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Review

# Postoperative delirium: from bundles to precision prevention

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Perioperative brain health, encompassing postoperative delirium (POD) and longer-lasting cognitive decline, has become a major priority for patient safety and quality of recovery in older surgical patients. The 2018 unified nomenclature introduced perioperative neurocognitive disorders as an umbrella term spanning pre-existing neurocognitive disorder, POD, delayed neurocognitive recovery, and postoperative neurocognitive disorder. The incidence of POD varies widely, reflecting differences in age, baseline cognition, surgical type, and ascertainment; however, its clinical footprint is consistently substantial, with increased mortality, longer hospitalization, and downstream cognitive deterioration. Electroencephalography (EEG)-guided anesthesia trials have yielded mixed results, favoring its integration with hemodynamic optimization and medication stewardship. Screening uptake remains < 10% in many settings, limiting the ability to provide scalable and equitable brain care. Current prevention standards prioritize multicomponent, non-pharmacological bundles such as mobilization, reorientation/cognitive stimulation, sleep promotion, sensory optimization, hydration, nutrition, oxygen delivery, and prompt management of precipitating factors. Nonetheless, translation to "precision prevention" is constrained by three gaps: low implementation of recommended screening pathways, heterogeneity and limited transportability of prognostic models, and an under-operationalized vulnerability domain in which frailty and malnutrition lack standardized tools, cut-offs, and linked interventions. Biomarkers and perioperative physiology including EEG suppression patterns and individualized perfusion targets are biologically coherent adjuncts for risk refinement; however, current evidence supports their use as additive stratifiers within bundles rather than stand-alone gatekeepers. Next-generation perioperative brain health studies should standardize vulnerability phenotyping, integrate evidence-based selective monitoring and biomarker-informed refinement, and embed these elements into scalable workflows that convert guidelines into practical bedside actions.

**Keywords:** Delirium; Frailty; Malnutrition; Perioperative cognitive disorder; Precision medicine.

## INTRODUCTION

As the surgical population ages, perioperative care is increasingly judged not only by survival and cardiopulmonary complications but also by whether patients "return to themselves." Therefore, perioperative brain health, which encompasses delirium and longer-lasting cognitive decline, has emerged as a major patient safety and quality of recovery priority in the older adult population. Contemporary perioperative brain health initiatives emphasize that cognitive outcomes are critical to patients and families and the perioperative period can unmask or accelerate neurocognitive vul-

nerability in susceptible individuals [1-3].

A key conceptual advancement was the adoption of a unified nomenclature for perioperative cognitive changes. The 2018 recommendations proposed perioperative neurocognitive disorders (PNDs) as an umbrella term that encompasses pre-existing neurocognitive disorders (including mild neurocognitive disorders that often overlap clinically with mild cognitive impairment [MCI]), acute postoperative delirium (POD), cognitive decline diagnosed for up to 30 days (delayed neurocognitive recovery), and postoperative neurocognitive disorders for up to 12 months. This framework aligns perioperative research with the terminology of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and clarifies that perioperative cognitive outcomes are not isolated phenomena but connected clinical entities along a trajectory of vulnerability and injury (Fig. 1) [4,5].

Beyond immediate morbidity, POD is associated with downstream cognitive deterioration and dementia risk, reinforcing the concept that delirium is not merely transient "confusion," but can be considered a marker (and possibly a mediator) of reduced brain resilience under stress [6]. The delirium–dementia relationship is bidirectional: dementia increases delirium susceptibility, and delirium episodes can accelerate cognitive decline trajectories [7].

Yet three persistent gaps limit translation into "precision prevention".

Although substantial progress has been made in understanding POD, several important gaps remain. First, the implementation of recommended screening strategies and clinical pathways remains limited in routine practice, reducing the real-world impact of the current evidence [8]. Second, POD is increasingly understood as a heterogeneous syndrome arising from multiple interacting mechanisms that may underlie the large number of reported risk factors and predictive models, which have shown limited validation or inconsistent performance across clinical contexts [6]. Third, frailty and malnutrition are now recognized as potentially modifiable vulnerability constructs that reflect reduced physiological reserves; however, standardized instruments, validated thresholds, and intervention pathways that meaningfully translate these constructs into improved delirium-related outcomes remain insufficiently established [6,8]. Collectively, these limitations highlight the need for a robust and clinically implementable framework for perioperative risk stratification and prevention of POD.

