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Prevalence of medication-induced delirium in older people admitted to intensive critical unit: a systematic review

Bruno DA SILVA[1], Ivis MARTINS[1], Beatriz HATA[2], Marcia DOS SANTOS[3], Priscila PACKEISER[4], Marilia CAMPOS[1], João Paulo RODRIGUES[1], Maria Teresa HERDEIRO[5], Fátima ROQUE[6,7], Helaine CAPUCHO[8], Maria Olívia ZANETTI[8], Júlia RASO[1], Nereida LIMA[10], Leonardo PEREIRA[1], Fabiana VARALLO[1]

[1]University of São Paulo, School of Pharmaceutical Sciences of Ribeirão Preto, Ribeirão Preto, Brazil; [2]University of São Paulo, Emergency Unit of the University Hospital, Ribeirão Preto Medical School, Ribeirão Preto, Brazil; [3]University of São Paulo, Central Library, Ribeirão Preto, Brazil; [4]Federal University of Rio Grande do Sul, School of Pharmacy, Postgraduate Program in Pharmaceutical Policies and Services; [5]iBiMED - Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Aveiro, Portugal; [6]Research Laboratory on Epidemiology and Population Health, Polytechnic of Guarda (IPG), Guarda, Portugal; [7]Health Sciences Research Centre, University of Beira Interior (CICS-UBI), Covilhã, Portugal; [8]College of Health Sciences of the University of Brasília, Brasília, Brazil; [9]University of São Paulo, Ribeirão Preto College of Nursing, Ribeirão Preto, Brazil; [10]University of São Paulo, Ribeirão Preto Medical School, Ribeirão Preto, Brazil.

Corresponding author: Varallo F, frvarallo@fcfrp.usp.br

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Abstract

Objective: to estimate the prevalence of medication-induced delirium and drug-related problems (DRP) in older people hospitalized in intensive care unit (ICU). **Methods:** A systematic review were conducted in PubMed, EMBASE, LILACS, Ageline, Web of Science, and Cochrane databases (until March 2023). Clinical trials and observational studies that investigated the contribution of medication in the occurrence of delirium and compared with critically ill older patients (aged≥65 years old) without the syndrome were included. We excluded emergency departments, medical wards, primary and secondary healthcare levels, patients with delirium tremens; metabolic encephalopathy; dementia; palliative care; and brain metastasis. The references were entered into Rayyan QCRI. Two pairs of reviewers selected the articles, extracted data, and assessed the risk of bias (ROBINS-I). **Results**: Of 12,492 studies retrieved, after de-duplication exclusion (n=6,025), title/abstract (n=6,467) and full reading (n=286), two met the inclusion criteria. Both were observational (cohort), developed in high-income countries, with high level of risk of bias (overall). The frequency of delirium and subsyndromal delirium was 15.8% to 33.9%. Independent risk factors were the exposure of opioids and use of corticosteroids. Delirium increased the length of hospital stay in ICU, and the mechanical ventilation. **Conclusion:** Further studies are necessary to understand the DRP and characteristics of pharmacotherapy associated with delirium in critically ill older people. Adverse drug reactions and deliriogenic load seem to contribute to the occurrence of syndrome.

Keywords: Delirium; Pharmaceutical preparations; Intensive care units; Pharmacovigilance; Patient safety; Aged.

Prevalência de delirium induzido por medicamentos em idosos hospitalizados em unidade de terapia intensiva: uma revisão sistemática

Resumo

Objetivo: estimar a prevalência de delirium induzido por medicamentos e problemas relacionados a farmacoterapia (PRF) em idosos hospitalizados em unidade de terapia intensiva (UTI). **Métodos:** Revisão sistemática foi conduzida nas bases de dados PubMed, EMBASE, LILACS, Ageline, Web of Science e Cochrane (até março de 2023). Foram incluídos ensaios clínicos e estudos observacionais que investigaram a contribuição do medicamento na ocorrência de delirium e compararam com pacientes idosos gravemente enfermos (idade ≥65 anos) sem a síndrome. Foram excluídos unidades de emergência, enfermarias gerais, níveis de atenção primária e secundária, pacientes com delirium tremens; encefalopatia metabólica; demência; cuidados paliativos; e metástase cerebral. As referências foram inseridas no Rayyan QCRI. Duas duplas de revisores selecionaram os artigos, extraíram os dados e avaliaram o risco de viés (ROBINS-I). **Resultados:** Dos 12.492 estudos recuperados, após exclusão de duplicação (n=6.025), título/resumo (n=6.467) e leitura completa (n=286), dois atenderam aos critérios de inclusão. Ambos foram observacionais (coorte), desenvolvidos em países de alta renda, com alto nível de risco de viés (geral). As frequências de delirium e delirium subsindrômico foram de 15,8% a 33,9%. Fatores de risco independentes foram exposição a opioides e uso de corticosteróides. O delirium aumentou o tempo de internação na UTI e de ventilação mecânica. **Conclusão:** Mais estudos são necessários para compreender os PRF e as características da farmacoterapia associadas ao delirium em idosos gravemente enfermos. As reações adversas aos medicamentos e a carga deliriogênica parecem contribuir para a ocorrência da síndrome.

