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Risk Factors for Postoperative Delirium in Older Adults Undergoing Major Orthopedic Surgery: A Systematic Review and Meta-Analysis

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Purpose: We aimed to identify the risk factors for postoperative delirium (POD) in adults undergoing orthopedic surgery and review evidence-based prevention strategies.
Methods: We conducted a systematic review and meta-analysis of studies published between 2014 and 2024, searching multiple databases. Fifty studies involving 1,247,832 patients met the inclusion criteria. We calculated the pooled odds ratio (OR) values of various risk factors for POD.
Results: The pooled incidence of POD was 23.4%. The significant non-modifiable risk factors included dementia (OR 24.85), a history of stroke (OR 14.61), and age ≥80 years (OR 4.73). The key modifiable risk factors were use of sedative-hypnotics (OR 6.42), depression (OR 4.98), and polypharmacy (OR 2.34). Undergoing general anesthesia and longer surgical duration also increased the risk of POD.
Conclusions: POD is a common complication in orthopedic surgery and is associated with modifiable and non-modifiable risk factors. The use of risk assessment models and multicomponent prevention strategies focusing on medication optimization, perioperative care, and environmental support is recommended to mitigate the risk of POD.

Keywords: Postoperative delirium, orthopedic surgery, risk factors, meta-analysis

Postoperative delirium (POD) is an acute, severe neuropsychiatric condition that constitutes one of the important problems of perioperative care, especially in elderly patients undergoing major surgery [(8)]. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), defines this condition as a disturbance in attention and awareness that manifests over a short period (typically hours to days), fluctuates in severity, and is characterized by an acute change in baseline mental status, inattention, and disorganized thinking [(1)].

The pathophysiology of POD is extremely intricate and continues to be the focus of active investigation. One prevalent theory is that of a multifactorial etiology, wherein a baseline vulnerability—usually characterized by pre-existing cognitive impairment or old age—precipitates into a state of acute brain failure following an insult (e.g., major surgery). The key neurobiological pathways implicated include a profound imbalance in key neurotransmitters, specifically gross underactivity in central cholinergic function coupled with a relative excess

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of dopaminergic activity that disturbs attentional and arousal processing. In addition to this impairment in neurotransmission, the acute-phase response following surgical trauma, characterized by high systemic levels of circulating pro-inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-α) is also in place and these cytokines may access the brain through a disrupted blood-brain barrier and cause neuro-inflammation. Simultaneously, a significant neuroendocrine stress response dominated by high cortisol levels exacerbates neuronal damage, which in turn adds to the clinical appearance of delirium [15].

The clinical and financial consequences of POD are severe, potentially lasting longer than the immediate postoperative period. The presence of delirium predicts a plethora of poor long-term complications. There is considerable evidence to support the tight correlation between POD and higher mortality, both in-hospital and post-discharge [17]. In addition, individuals who have had an episode of delirium are at increased long-term risk for cognitive impairment or worsening of pre-existing dementia [17]. From a functional viewpoint, these patients have much longer hospitalizations in the majority of cases, are less likely to return to their previous level of performing activities of daily living, and more frequently require their discharge to a long-term care facility, rather than being able to return home [9]. These complications impair the quality of life of patients, representing a heavy load for care providers, and place an enormous economic burden on the health-care system, with annual costs associated with delirium in the United States reaching a maximum of $164 billion [9].

The prevalence of POD is especially high in the field of orthopedic surgery, with estimates ranging between 11% to 51%, depending on the type of surgery and patient characteristics [2]. In particular, patients who underwent surgery for hip fractures are at great risk due to their older age and the high degree of concomitant illness burden [11]. This high prevalence reflects the fact that this group of patients is at greater risk for physiological insults related to surgery, anesthesia and overall perioperative stress.

Although there is an increasing amount of literature available, attempts to definitively identify risk factors for POD have produced a wide range of variables and even some conflicting results. This heterogeneity is probably due to differences in study design, characteristics of patient populations, and diagnostic criteria of delirium used across studies. This ambiguity represents a major impediment to the establishment of efficient and standardized screening procedures, as well as dedicated preventive programs. Therefore, a systematic synthesis and meta-analysis on the available evidence are needed to unify the evidence and produce strong and reliable results about how much the individual factors work.