In this review article, we aimed to examine POD among PNDs, focusing on its pathophysiology, diagnosis, risk factors, biomarkers, prevention, and actionable plans based on a review of recent literature.

## EPIDEMIOLOGY AND CLINICAL IMPACT

Across cohorts, POD incidence varies widely (approximately 5–50%), reflecting differences in age, baseline cognition, surgical type, and ascertainment methods [6]. POD is associated with increased mortality, longer hospital stays, and subsequent cognitive decline, including dementia [6,8].

POD is not a transient, benign complication. Large real-world cohorts have shown that POD is associated with substantially higher odds of major complications, mortality, and non-home discharge after major surgery in older adults [6]. Beyond index hospitalization, delirium is consistently linked to worse long-term outcomes, including mortality, institutionalization, and dementia risk in older patients [7]. POD has also been associated with subsequent functional decline [9,10] and higher long-term mortality after anesthesia and surgery, underscoring the lasting clinical impact of an event that is often still under-detected [6,10].

These outcomes justify the shift in delirium prevention

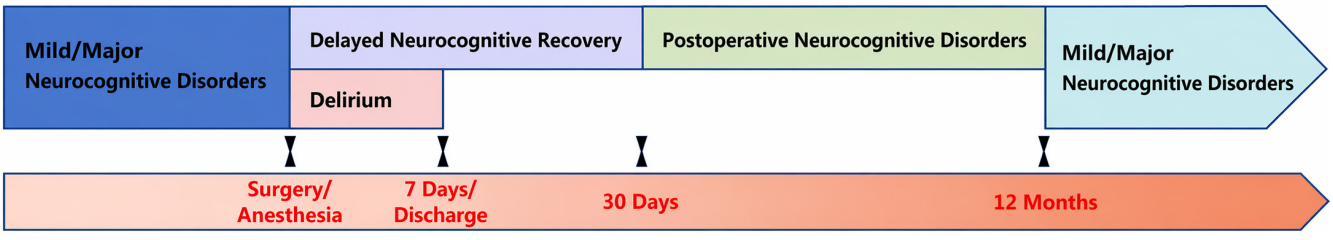


**Fig. 1.** Proposed perioperative neurocognitive disorders as an umbrella term that includes pre-existing neurocognitive disorders (including mild neurocognitive disorder that often overlaps clinically with mild cognitive impairment), acute postoperative delirium, cognitive decline diagnosed for up to 30 days (delayed neurocognitive recovery), and postoperative neurocognitive disorder for up to 12 months [4,5,34]. Adapted from the article of Kong et al. (CNS Neurosci Ther 2022; 28: 1147-67) [34].

from being an optional quality improvement to a core perioperative safety objective.

## PATHOPHYSIOLOGY

Modern frameworks converge on delirium as a final common clinical phenotype arising from interacting insults on a vulnerable brain—including systemic inflammation, neuroinflammation, blood-brain barrier (BBB) dysfunction, neurotransmitter imbalance, metabolic stress, and network disconnection [7]. Importantly, BBB disruption appears particularly relevant; clinical observations link BBB disruption with delirium/subsyndromal delirium. Animal studies have shown that surgery-associated neuroinflammation, BBB disruption, microglial activation [11], and cognitive deficits can be mitigated by anti-inflammatory treatment [7].

Despite the mechanistically central role of inflammation, biomarker translation is constrained by heterogeneity in definitions, small cohorts, mixed dementia subtypes, and variable study designs [7]. This is a key reason why guidelines and pathways have gravitated toward broad multicomponent prevention rather than biomarker-gated algorithms.

## DIAGNOSIS

POD is defined by the DSM-5 criteria as an acute disturbance in attention and awareness, characterized by a fluctuating course and cognitive deficits that are not better explained by other neurocognitive disorders. In the perioperative context, POD specifically refers to delirium occurring within seven days of surgery or prior to hospital discharge [4,6]. Clinically, it presents as a sudden alteration in consciousness, disorganized thinking, and variable behavioral disturbances that develop over a short period of time and often wax and wane throughout the day.

Since formal DSM-5 assessments are often impractical in routine clinical practice, several validated bedside instruments have been developed for rapid detection. The Confusion Assessment Method (CAM) and its derivatives, including the CAM-intensive care unit (ICU) for critically ill patients and abbreviated versions, such as 3-Minute Diagnostic Interview for CAM (3D-CAM) and Brief Confusion Assessment Method (bCAM), remain the most widely used and validated tools [7,12-15]. In ward settings, screening commonly relies on brief instruments, which can be completed within 1–2 min, such as the Nursing Delirium Screening Scale (Nu-DESC) or the 4 'A's Test (4AT) [16,17]. In research settings, delirium severity is frequently quantified using structured scales such as the Delirium Rating Scale-Revised-98 (DRS-R-98) and Memorial Delirium Assessment Scale (MDAS) [18-20].