Palavras-chave: Delirium; Preparações farmacêuticas; Unidades de terapia intensiva; Farmacovigilância; Segurança do paciente; Idoso.

Introduction

Delirium is a complex syndrome characterized by disturbance in attention (reduced ability to direct, focus, sustain, and shift attention), awareness (reduced orientation to the environment), and an additional disturbance in cognition (memory deficit, disorientation, language, visuospatial ability, or perception), which are not better explained by another preexisting, established, or evolving neurocognitive disorder.[1] There is evidence that it is a direct physiological consequence of another medical condition; substance intoxication, withdrawal (i.e., due to a drug abuse or medication), or exposure to a toxin; or due to multiple etiologies.[1] The clinical presentation is based on the psychomotor behavior changes, being classified in hyperactive, hypoactive and mixed.[1]

Despite first being described more than 2,500 years ago, delirium remains poorly understood, overlooked, misdiagnosed, or treated inappropriately.[2,3] Nevertheless, the syndrome is considered a key quality indicator for health care assistance, mainly for older people,[4] since 30–40% of the occurrence could be avoided.[5]

Delirium is most commonly observed in intensive critical unit (ICU),[6-8] which is defined as a specially staffed and equipped, separate and self-contained area of a hospital dedicated to the management and monitoring of patients with life-threatening conditions. It provides special expertise and the facilities for the support of vital functions, and engages the skills of medical, nursing, and other personnel experienced in the management of these problems.[9]

The syndrome in critically ill patients is multifactorial[7] and associated with higher mortality rate, more complications, longer duration of mechanical ventilation, and longer length of stay in ICU and and other hospital units.[10] Consequently, the economic burden of delirium rises for health institutions and families, which could range between $806 and $24,509 (in 2019 US$), depending on the setting and methods applied.[11]

Dementia, prescriptions of benzodiazepines before ICU admission, elevated creatinine level, and low arterial pH were detected as admission risk factors for medical ICU delirium among older people.[12] Advanced age[13] and frailty[14] also have been reported as risk factors for occurrence and prognosis.[14]

It is estimated that 12 to 39% of delirium in older people are related to the patient's pharmacotherapy.[15,16] ICU-specific factors that may increase the risk for medication-induced delirium include untreated pain (although the association between pain and delirium is not clearly established),[17] polypharmacy,[18] psychoative drugs, or drugs with anticholinergic properties.[19,20]

Nonetheless, ascribing delirium at the ICU bedside solely to the use of a particular medication could be a mistake,[20] since the association of several medicines with different deliriogenic and anticholinergic properties[19] increases the likelihood of the occurrence.[20] Thus, it is plausible to presume that other drug-related problems (DRP), besides adverse drug reactions (ADR), might precipitate the syndrome,[21] depending on patient's baseline vulnerability.[3] Therefore, medications may be one modifiable risk factors that clinicians can target to prevent the development of delirium.[22]

To the best of our knowledge, there are three systematic [15,23,24], and four narrative review publications[16,25-27] which reported the contribution of medication in inducing delirium. However, none of these focused on critically ill older people. Hence, it remains unclear which DRP might precipitate the syndrome [for instance those related to safety (i.e., ADR, deliriogenic and/or anticholinergic loads) and/or necessity (i.e., overtreatment or untreated medical condition, such as pain)] in ICU. The proper identification of DRP and their causes contributes to the appropriate management of the syndrome and patient safety. The aims of our systematic review were to estimate prevalence of prevalence of drug-induced delirium, the outcomes, the characteristics of pharmacotherapy, and the causes of DRP associated with neurocognitive disorders in older people hospitalized in ICU.

Methods

Systematic review protocol registration

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (CRD42021266535) and was performed according to recommendations of Cochrane Collaboration.[28] The report of the protocol was carried out based on the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[29] This method was applied to answer the following guiding question: "Which DRP contributes to the occurrence of delirium in older people hospitalized in the ICU?"

Eligibility criteria

The inclusion and exclusion criteria of the studies were related to the guiding question of the systematic review, which was elaborated according to the PECOS acronym (population, intervention, comparator, outcomes, and type of study). Therefore, the inclusion criteria included:

Population: older people (65 years old or more) without restriction of gender or health conditions, hospitalized in the ICU.

