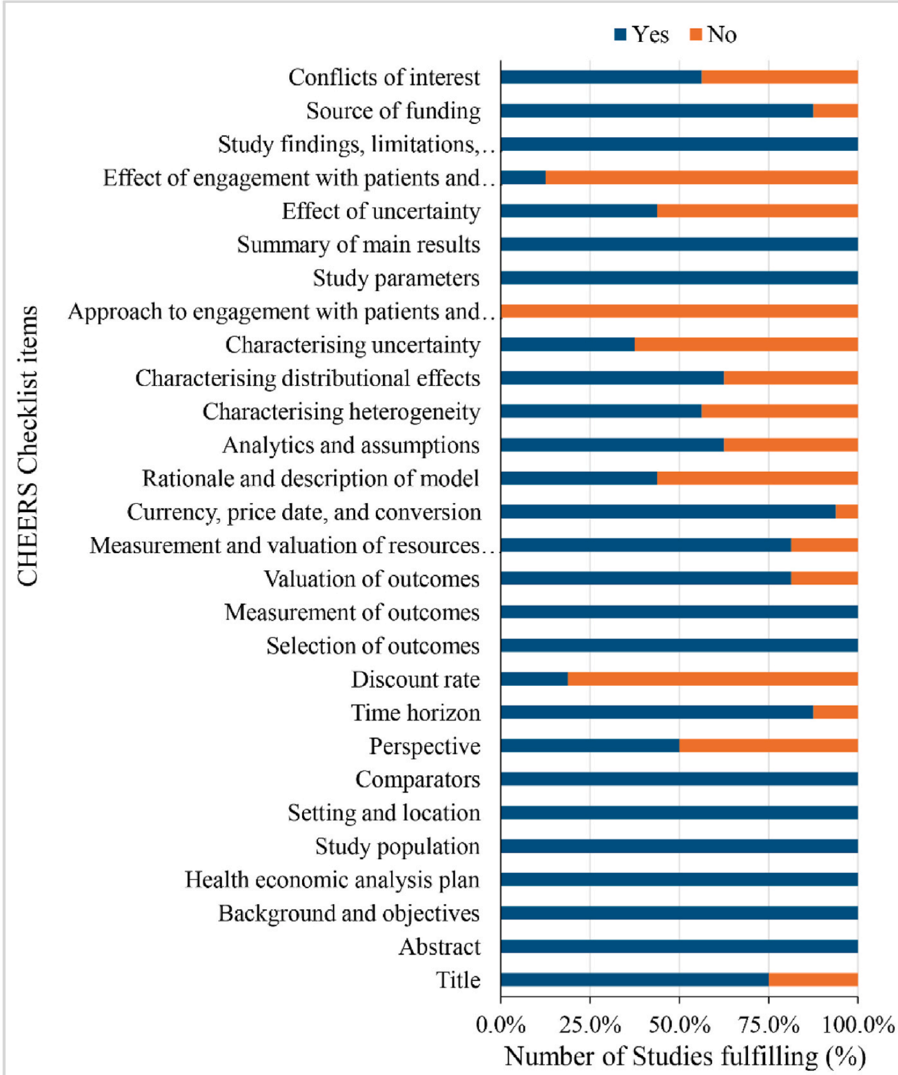

Fig. 3. Quality assessment according to CHEERS checklist.

The current review determined that only five studies were conducted in ICU settings, whereas eleven were conducted in other hospital settings. The drug interventions were cost-saving for delirium while the multi-component non-pharmacological interventions were cost-effective and reduced the costs for delirious patients. Delirium and other cognitive issues are highly prevalent among ICU patients compared to other hospital settings (Cavallazzi et al., 2012). The current review demonstrates that the ICU-based interventions were not rigorously implemented compared to other settings. More rigorous interventions and research should be implemented for treating, preventing, and managing ICU delirium.

The review outlined the cost consequences of the interventions for managing delirium. Most of the interventions were cost-effective and demonstrated effectiveness in managing delirium in hospital settings, including the ICU. The delirium management protocol intervention showed that they decreased the hospital cost, however, the incidence rate of delirium remained consistent with that of the control setting (Awissi et al., 2012). Another study reported that standardized delirium management improved early detection and increased awareness, leading to longer ICU stays and higher costs, however, it did not affect mortality rates (Schubert et al., 2018). Similarly, Otusanya and colleagues (Otusanya et al., 2022) implemented the ABCDE bundle intervention which decreased total hospital laboratory costs and total hospital laboratory and diagnostic resource utilization while leading to an increase in physical therapy costs. On the other hand, the CEA conducted by Collinsworth et al. (2020); Collinsworth et al. (2020) and Tanajewaski (Tanajewski et al., 2015) showed the effectiveness of the ABCDE bundle intervention and the MMHU intervention which Tanajewaski and colleagues suggested for further evaluation. Rizzo (Rizzo et al., 2001) reported that the multicomponent treatment intervention (MTI) did not lower non-intervention expenditures for patients at high risk; however, it did for those at moderate risk. It raised prices for the high-risk group but had no discernible impact on the total expenditure of the intermediate-risk group when MTI costs were taken into account. The existing literature (Han et al., 2009b; López-Otín et al., 2013; Wilson et al., 2020b) and based on the above findings, differentiating and focusing on patients with various baseline risks of developing delirium should be taken into account in economic assessments of delirium therapies.