Based on psychomotor activity, delirium is classified into three clinical subtypes: hyperactive, hypoactive, and mixed. Hyperactive delirium is characterized by agitation and heightened psychomotor activity, whereas the hypoactive subtype presents with lethargy and reduced responsiveness. Mixed delirium involves fluctuating features of both states during the course of illness [12]. Notably, hypoactive delirium is the most prevalent subtype in postoperative populations, yet it remains frequently underrecognized in clinical practice due to its subtle presentation [20].

## RISK FACTORS

Older adults rarely enter the operating room with a "fully intact" brain. Instead, many show layered preoperative vulnerability encompassing subtle cognitive decline, mood disorders, cerebrovascular disease, sensory impairment, slowed mobility/gait speed, global frailty, high comorbidity burden, and polypharmacy, which together form a "vulnerable brain" (or "brain frailty") phenotype that is primed for perioperative stress [6]. Across syntheses, baseline cognitive impairment is recognized as one of the most consistently associated predictors of POD, along with age, cerebrovascular disease, and psychiatric disorders [6]. In diverse surgical populations, preoperative cognitive impairment has been repeatedly linked not only to higher POD risk but also to worse postoperative trajectories, including mortality and discharge to assisted care [9,21]. Studies focusing on the MCI–POD relationship further support that MCI is not merely a background comorbidity, but rather a clinically meaningful vulnerability state that can be "stress-tested" by surgery and anesthesia [9,22].

At the same time, the umbrella review literature highlights a key limitation: although many risk factors have been examined, findings can be inconsistent across studies, and many existing prognostic models remain unvalidated or not readily generalizable [6]. This helps explain why "classic" risk-factor studies may disagree because patients can share similar surface phenotypes such as age or American Society of Anesthesiologists physical status class while differing substantially in their latent brain vulnerability and physiologic reserve [6]. Consequently, the following pragmatic conclusion emerged: POD risk is not driven by a single domain but

by baseline vulnerability interacting with perioperative insults, an argument for integrated, multimodal risk stratification that combines clinical vulnerability markers (including MCI/brain frailty), neurophysiology, and biomarkers [6]. Critically, accumulating more "known" predictors has diminishing returns. Future work should prioritize validating and transporting existing models and ensuring they map directly to actionable prevention or treatment pathways, rather than re-cataloging traditional risk factors repeatedly [6].

## Perioperative modifiable risk factors that "trigger" a vulnerable brain

A clinically actionable narrative is: (1) identify vulnerability preoperatively (MCI/brain frailty) and then (2) minimize modifiable precipitating factors that convert vulnerability into POD.

### *1. Depression (and affective vulnerability)*

Depression is common in older surgical patients and is associated with an increased risk of delirium. A systematic review and meta-analysis focusing on patients with preoperative depression undergoing major surgery reported an increased relative risk of POD (approximately 1.9 × in pooled estimates) [23]. Beyond being a "risk factor," depression can be conceptualized as a system amplifier. It interacts with sleep disturbance, pain catastrophizing, reduced mobility, and inflammatory priming, domains that are directly relevant to perioperative management and delirium-prevention bundles.

### *2. Benzodiazepines: reconcile observational signals with randomized evidence*

Benzodiazepines remain a practical dilemma. Many observational datasets link benzodiazepines (especially repeated or prolonged exposure) to delirium risk, and multiple guidelines caution against their routine use in older adults at risk of POD [24]. However, an important nuance for perioperative practice is that meta-analytic evidence from randomized controlled trials has not shown a consistent increase risk of POD with perioperative benzodiazepine use overall, suggesting that confounding by indication (e.g., comparisons against dexmedetomidine or sicker/anxious patients) may partly explain the observed associations [25]. This discrepancy supports the pragmatic interpretation that benzodiazepine use should be selectively minimized in high-risk older adults, with attention to dose, timing, alternatives, and cumulative sedative burden, rather than being treated as a single binary exposure.