Exposure: hypoactive, hyperactive, or mixed delirium which has been diagnosed according to the DSM-5 criteria or identified by a validated instrument.

Comparator: inpatients without delirium (control group).

Outcomes: primary outcomes were prevalence or incidence of medication-induced delirium and DRP associated with the mental status change (necessity, safety, or effectiveness).

Types of studies: observational (cohort, case-control, cross-sectional studies) and clinical trials. Gray literature was not considered.

The study population comprised older people (65 years and above) hospitalized in the ICU, who developed delirium regardless of the subtype (mixed, hyperactive or hypoactive) diagnosed according to criteria of the DSM-5 or identified with the aid of a validated instrument, whose outcomes have been compared with geriatric patients without the syndrome (control group). Individuals who have at least one of the following conditions were not included: *delirium tremens*; metabolic encephalopathy; previous diagnosis of dementia; palliative care; brain metastasis, hospitalized in emergency departments or assisted to primary or secondary healthcare level. Individuals with life-threatening health conditions related to significant mortality or morbidity in the absence of medical intervention were considered critically ill patients.[30] These individuals may have vital organ dysfunction that result in cardiovascular, respiratory, neurological, renal and/or metabolic instability.[31] The absence of organic dysfunction and/or disease prognosis scores were not criteria for the exclusion of articles.

Pharmacotherapy was defined as the use of medicines use of drugs to treat disease or its symptoms.[32] Polypharmacy was defined as the concurrent use of five or more medications.[33] A drug-related problem (DRP), defined as a drug therapy problem, is any undesirable event experienced by a patient that involves, or is suspected to involve, drug therapy and that interferes with achieving the desired goals of therapy.[34]

Information sources and search strategy

The search strategy was reviewed by a librarian (MS) and conducted in online databases: PubMed, EMBASE, LILACS, Ageline, Web of Science and Cochrane (**Supplementary material**), from inception to 30th March 2023 with no restrictions. In addition, a manual search was performed in the bibliographic references of articles eligible for review. Articles which were written in Portuguese, English or Spanish languages were included during the screening of titles, abstracts, and full reading. All references found were entered into Rayyan QCRI, the online tool for systematic reviews.[35]

Selection of articles and data collection process

The search was performed within the period March 2023. Two pairs of independent reviewers (BS and BH; IM and PP), screened titles and abstracts to identify potentially eligible studies. Each pair was made up of a reviewer with experience in conducting systematic reviews, while the other was experienced in clinical practice. Subsequently, two independent reviewers evaluated the full texts for eligibility (BS and BH). Disagreements were resolved through discussion and consultation with a third reviewer (FV), when necessary.

Extraction and tabulation of data

Primary outcomes: frequency of medication-induced delirium (number of patients and % of occurrence) and the DRP associated with the mental status change (number and classification of the causes regarding necessity, safety or effectiveness). Secondary outcomes: number of inpatients who died (mortality); length of hospital stay (LHS); length of mechanical ventilation (LMV); prognostic [duration (days); resolution (days) and severity (mild, moderate, and severe)]; risk-factors (relative risk or odds ratio); and number of inpatients with disabilities arising from delirium (falls, fractures, pressure injury and cognitive impairment identified by validated instrument, such as mini-mental state exam).[36]

Two reviewers (BS, BH) extracted data independently from included studies using a standardized electronic data form, which was developed with the aid of the Microsoft Excel® software and included the following variables: i) the characteristics of the study (authors, year of publication, country, type of study, objectives, inclusion and exclusion criteria, sample size); ii) of the patients (age, gender, health condition, comorbidities, frail and geriatric syndromes, follow-up, scores of organ dysfunction/failure - (Sequential Organ Failure Assessment – SOFA,[37] mortality - Acute Physiology Score Chronic Health Evaluation-APACHE III or IV,[38] Glasgow Scale[39] or Simplified Acute Physiology Score -SAPS II or III[40]); iii) pharmacotherapy [(number of medicines, medicine and/or pharmacological classes associated with delirium, dose, posology, route of administration, DRP and their associated factors (deliriogenic load, polypharmacy, drug-drug interactions, health condition without treatment, ineffectiveness of medicine, drug load, anticholinergic property, medicines potentially inappropriate for older people)]; iv) delirium (frequency, subtype, instrument of diagnosis, time of duration and resolution); v) clinical outcomes (LHS, LMV, mortality, number of inpatients with disabilities arising from delirium (pressure injury, falls, fractures and cognitive impairment). Data extracted were independently checked by a third reviewer (FV).