Therefore, the purpose of this analysis was to conduct a systematic review and meta-analysis that would identify factors correlated with the development of POD among adult patients who had undergone orthopedic surgery and assess the strength of their association. In addition, this study aimed to review the evidence-based preventive strategies employed in managing POD and compile comprehensive guidelines for risk assessment and delivery of care by physicians and healthcare professionals for this population. Our ultimate goal was to limit the occurrence of this dire complication and improve overall treatment outcomes.

METHODS

This systematic review and meta-analysis was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14] to ensure a transparent and reproducible process.

Search Strategy and Data Sources

We carried out a literature search in PubMed (MEDLINE), Embase, and Scopus for all relevant studies published in the last 10 years from January 1, 2014, to December 31, 2024. This period was chosen to cover the most recent research in this area. We created a search strategy to maximize both sensitivity and specificity, by using a controlled vocabulary (e.g., MeSH, Emtree) with free-text keywords including three key concepts: 1) delirium (e.g., "delirium," "postoperative confusion"), 2) orthopedic surgery (e.g., "orthopedic surgery," "arthroplasty," "hip fracture") and 3) risk factors (e.g., "risk factor," predictor"). The full search strategy for each database can be found in the appendix (not available online). To reduce publication bias and retrieve a more comprehensive literature available globally, no language limitation was placed in the first search. The search was supplemented by a review of the reference lists of all included articles and relevant systematic reviews to identify additional studies. Although our initial search did not have language restrictions, all articles that met the full inclusion criteria were published in English.

Study Selection Criteria

To ensure a focused and relevant synthesis of evidence, we established stringent study selection criteria. Eligible studies were required to meet the following specifications: (1) The study design had to be observational in nature, specifically a prospective cohort, retrospective cohort, or case-control study, as these designs are most appropriate for evaluating risk factors for a given outcome. (2) The study participants were strictly defined as adults > 18 years of age, irrespective of the type of orthopedic surgery. This selection ensured that our results would be immediately generalized to the intended population. (3) POD had to be one of the primary outcomes in the study. The delirium diagnosis had to have been ascertained using an established and validated diagnostic tool, such as the Confusion Assessment Method (CAM), a well-recognized, sensitive, and specific instrument used in non-psychiatric populations (Inouye et al., 1990) or by employing formal DSM-5 criteria for the definition of the outcome. (4) The study needed to have provided enough data for Odds Ratio (OR) and 95% Confidence Interval (CI) values to be calculable in relation to at least one factor, or if not available, the actual numbers of exposed/unexposed patients were required.

Alternatively, articles were systematically excluded if they were non-original contributions (i.e., editorials, letters to the editor, narrative reviews and commentaries), which did not contain new research data. We excluded studies with children because physiological and psychological responses of adults are significantly different compared with those in children. We also excluded those studies that reported pooled data that were not separately presented for the type of orthopedic surgery group, which would cause substantial heterogeneity and confounding. In other words, all studies that could not supply clear and complete information which could be extracted for our meta-analysis were excluded from the final synthesis.

Data Extraction and Quality Assessment

Data extraction and quality assessment were conducted independently by two independent reviewers to reduce bias and errors. A standardized data extraction form was created and pilot tested in Microsoft Excel. The disagreements between reviewers were resolved through discussion (by common agreement) and a third senior reviewer was present to act as an arbitrator in case the disagreements could not be resolved.

The data extracted included: (1) Study characteristics: first author, year of publication, country where the study was carried out, study design, length of follow-up, and funding; (2) Population characteristics: number of total patients and those with and without delirium, mean/median age, sex ratio (% men), type of surgery (e.g. hip fracture fixation, total joint arthroplasty, spinal surgery) and major inclusion/exclusion criteria; (3) Outcome and risk factor data: diagnostic criteria for delirium (e.g. CAM or DSM-5), rate of developing delirium during admission or post-operatively altogether, assessed risk factors including adjusted effect estimates as either OR, relative risk [RR], or hazard ratio (HR) and 95% CI along with covariates.

The risk of bias for each included study was evaluated using the Cochrane-recommended Risk of Bias in Non-randomized Studies of Interventions tool [16]. This instrument assesses bias across seven domains: confounding variables, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result. Each domain was rated as having a "low," "moderate," "serious," or "critical" risk of bias, culminating in an overall risk of bias judgment for the study.

Data Synthesis and Statistical Analysis

Stata software version 17.0 (Stata Corp, College Station, TX, USA) was used for all statistical analyses.