The model-based economic evaluation studies showed that interventions are cost-effective (Akunne et al., 2012, 2013) compared to usual care among patients in UK-based hospital or surgical settings. The multicomponent geriatric treatment intervention was found to have an insignificant cost difference compared to usual care but improved cognition resolved delirium symptoms more promptly and improved patient health-related quality of life (HRQoL) (Pitkala et al., 2008). The intervention indicates better service and outcomes with a similar cost compared to usual care. Rudolph and colleagues implemented a quality improvement project focusing on addressing the delirium risk (Rudolph et al., 2014). The study concluded that more interventions were linked to better outcomes and cost savings. The study also suggested that the risk modification programs for delirium are beneficial and should be seriously considered. These indicate that intervention targeting delirium risk factors should be undertaken.

The review identified two studies (Carrasco et al., 2016; Lachaine and Beauchemin, 2012) that implemented a pharmacological drug intervention (Dexmedetomidine) to check its effect on overall cost and patient outcome which is a significant step for therapeutic development for delirium. The current review found a limited number of studies that implemented pharmacological interventions. Although studies were conducted to check the drug effectiveness over the decades (Inouye et al., 2014b), rigorous research and clinical trials including economic evaluation should be incorporated to assess the cost-effectiveness of drugs to treat delirium.

As per our knowledge, this is the first meta-analysis ever that evaluated the cost-effectiveness of multicomponent non-pharmacological interventions using INB data. The meta-analysis of the economic evaluation of the cost-effectiveness revealed that the multicomponent non-pharmacological interventions were cost-effective compared to their comparator interventions. Despite the number of included studies being lower, the subgroup analysis based on the economic evaluation type analysis revealed the model-based economic evaluation has a higher significant INB than the usual overall estimation. The downstream analysis including the publication bias test, and Trim-and-Fill analysis ensured the robustness of the findings. Model-based economic evaluations showed more INB values compared to within-trial economic evaluations which seek more attention for further investigation about the model-based economic evaluation. This study reflected the challenges for conducting a meta-analysis about the cost-effectiveness studies of delirium including the lack of studies, heterogeneity of the economic evaluations, type of models, discount, population, GDP and WTP threshold, and time perspective. In this study, we attempted to mitigate the heterogeneity among the study assuming a uniform WTP threshold by considering a variation in WTP since it might affect the overall analysis (Dilokthornsakul et al., 2022; Veettil et al., 2022). The analysis revealed that the WTP threshold variation did not mitigate the heterogeneity among the studies in this analysis. Significant heterogeneity was demonstrated by two-thirds of published meta-analyses of CEA (Veettil et al., 2022). If a larger number of studies were available then these explorations, including subgroup analysis according to settings, perspective, level of country income, study type and so on could provide more in-depth insights. Future studies should be conducted to produce more CEA which could provide rigorous space to conduct further meta-analysis. In addition, methodological heterogeneity, country-specific CEA, context-specific CEA, potential source of bias, and other sources of heterogeneity should be considered in meta-analysis during decision-making and policy implication.

This review illustrated some adverse consequences of interventions implemented in distinct studies. The lower quality and failure of a few interventions included in this study might be due to a lack of required evaluations, proper justification, rationale, and a lack of focus on mandatory assessment. A thorough economic evaluation, quality appraisal, comparison of multiple options, and consideration of both immediate and long-term effects, including adverse effects, are essential for better assessing delirium interventions. Improving their quality requires standardized reporting, addressing biases, and using transparent frameworks. The intervened pharmaceuticals and medical technologies, protocols, and management strategies that are assessed are not often focused on the delirium treatment aspect. During the implementation of the interventions, it is important to consider the comorbidities, unusual event management, and any adverse events. The cost and outcomes analysis considering these could provide better intervention outcomes and mitigate the bias of cost calculation.

During the intervention in a hospital or medical setting, some 'hidden services and their relevant costs' were ignored, including the non-medical information desk, administrative support, volunteering nursing support, peer support, and emotional provision from family members, as well as out-of-pocket expenditures, and others (Handy and Srinivasan, 2004; Salamon et al., 2011). These supports and relevant costs could be considered as opportunity costs of time and evaluated during the intervention for a more transparent and effective approach for future implications. The transparent reporting of cost and utility data, and implementing standard reporting following the checklists and appraisal tools (i.e., CHEERS checklist (Husereau et al., 2013), Drummond's Statement (Drummond and Jefferson, 1996)) should be taken into consideration so that it motivates the reader to use and facilitate the studies for further investigation. More studies ought to be conducted focusing on risk and causal factors, molecular, pathophysiological, and pharmacological aspects which will enhance drug development and treatment for delirium.