Risk of bias

Two pairs of reviewers (BS, MZ, JR, MC) assessed methodological quality of included studies independently and in duplicate. ROBINS-I tool[41] was applied to assess the risk of bias of observational studies and ROB-2[42] for clinical trials, based on Cochrane Collaboration.[28] To assess the quality of evidence, the GRADE Working Group guidelines were considered.[43]

The ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) is a tool used to assess the risk of bias in non-randomized studies of interventions. It consists of seven domains that are evaluated to determine the overall risk of bias, which are: bias due to confounding (the extent to which confounding has been controlled in the study design or analysis); bias in selection of participants into the study (such as selection bias, exclusion bias, or incomplete reporting of eligibility criteria); bias in classification of interventions (such as inadequate description of the intervention or lack of blinding); bias due to deviations from intended interventions (the extent to which participants adhered to the assigned interventions and the extent to which the interventions were delivered as intended); bias due to missing data (such as differential dropout rates or incomplete outcome data); bias in measurement of outcomes (such as reliance on self-reported outcomes or lack of blinding in outcome assessment); bias in selection of the reported result (such as selective reporting of outcomes or selective analysis). For each domain, the study is classified into one of three categories: low risk of bias, moderate risk of bias, or high risk of bias. The overall risk of bias in the study is determined by the highest risk of bias rating across all domains.[41] The tool was applied in its entirety, without adaptations.

Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) is the recommended tool to assess the risk of bias in randomized trials included. The tool provides a framework for considering the risk of bias in the findings of any type of randomized trial. It is structured into five domains through which bias might be introduced into the result, such as: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; and 5) bias in selection of the reported result.[42]

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool is a widely used approach for evaluating the quality of evidence and strength of recommendations in systematic reviews. The GRADE approach assesses the quality of evidence based on five domains: risk of bias in the included studies, degree of inconsistency in the results across studies, indirectness (extent to which the included studies address the clinical question of interest), degree of imprecision in the estimates of effect, and likelihood of publication bias in the included studies. For each domain, the quality of evidence is classified as high, moderate, low, or very low. The overall quality of evidence is then determined based on the domain with the lowest quality rating. The GRADE approach also evaluates the strength of recommendations based on factors such as the balance of benefits and harms, values and preferences, and resource implications. Recommendations are classified as strong or weak.[43]

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Presentation of data synthesis

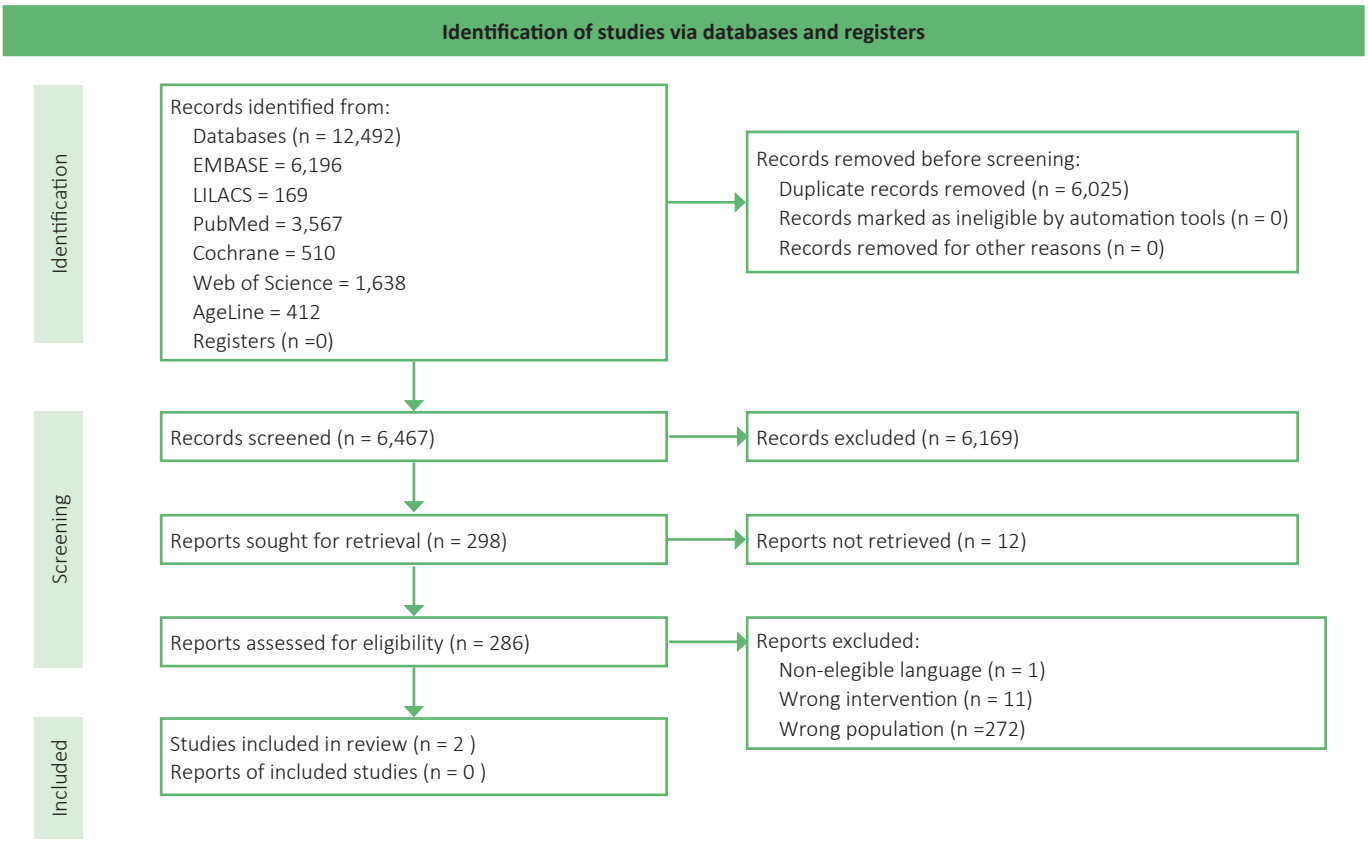
The extracted data were presented in schematic form. The tables and/or figures and/or graphs showed findings related to: (I) stages of screening and selection of studies; (II) medicines and/or pharmacological classes associated with delirium; (III) DRP and their causes; (IV) impact of medication-induced delirium on outcomes assessed; (V) clinical and demographic characteristics of older people that increase the vulnerability of occurrence of medication-induced delirium.