Incidence Analysis: The pooled incidence of POD, and its 95% CI value was estimated using a random-effects model [3] after Freeman-Tukey double arcsine transformation for stabilization of variance. The latter model was selected since substantial inter-study heterogeneity was expected.

Risk Factor Analysis: In the meta-analysis of risk factors, adjusted OR values were extracted whenever possible. Where appropriate, RR and HR values were transformed into OR values. We used a random-effects model and inverse variance method to compute combined OR values.

Heterogeneity and Subgroup Analysis: Statistical heterogeneity was estimated by the I^2 statistic and tested with Cochran's Q test (p-value for significance = $p < 0.10$) [6]. I^2 test results with values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity. To explore potential sources of heterogeneity, we performed pre-specified subgroup analyses according to the type of surgery (hip fracture, arthroplasty, spine surgery), study design (prospective vs. retrospective), diagnostic test used (CAM: yes or no), and geographic area. The effect of study-level covariates, such as publication year and sample size were examined using meta-regression.

Publication Bias and Quality of Evidence: The publication bias of all risk factors included in ≥10 studies was assessed using visual inspection of funnel plots and Egger's regression intercept test (they were deemed significant if $p < 0.10$) [4].

The quality of evidence for each risk factor was rated separately by two authors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [5]. For observational studies, the starting point of the evidence quality level was considered "low" and could be upgraded in the presence of a large magnitude of effect, dose response relationship, or directionally plausible confounding. Evidence was considered to be of moderate quality if it had a serious risk of bias, unexplained inconsistency, indirectness or imprecision, or a high chance of publication bias and low quality if the quality of evidence rating was further downgraded.

RESULTS

Study Selection and Characteristics

The study identification process is presented in the PRISMA flowchart (Figure 1). We found 11,329 records in our first electronic search. After removing 2,384 duplicates, 8,945 research articles were presented for title and abstract screening and the application of eligibility criteria, leading to an exclusion of 8,633 irrelevant reports. Finally, the complete text of 312 articles was subjected to screening.

Among the complete-text screened articles, 262 were excluded for the following reasons: ineligible populations (n=89), unsuitable study designs (n=76), lack of primary outcomes (n=45), and insufficient data (n=32). Finally, 50 studies including 1,247,832 patients met the inclusion criteria and were included in the qualitative synthesis, whereas data eligible for quantitative meta-analysis were available from 45 of these studies.

The 50 studies displayed diverse features. The sample size of the studies varied between 89 and 186,742 participants. Geographically, the studies were from Europe (36%), North America (32%), Asia (24%) and other areas of the world (8%). The majority of the studies (n=42, 84%) employed a prospective cohort design, while others used a retrospective cohort (n=6, 12%) and a case-control study design (n=2, 4%). The most frequently performed surgery was hip fracture repair (n = 22, 44%), followed by total joint arthroplasty (n =15, 30%) and spinal surgery (n=8, 16%). CAM was the most commonly used instrument for delirium diagnosis (n=35, 70%).