5. Implications

The summarized evidence from the included studies indicates that multicomponent strategies are highly effective in managing delirium, particularly in ICU settings where it is prevalent. There is strong support for non-pharmacological interventions, emphasizing their cost-effectiveness and necessity for integration into patient care protocols. However, most studies are from high-income countries, highlighting a gap in delirium research in regions such as Africa, Asia Pacific, and Northern Europe. More geographically diverse research should be implemented in these underrepresented areas to evaluate the economic and clinical impacts and outcomes of delirium interventions. Based on the meta-analysis output, the current study emphasizes more studies on economic evaluation, especially the cost-utility analysis through different clinical trials. More rigorous studies should be implemented to produce more evidence which will lead to evidence-based studies that help the policy implication. This could lead to more globally applicable delirium diagnosis, prevention, and management strategies. Despite its high prevalence, delirium often remains undiagnosed, especially in hypoactive cases and those occurring concurrently with dementia. This underscores the need for improved training for healthcare professionals for better detection and early intervention, potentially reducing hospital stay costs and improving patients' outcomes. The evidence of cost-effectiveness in delirium management suggests that policymakers should amend clinical guidelines to incorporate standardized strategies that improve patient outcomes and lower healthcare expenses.

6. Strength and limitations

The current review accumulated and summarized the existing literature regarding the economic evaluation of distinct interventions for the prevention, management, and treatment of delirium. This study drew together outcomes, cost-effective interventions, different economic evaluation and their estimation methods, and implementation settings to prevent, reduce, and treat delirium. As an update of previous existing reviews (Caplan et al., 2020; Kinchin et al., 2021, 2023), the outcome of this study provided an opportunity to evaluate whether the barriers and facilitators for effective interventions are consistent or varied over time. The current review focused only on clinically diagnosed delirium, excluding the cost-analysis ordinary of standard interventions. The included studies were based on a clear and concise description of delirium and the implemented intervention. The CHEERS checklist examined the quality of the included studies which reflect the robustness of the selection criteria and the entire review process. Therefore, this study signifies the importance of implemented interventions to prevent and manage delirium. The study facilitates as a guide for decision-making and delirium management research for a better understanding of cost-effective interventions for treating delirium.

Regarding the study's limitation, first, the study only focused on articles published between January 1, 2000 to December 31, 2023 across the electronic bibliographic databases PubMed, MEDLINE, Scopus, and EBSCOhost (CINAHL, PsycINFO, and ECOLIT) which means that any economic evaluation conducted before and after that period and out of those databases may have limited the study's scope and findings. Articles published in languages other than English have also been omitted by this review. The cost information reported in this article was directly sourced from the included articles, which restricts the potential for comparative analysis across countries and over time. The insufficiency of the number of included papers in the meta-analysis resulted in constrained exclusive meta-analytical comparisons and inadequate conclusions. The general comparison and interpretation were limited since the meta-regression analysis was not carried out due to the disproportionate number of studies and the heterogeneity of the variables. Most of the published (two-thirds) meta-analyses of CEA showed substantial heterogeneity among the studies (Veettil et al., 2022). Due to the very low number of studies, the sources of heterogeneity were difficult to investigate, although the authors tried to mitigate it by conducting a subgroup analysis and the WTP threshold-based analysis. Furthermore, the study setting, absence of random allocation, estimate and assessment process variance, cofounding factors, and study context were all disregarded. Owing to the lack of data and the heterogeneity of the study results, there was limited room for doing an in-depth meta-analytical analysis and comparison, which calls for more investigation in future studies.

7. Conclusions

Economic assessments of healthcare and efficiency indicators now play a bigger part in determining how resources should be allocated and how to set priorities in the healthcare sector. In this review, we have investigated economic evaluations of interventions for the prevention, management, and treatment of delirium. The review demonstrated that most of the studies implemented and evaluated a prevention or management intervention for delirium whereas only two studies conducted an economic evaluation for pharmacological treatment. From the therapeutic point of view, the current study recommends more research on molecular drug target identification and therapeutic development against delirium and also conducting economic evaluation of those drug molecules through randomized clinical trials and interventions. Delirium prevention and management interventions showed significant effectiveness with respect to health outcomes. The multi-component non-pharmacological interventions were most effective in preventing and managing delirium in hospital settings. Since delirium is considered a multifactorial neurological complication, more risk factors targeted for intervention ought to be implemented. We believe that this study will enhance the existing literature on the economic evaluation of interventions for delirium and provide ground for further investigation.

CRediT authorship contribution statement

Md Parvez Mosharaf: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Khorshed Alam:** Writing – review & editing, Supervision, Investigation, Funding acquisition. **Jeff Gow:** Writing – review & editing, Supervision, Investigation, Funding acquisition. **Rashidul Alam Mahumud:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Availability of data and materials

All data generated or analyzed during this study are either publicly available or included in this article.

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Declaration of competing interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmmh.2025.100408.

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