Results

Results of the search

The search results are summarized in a PRISMA diagram (**Figure 1**). Of the 12,492 articles retrieved, after de-duplication, 6,467 unique references remained, which were screened by title and abstract. Of these, 286 full-text articles were assessed for eligibility and two were included in the review (**Figure 1**).

Figure 1. Review flow diagram.



Included studies

The studies were conducted in the United States[17] and Japan[49]. Both used the observational epidemiological cohort design, one retrospective[17] and the other prospective.[49] The total number of participants included was 552 patients, the majority being male [59.5% (326/552)]. The monitoring time of the studies ranged from five to seven months, with an average of six months (**Table 1**). The aims, inclusion and exclusion criteria of each study are shown in Table 1.

Participants

No study reported health conditions, comorbidities and the presence of frailty or geriatric syndrome among the inpatients enrolled. However, Pavone et al.[17] reported that the assessed cohorts were comparable regarding demographic characteristics, since no differences were observed in the diagnosis at admission (data not shown).

Both studies did not use indicators scores of organ dysfunction/failure (SOFA). To assess the prognosis of disease severity, Yamaha et al.[49] used the APACHE II score system. Pavone et al.[17] used the Richmond Agitation-Sedation Scale (RASS) to assess the level of consciousness and to analyze the association between this score and delirium diagnosis.

Primary outcome

The frequency of occurrence of delirium varied between 15.8% and 33.0%. For subsyndromal delirium, it was 33.9% (**Table 2**). The detection of the syndrome was performed using the CAM-ICU[17] and Intensive Care Delirium Screening Checklist (ICDSC) tools[49] (**Table 2**). Authors did not classify the subtype, duration, severity, and resolution of the syndrome. Besides, the classification of DRP associated with delirium were not reported.

Pavone et al.[17] observed that delirium was significantly associated with a greater number of days of exposure to opioids (p = 0.0018)

Table 1. Characteristics of the studies and participants enrolled (n = 2)

Authors (year)	Country	Study design	ICU	Objectives	Participants				
					Inclusion criteria	Exclusion criteria	N enrolled (total)	Male n (%)	Follow-up (months)
Pavone et al.[11] (2021)	United States	Retrospective cohort	Surgical	Evaluate the relationships among acute pain severity, opioid analgesic administration and the onset of delirium among older adults in the surgical ICU	Age ≥ 65; E; admitted to the SICU for > 24 hours; and screened for delirium using the confusion assessment method for the intensive care unit (CAM-ICU) anytime between day 1 and day 7 during their SICU stay	Patients were excluded if they had an admitting diagnosis related to neurological or central nervous system injury; for patients readmitted to the SICU, only the index admission was evaluated.	172	108 (63.0)	5
Yamada et al.[28] (2018)	Japan	Prospective cohort	Medical and Surgical	Evaluate the incidence of delirium and sub-syndromal delirium as well as the risk factors and progression to delirium	Adult patients admitted to the ICU for more than 12 hours	Patients under 20 years of age; those in deep coma, and those who were deeply sedated (RASS; score of -4 and -5)	380	218 (57.4)	7

ICU = intensive care unit; SICU = surgical intensive care unit; RASS = Richmond Agitation-Sedation Scale.

and propofol (p < 0.001) compared to the group without delirium. Exposure was defined as any instance of opioid administration (any type or route) during a 24-hour period. No association was observed with the number of days of exposure to benzodiazepines (p = 0.1253) and the level of sedation (p = 0.39). However, the only independent predictor for the occurrence of next-day delirium was opioid exposure (**Table 2**).