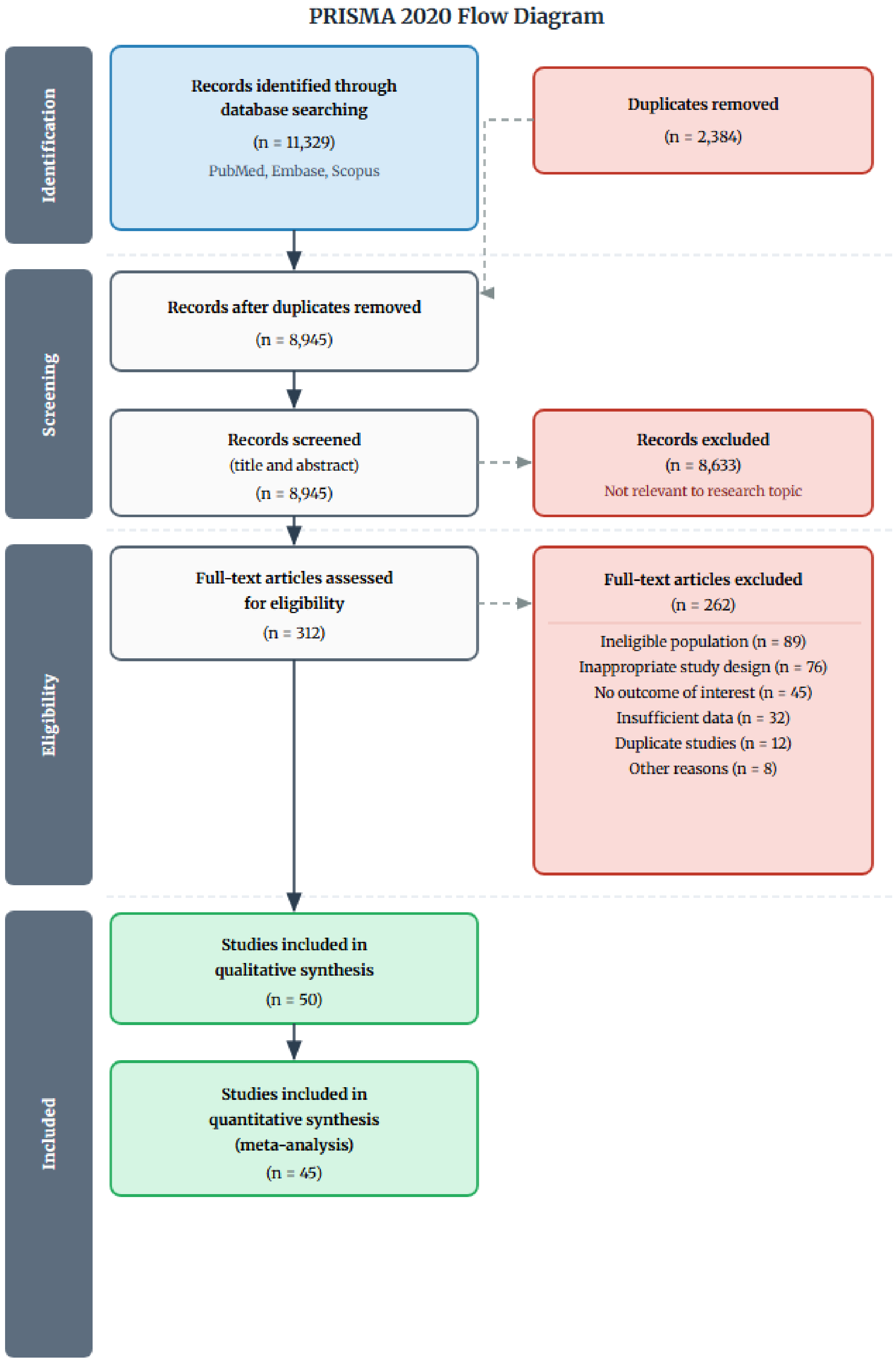

Fig. 1 PRISMA 2020 flow diagram of the study selection process.

Incidence of Postoperative Delirium

The incidence of POD in the pooled population from 45 eligible studies was estimated to be 23.4% (95% CI: 19.8%–27.1%). This result was associated with significant inter-study heterogeneity ($I^2 = 98.7\%$, $p < 0.001$).

When we analyzed the included studies by subgroups, we found variations ranging over one order of magnitude according to the type of operation. The highest pooled overall incidence value was observed in patients who underwent hip fracture repair and was computed to be 31.2% (95% CI: 26.5–36.1), while lower values were associated with patients who underwent elective total joint arthroplasty workup (15.8%, 95% CI: 12.3–19.6) and spinal surgery (14.9%, 95% CI: 10.5–19.8%).

Risk Factor Analysis

Meta-analyses were conducted for 15 potential risk factors reported in three or more studies. The results, categorized as non-modifiable and modifiable factors, are summarized in Table 1.

Table 1 Meta-analysis of Risk Factors for Postoperative Delirium.

Risk Factor	Number of Studies	Pooled OR (95% CI)	I^2 (%)	Quality of Evidence (GRADE)
Non-Modifiable				
Dementia	12	24.85 (15.23–40.54)	92.1	Moderate
History of Stroke	8	14.61 (9.87–21.62)	88.5	Moderate
Age ≥ 80 years	25	4.73 (3.58–6.25)	95.3	Low
Male sex	38	1.21 (1.09–1.34)	78.2	Low
Modifiable				
Sedative-Hypnotic Use	10	6.42 (4.11–10.03)	85.4	Moderate
Depression	14	4.98 (3.61–6.87)	90.1	Moderate
Polypharmacy (>5 drugs)	11	2.34 (1.89–2.90)	82.6	Low
General Anesthesia	28	1.89 (1.55–2.31)	89.7	Low
Long Surgical Duration (>3h)	18	1.76 (1.48–2.09)	75.5	Low
Blood Transfusion	16	1.65 (1.38–1.97)	68.9	Low