The independent risk factors for the occurrence of subsyndromal delirium or delirium identified by Yamada et al.[49] were related to demographic and clinical characteristics [age, predisposing cognitive impairment, higher scores of APACHE II, lower blood cell count and higher concentration of C-reactive protein)], in addition to invasive procedures (blood transfusion) (**Table 2**). For the progression from subsyndromal delirium to delirium, pharmacotherapy (use of corticosteroids), demographic and clinical characteristics (age and PaO_2), health care (type of ICU admission and use of physical restraint were detected as risk factors (**Table 2**).

Other characteristics associated with pharmacotherapy that might contribute for precipitating delirium were not evaluated, such as polypharmacy (number of drugs used), anticholinergic and/or deliriogenic loads, as well as potentially inappropriate medication for older people, dose and period of use of medication. Regarding the route of administration, only one study[17] described that opioids were administered by oral, intravenous (including patient-controlled analgesia) and epidural rotes. However, no statistical analysis was performed to evaluate whether route might be considered risk factor.

Table 2. Frequency and independent risk factors for delirium (occurrence and progression) in older people hospitalized in ICU (n = 2)

Author (year)	Frequency (%)	Independent risk factors [OR (95% CI), P value]
Pavone et al.[11] (2021)	33.0	*Opioid exposure: [1.84 (0.97–3.50), P = 0.0311*]* Propofol exposure: **[1.91 (0.91–4.03), P = 0.1265]** Pain severity (average): **[0.95 (0.85–1.06), P = 0.3701)]** Mechanical ventilation: **[0.47 (0.14–1.52) P = 0.2275]** RASS: **[0.54 (0.23–1.26), P = 0.1533]**
Yamada et al.[28] (2018)	15.8 (delirium) 33.9 (Subsyndromal delirium)	**Subsyndromal delirium or delirium** Age: **[1.02 (1.00–1.04) P = 0.0353**] Predisposing cognitive impairment: **[13.1 (2.40–244.6), P = 0.0012]** Blood transfusion: **[2.68 (1.42–5.11), P = 0.0021]** APACHE II: **[1.12 (1.03–1.19), P = < 0.0001]** Red Blood Cell: **[0.70 (0.49–0.99), P = 0.0480]** C reactive protein: **[1.10 (1.04–1.18), P = 0.0005]** **Progression from subsyndromal delirium to delirium** Age: **[1.07 (1.02–1.14), P = 0.0013]** History of hospitalization (emergency, scheduled entries): **[3.53 (1.26–11.0), P = 0.0154]** *Steroid use:* Restrain use: **[4.38 (1.77–11.0), P = 0.0014]** PaO2 (mmHg): **[0.98 (0.97–0.99), P = 0.0156]**

ICU = intensive care unit; OR = odds ratio, CI = confidence interval; APACHE II = Acute Physiology Score Chronic Health Evaluation; RASS = Richmond Analgesia and Sedation Scale.

Secondary outcomes

The studies did not report patients who died or developed temporary or permanent disability resulting from delirium. However, by univariate analysis, the occurrence of delirium was associated with longer ICU LHS[49], and LMV[17,49] (**Table 3**). The progression from subsyndromal delirium to delirium also showed association between ICU LHS and LMV[49] (**Table 3**).

Table 3. Outcomes related to delirium in older critically ill patients hospitalized in ICU.

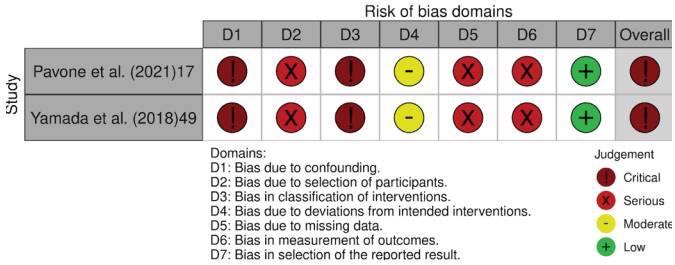
Outcome	PAVONE et al. (2021) DELIRIUM			YAMADA et al. (2018) DELIRIUM				
	Yes	No	p valor	No	Yes- SS	p valor	Progression (SS-D)	p valor
LHS (days)	NR	NR	NR	2.0 (2.0–2.0)	2.0 (2.0–3.0)	**<0.001**	4.0 (2.0–6.0)	**<0.001**
Mechanical ventilation- N (%)	29 (25%)	40 (71%)	**<.001***	NR	NR	NR	NR	NR
LMV -hr (range)	18 (1–168)	66 (9–168)	**<.001***	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.001	0.0 (0.0–53.5)	**0.017**
RASS mean (range)	0 (−4 a 0)	−1 (−2 a 0)	**0.39**	NR	NR	NR	NR	NR