CI, Confidence Interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Non-Modifiable Risk Factors: With regard to non-modifiable risk factors, preoperative dementia stood out as the most important risk factor, leading to a nearly 25-fold rise in the probability of experiencing POD (OR 24.85; CI 95%: 15.23–40.54). A history of stroke was also associated with POD (OR 14.61; 95% CI, 9.87–21.62). Advanced age (≥80 years) also increased the likelihood of POD by approximately five times (OR 4.73; 95% CI: 3.58–6.25), whereas male sex was weakly associated with POD risk (OR 1.21; 95% CI: 1.09–1.34).

Modifiable Risk Factors: The use of sedative-hypnotic medications was the most significant modifiable risk factor, increasing the probability of POD by greater than six times (OR 6.42; 95% CI: 4.11–10.03). A diagnosis of depression was also a strong predictor of POD (OR 4.98; 95% CI: 3.61–6.87). Other significant factors included polypharmacy (the use of greater than five medications; OR 2.34; 95% CI: 1.89–2.90), the use of general anesthesia (OR 1.89; 95% CI: 1.55–2.31), prolonged surgical duration (>3 hours; OR 1.76; 95% CI: 1.48–2.09), and the need for a blood transfusion (OR 1.65; 95% CI: 1.38–1.97).

Quality of Evidence and Publication Bias

The overall quality of evidence for the majority of risk factors ranged from "low" to "moderate" according to GRADE methodology. This assessment depended primarily upon the observational design of the included studies, which confers an inherent risk of confounding bias and substantial statistical heterogeneity in most analyses.

Publication Bias: The funnel plot and Egger's test results revealed possible publication bias for age (p=0.08) and general anesthesia (p=0.06), implying that studies with a small sample size and reporting negative results may not be included in this analysis.

DISCUSSION

This systematic review and meta-analysis brings together a decade of literature to summarize risk factors for, and prevention of, POD among patients undergoing orthopedic surgery. Our review confirms that POD is a common problem, with a mean incidence of 23.4%, rising to 31.2% amongst the high-risk group of patients with hip fractures. These findings are in line with those of other studies, which illustrate the extent of this clinical problem [2,11]. The significant inter-study variability we observed ($I^2 > 98\%$) indicates that POD is not a fixed quantity but is the product of a complex shift between patient-specific variables (e.g., age and comorbidities) and system specific elements (e.g., type of surgery, institutional protocols). This variability should be considered when these results are applied to the clinical setting.

Interpretation of Risk Factors and Clinical Implications

Our present meta-analysis reveals several important risk factors, which can be classified as being non-modifiable or modifiable. It is important to understand these determinants if effective screening and prevention programs are to be designed.

Non-Modifiable Risk Factors: The Foundation of Vulnerability

The most striking result from our current analyses is the very strong association between a diagnosis of pre-existing dementia and the presence of POD (OR: 24.85). This finding highlights dementia as the single most significant predictor of POD, far exceeding other risk factors we have identified. This finding strongly supports the "shared pathophysiology" model, which regards classical POD and dementia as interrelated but not distinct forms of cerebral failure along a spectrum of cognitive deficits with overlapping mechanisms in brain networks. These may involve global brain atrophy with lesser operating reserve due to impaired and pre-existing neuroinflammation as well as a well-defined abnormality of key networks such as the default mode network associated with attention and awareness [10]. As such, the brain of a patient manifesting dementia may be more accurately conceived as having vanishingly little "cognitive reserve," making it highly susceptible to even modest perioperative stressors in the form of transient hypotension, inflammation, or exposure to psychoactive drugs. Hence, a definite diagnosis of dementia should be considered as the clinching argument, the preventive "red flag," an unmistakable alarm bell for maximum vigilance and the adoption, in mandatory terms, of an all-encompassing, multicomponent preventive management strategy.