Note: D = delirium; LHS = length of hospital stay; LMV = length of mechanical ventilation; NR = not reported; SS = subsyndromal delirium; RASS = Richmond Analgesia and Sedation Scale

Risk of bias in included studies

Both studies were vulnerable to bias, mainly due to small sample size and confounding bias. The analysis through ROBINS-I showed a low risk of bias in one of the evaluated criteria (selection of the reported result) **(Figure 2)**, while critical risk was observed in two analyzed domains (confounding, and classification of interventions) **(Figure 2).**

Figure 2. Quality assessment of included studies, according to the ROBINS-I.



Missing data domain due to limitation in the follow-up methods, also due to uncertainty in determining whether the statistical analysis considered all patients included despite dropouts. In both studies, it is unclear if the same monitoring for patients with or without delirium was applied. From our perspective, it appears as if patients with delirium had serious health conditions and used higher doses of medicines, which could imply the different strategies used in performing the ICU monitoring. We also did not identify if the results from patients who died during the follow up was considered in the statistical analyses. The quality of the evidence is summarized in Figure 2.

Moreover, it was difficult to carry out meta-analyses due to the heterogeneity across the observational studies. Therefore, GRADE tools was not applied.

Discussion

The studies included in this systematic review were observational, developed in high-income-countries, whose designs showed a high level of risk of bias. The exposure to opioids was observed as independent predictor factor for the precipitation of medication-induced delirium. In addition, the results indicated that opioid use is a risk factor for the progression from subsyndromal delirium to delirium. The evidence did not include the classification of DRP, but it suggests that issues related to safety were notably influential in either triggering or exacerbating delirium. It seems the contributing factors were ADRs and deliriogenic load.

Delirium in the ICU has multifactorial causes.[7] In older people, precipitating factors previously described was sleep disturbance arising from the characteristics of the ICU environment (e.g.: room lighting at night; excessive noise; and constant patient care).[7,50,51] Other causes have also been shown in this age group, such as the use of sedation and analgesics,[52] the high number of prescribed drugs,[20] life-threatening conditions at the time of admission (infection), physical restraint, amongst others.[52] Therefore, real-life studies, can provide valuable information about the real-world safety of medication.[53] Thus, adequate control of confounding bias is necessary. Regarding studies intended to assess delirium, the use of time-varying confounding analysis techniques (for example, multivariable Markov models) might contribute to improving the robustness of data.[20]

Our findings identified that opioid administration predicted the onset of next-day delirium.[17] Opioids are the mainstay for treatment of acute pain in critically ill patients.[33] However, the prolonged use has been associated with high incidence of ADR such as delirium,[54] whose likelihood of occurrence does not differ depending on the opioid, the route, or the regimen used.[54]

Duprey et al.[55] found that the use of opioids in the ICU increased the risk of delirium in a dose-dependent association. Our hypothesis is the greater exposure to opioids, the higher deliriogenic load. Consequently, the risk of delirium occurrence is increased. This data is important to improve the management of analgesia in this age group, as inadequate pain management can also contribute to the development of delirium. However, exposure to lower deliriogenic loads seems to be effective and tolerated in hospitalized older people.[56]

The Joint Commission, with its mission to enhance healthcare institutions globally for better quality care and patient safety, identifies delirium as an adverse event linked to opioid use. Contributing factors to these events include insufficient awareness of potency variations among opioids, inappropriate prescribing or administration practices, and inadequate patient monitoring. It is recommended to implement a comprehensive monitoring policy in hospitals. This should should involveeducation and training of staff along with the establishment of effective processes, such as

integrating alerts into electronic prescribing systems for all opioids, specifying dosing limits, and providing other usage instructions.[57] It is worth emphasizing that the serious events associated with the use of opioids are a relevant public health problem and affect the health system in different ways. In US, the opioid crisis or opioid epidemic observed since the late 1990s is characterized by an overprescribing of these drugs being responsible for 75% of the approximately 100,000 drug overdose deaths between 2020 and 2021.[58] The indiscriminate use of opioids by outpatients causes hospitalizations and deaths, which could be avoided. Owing to the physiological changes normally presented by older people, including reduction reduction of renal mass and drug clearance, these individuals are more susceptible to adverse events.[59] Therefore, the indication for use and monitoring of opioid use in this population require special attention.[60]

Although sedation was not associated with next-day delirium,[17] Burry et al.[19] noticed association between delirium and the use of benzodiazepines when the window of exposure was expanded to 48 hours among critically ill adults. Findings corroborate the hypothesis of deliriogenic load as possible cause of medication-induced delirium, besides ADR. Nevertheless, despite the fluctuating nature of delirium, which impairs the determination of the precise onset times and endpoints,[61] these variables are important to be determined, in order to assess the characteristics of pharmacotherapy and DRP associated with the syndrome in older people hospitalized in ICU.

As previously highlighted, our systematic review identified the use of corticosteroid as a modifiable risk factor for progression from subsyndromal delirium to delirium.[49] Glucocorticoids are widely used in ICU for their anti-inflammatory and cardiovascular effects.[62] Scheriber et al.[63] applied multivariable Markov models to assess the transition to next-day delirium in mechanically ventilated patients with acute lung injury. The authors did not detect a significant dose-relationship, but old age and administration of any systemic corticosteroid in the prior 24 hours were identified as independently risk factors. Life-threatening illness may change blood-brain barrier permeability. Therefore, low doses of glucocorticoids could have implications for brain function in critically ill patients and ICU survivors.[62] A prospective cohort conducted by Vondeling et al. [64] showed that the anticholinergic drug exposure at ICU admission increases the risk of delirium in critically ill older inpatients regardless of severe sepsis and/or septic shock.

Our results suggest that further studies are need in order to assess the risk/benefit of medicines commonly prescribed in ICU and their impact on progression to delirium in older people. Deprescribing strategies should be considered when feasible.

Despite the fact that no study had described severity and subtype of delirium, there were evidence that delirium severity is associated with increased ICU LHS[65] and LVM,[10] being the hypoactive subtype often observed in older people.[66] Patients with hypoactive delirium are most commonly missed (not identified) in ICU, and agitated delirium is treated with sedation, which masks the condition without treating it.[67] The role of medications has particular interest, as they may be one of the few modifiable risk factors, besides immobilization and sleep disturbance,[67] that clinicians can target to prevent,[22] and minimize the impact on health outcomes. [68]

Pharmacotherapeutic follow-up, including the identification, prevention, and resolution of real and potential DRP, as well as the avoidance of medications with deliriogenic properties, and adjusting doses in cases of renal and hepatic failure, are important strategies. Additionally, decresing the precipitating factors such as daily sedation breaks and dehydration, ensuring good nutrition, creating a normalized environment, and effective sedative management are all beneficial. Furthermore, actively engaging with the patient as much as possible might significantly contribute to prevent the syndrome.

Finally, it is important to highlight that opioids and corticoesteroids are considered potentially inappropriate for older people (PIM).[60] Therefore, it is necessary to evaluate whether the higher number of PIM in ICU environment might be related to the increase of cases of neurocognitive disorders potentially avoidable.

Limitations

Gray literature was not assessed, because the authors considered it lacking necessary information on all the variables and outcomes pertinent to this review. Gray literature can be more difficult to assess in terms of its relevance, reliability and may not have gone through the same peer review. Therefore, the quality and reliability of information in the gray literature may be questionable.

Our search strategy may be a limitation of the study. For pragmatic reasons, we excluded studies that did not report in non-Roman characters and, we did not extract data from otherwise eligible trial database registries or from gray literature. We could not precisely identity the DRP, the outcomes and severity of delirium due to the high level of risk of bias of the included studies. We also did not contact the corresponding authors of included articles to obtain additional relevant information. Furthermore, meta-analysis could not be performed due to heterogeneity of data.

Conclusion

Approximately one-third of older people showed delirium or the progression from subclinical delirium to delirium in ICU. The independent predictive factors for occurrence and progression of medication-induced delirium were the exposure of opioids and corticosteroids, respectively. Owing to the lack of causality assessment, it was not possible to precisely identify the characteristics of pharmacotherapy and DRP related do delirium. However, those related to safety, such as ADR and deliriogenic load were suggested. Therefore, further studies are needed to clarify the contribution of medicines in delirium occurrence among critically ill older people.

Collaborators

BS, BH, IM and PP: screened titles and abstracts to identify potentially eligible studies; evaluated the full texts for eligibility; and extracted data. JR, MS: performed the search strategy. BS, MOZ, JR, MC: risk of bias analysis. HC, MTH, FR, NL: contributed to the development of the study design, discussion and revision of the manuscript. LRLP, FRV: contributed to the conception, supervision of the research and revision of the manuscript.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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