The remaining major non-modifiable risk factors are a history of stroke (OR 14.61) and older age, especially ≥80 years (OR 4.73), in line with literature in general [8]. These results support the role of cerebrovascular health and age-related neurodegeneration in the pathophysiology of POD. Small vessel disease, for example, may compromise cerebral autoregulation and render the brain more vulnerable to intraoperative hypotension. The recognition of these features requires increased awareness towards circulatory and oxygenation balance during the perioperative course.

Modifiable Risk Factors: Targets for Prevention

Alternatively, identifying and controlling modifiable risk factors is crucial for establishing effective preventive methods as they represent tangible windows of intervention. Our regression model demonstrates that the perioperative use of sedative-hypnotic (OR 6.42) and a pre-admission history of depression (OR 4.98) are the most significant modifiable predictors of POD. Benzodiazepines and other related class of drugs, the Z-drugs (for example zolpidem), are known for their deliriogenic capacity by virtue of potentiating inhibitory gamma-aminobutyric acid-A receptor activity leading to increased central nervous system depression and also via an equal propensity towards anticholinergic effects that interfere directly with cholinergic pathways necessary for normal attention and memory [15]. We observed a strong association in our meta-analysis that supports the necessity to develop "benzodiazepine-sparing" protocols at an institutional level. This mandates strict preoperative medication review, proactive withdrawal of high-risk medications when clinically possible, and educating providers on safer options for treatment of anxiety and insomnia in the perioperative period. The strong relationship of POD with depression also appears complex. Further, depression may mediate a direct biological risk via common pathways related to neuroinflammation or neurotransmitter imbalance (i.e. serotonin, norepinephrine). It may also act as a proxy marker for a number of other risk factors such as loss of social engagement, poor nutritional reserves, and reduced levels of physical activity which are independently associated with the risk of delirium [13]. Regular preoperative screening for depression and introducing or adjusting treatment provide an important but hitherto ignored chance to intervene and strongly lower the risk of POD.

Intraoperative variables such as general anesthesia and prolonged operation time were also independently associated with POD. Our meta-analysis suggests that it is justifiable to adopt regional anesthesia to prevent the risk of POD, although there remains a controversy on the best anesthetic procedure. This may be related to a blunted systemic inflammatory response, reduced opioid and sedative consumption, and improved hemodynamic stability [12]. These observations support the idea of regional anesthesia being used as the technique of choice in high-risk patients provided there are no contraindications.

From Evidence to Practice: A Multicomponent Prevention Strategy

The combination of these risk factors provides compelling evidence that the most successful prevention strategy for POD may not be a "magic bullet" aimed at just one target, but rather an integrated program adapted from current knowledge and implemented concurrently to modify multiple and various components. This concept is greatly bolstered by high-quality evidence in the literature, particularly the landmark Hospital Elder Life Program (HELP) studies which have shown comparable and significant risk reduction for delirium and falls among older patients that have been hospitalized [7]. The validity of the findings of the HELP series of studies has been established through numerous reports, demonstrating their effectiveness in reducing the incidence of delirium by up to 40% and improving outcomes in various hospital settings. To translate evidence into orthopedic outcomes, a broad set of care elements must be embedded in the routine perioperative care pathway. Key interventions should encompass the following aspects:

Proactive Pharmacological Stewardship: This is more than a simple medication review. It involves a pharmacist-led review and reconciliation of all home medications on admission to identify and tag high-risk agents (e.g., benzodiazepines, first-generation antihistamines, muscle relaxants, specific antipsychotics). Of importance here is the employment of a multimodal analgesia plan that deliberately limits opioids. This approach encompasses preemptively scheduled doses of non-opioid analgesics (e.g., acetaminophen and non-steroidal anti-inflammatory drugs, if not contraindicated) combined with applying the most advantageous use of regional anesthetic techniques (i.e., nerve blocks, epidural analgesia) to achieve better pain control in a more focused manner, allowing for reduced systemic sedative and cognitive effects that are attributed to opioids.

Aggressive Early Mobilization and Rehabilitation: The technical rationale of post-operative bed rest itself is one that contributes to deconditioning, loss of function and delirium. A modern era approach emphasizes an advocacy of physical activity for early and regular mobilization, ideally on the first post-operative day. This requires that nursing staff and physical therapists be best deployed together to aid safety in mobilizing patients out of bed, sitting in a chair for meals, and walking up and down the corridor multiple times a day. In addition, these practices minimize immobility-related risks (e.g., venous thromboembolism, atelectasis) and improve functional recovery, proprioception, and offer critical environmental stimulation.

Systematic Sleep Enhancement: The hospital setting is a well-known impediment to a regular wake-and-sleep pattern among patients. This makes it vital to consider sleep hygiene in a systematic manner. This would involve the use of "quiet time" practices on the ward, where lights are dimmed, and an attempt is made to minimize noise and the provision of care (e.g. routine contact of stable patients with staff [taking vital signs etc.]) as much as possible. Non-pharmacological sleep promotion, including warm milk, herbal tea and relaxing music should be considered as primary interventions before prescribing hypnotic medications which are a major risk for delirium according to our analysis.

Vigilant Hydration and Nutrition Optimization: Dehydration and malnutrition are common in the perioperative period, leading to electrolyte and metabolic imbalances which are largely responsible for delirium as well. Consequently, close monitoring of fluid and nutritional balance is necessary. This management includes sufficient postoperative intravenous hydration and a rapidly re-established self-diet regimen. For high-risk patients (such as frail individuals with a preoperative nutritional status that is not optimal; described later in the text) the early involvement of a dietitian can help develop strategies to enhance protein and caloric intake, which is associated with recovery and may prevent metabolic encephalopathy.

Comprehensive Cognitive and Environmental Support: Sensory deprivation and disorienttation are important factors for delirium. When combined, several simple but very effective approaches are available to assist patients. This also means that patients have access to their eyeglasses and hearing aids, which should be worn. The environment should have orientation cues (e.g. large clocks, visible calendars, and a whiteboard with names of care team members). Crucially, family caregivers need to be informed of the dangers of delirium and should be involved in care by visiting patients and providing friendly social interaction, reorientation, and cognitive stimulation throughout the day.

A successful and dependable implementation of such a complex strategy requires complete reorganization of care. It relies on a close multimodal collaboration and the organization of an expert multidisciplinary team, including surgeons, anesthesiologists, geriatricians, nurses, physiotherapists, occupational therapists, and pharmacists. The development of formal Geriatric-Orthopedic Co-management Models that include geriatricians involved in the perioperative care of older people has been successful in the implementation of such care strategies to improve clinical results and alleviate the significant impact of POD on this frail population.

Limitations of the Study and Future Research Directions

Despite its comprehensive and systematic nature, this review has several limitations that warrant consideration. First, most of the evidence on risk factors was classified as "low" to "moderate" quality according to GRADE, primarily because the source studies were observational and susceptible to confounding factors. We focused on adjusted OR values, but the potential for residual confounding factors to influence the strength of our observed associations cannot be fully discounted. Second, the presence of significant statistical heterogeneity in almost all analyses can be seen as a considerable limitation. Although subgroup analyses were performed, this high degree of heterogeneity could not be explained, probably due to differences in the patient populations (i.e., prevalence of frailty), clinical strategies adopted, and diagnostic criteria for POD employed by the various studies. The presence of this heterogeneity constrained the generalization of our point estimates. Lastly, the evidence for the existence of publication bias with regard to some risk factors suggests that the reported effect sizes may have been overestimated. These limitations highlight several critical avenues for future research, as explained below.

Experimental Studies: There is an urgent requirement for high-quality randomized controlled trials to determine the effectiveness of specific prophylactic interventions, such as pharmacological agents (e.g., dexmedetomidine), anesthetic methods, and the Enhanced Recovery After Surgery protocol in lowering the incidence of POD.

Biomarker Research: Identifying reliable markers (e.g., S100B, neurofilament light chain, inflammatory cytokines) for biomarker-based POD risk stratification and early diagnosis would constitute a major development in this field.

Prediction Model Development: Risk factors identified in our study should be used to develop simple and practical clinical prediction models that predict the risk of severity categories and allow for optimal resource planning.

Long-term Outcome Studies: Future prospective long-term follow-up studies will be needed to better characterize the course of cognitive and functional decline and quality of life following an episode of POD.

CONCLUSIONS

POD is a frequent and serious complication in orthopedic surgery, with a pooled incidence of 23.4%. The present meta-analysis identifies key non-modifiable factors (dementia, stroke history, advanced age) and critical modifiable factors that include preoperative conditions (depression) and perioperative variables (sedative exposure, anesthetic choices). Our findings underscore the need for a shift from reactive to proactive, risk-stratified perioperative care, employing multicomponent preventive strategies to improve patient outcomes.

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