### *3. Comorbidity burden: Charlson Comorbidity Index (CCI)/age-adjusted CCI (ACCI) serve as a "risk density" metric*

Comorbidity burden operationalizes vulnerability beyond age alone. A prospective cohort study reported that ACCI was independently correlated with POD in older patients after thoracic/abdominal surgery, along with baseline cognition (e.g., Mini-Mental State Examination), albumin, and pain [26]. Clinically, the ACCI can be used as a "risk density" marker to complement cognitive screening, particularly in settings where a full geriatric assessment is not feasible.

### *4. Electroencephalography (EEG)-derived "brain frailty" and deep anesthesia signatures (alpha attenuation, burst suppression)*

For anesthesiologists, intraoperative EEG offers an attractive bridge between preoperative vulnerability and real-time modifiable physiology. Meta-analytical evidence supports a positive association between intraoperative burst suppression patterns and POD (while emphasizing heterogeneity and low to very low certainty in parts of the evidence) [27]. Contemporary perioperative delirium guidelines increasingly endorse EEG monitoring for depth titration, with attention paid to index values as well as to patterns such as suppression and spectral changes [20]. More broadly, EEG features (e.g., reduced frontal alpha power or early perioperative alpha attenuation) have been investigated as candidate vulnerability markers, consistent with the concept that some patients manifest "fragile" cortical dynamics under anesthetic stress [28].

Importantly, randomized trials of EEG-guided anesthetic administration have yielded mixed results. In particular, the ENGAGES randomized clinical trial, an intervention that monitored and attempted to reduce burst suppression during anesthesia, did not demonstrate a reduction in the incidence of delirium with EEG-guided administration in older adults undergoing major surgeries [29]. Similarly, in patients undergoing cardiac surgery, EEG-guided approaches do not consistently reduce POD [30]. In contrast, another trial that compared deeper (bispectral index [BIS] 35) and lighter anesthesia (BIS 50) reported a significant reduction in POD [31]. Taken together, these findings suggest that EEG functions best as part of a multi-domain strategy (vulnerability screening, hemodynamic optimization, medication

stewardship, and bundle care) rather than as a stand-alone intervention.

### *5. Hemodynamics, cardiopulmonary bypass (CPB), and cerebral perfusion: mean arterial pressure (MAP) dose, autoregulation, and perfusion stability*

Hemodynamic instability may contribute to POD through several interrelated mechanisms that are particularly relevant in cardiac surgery, where CPB introduces additional cerebral stressors. In addition to systemic hypotension, CPB may increase the risk of cerebral microemboli, which can impair microvascular cerebral perfusion and exacerbate neuronal vulnerability [32,33]. CPB is also associated with systemic inflammation, which may propagate neuroinflammatory responses, disrupt the BBB, and amplify the risk of delirium in susceptible patients [34]. Simultaneously, episodes of cerebral hypoperfusion and ischemic injury may occur when blood pressure or blood flow deviates from the patient's autoregulatory range, particularly in older adults or those with impaired cerebrovascular reserve [32]. Collectively, these mechanisms suggest that delirium risk in cardiac surgery is not only shaped by absolute blood pressure values but also by the interaction between perfusion instability, embolic burden, and inflammation.

In this context, excursions of blood pressure away from an individualized optimal MAP have been associated with delirium in prospective observational studies, supporting the concept of a patient-specific perfusion target rather than a uniform threshold [35]. Related work has linked impaired cerebrovascular autoregulation (including near-Infrared spectroscopy-based measures) with POD, again highlighting that "adequate MAP" may differ across patients [32]. Therefore, maintaining perfusion near these individualized physiological thresholds may help reduce the cumulative impact of hypoperfusion, embolic insult, and inflammatory injury on the vulnerable brain. Specifically, in cardiothoracic surgery, a recent study analyzing CPB perfusion data reported that deviations from target flow during bypass were associated with POD, highlighting perfusion stability during CPB as a potentially modifiable exposure [36].

In non-cardiac surgery, intraoperative hypotension has also been associated with increased odds of delirium in recent large-scale observational analyses, supporting the generalizability of perfusion-related triggers beyond CPB [37]. Collectively, these data justify a "brain-centered hemodynamic" approach in older high-risk patients through avoiding prolonged hypotension, reducing variability, considering autoregulation-informed targets when available, and integrating cerebral monitoring selectively for the highest-risk cases.

## BIOMARKERS

The dementia–delirium interrelationship review compiles candidate plasma biomarkers spanning systemic inflammation (e.g., C-reactive protein and interleukin-6), neuronal injury markers (e.g., neurofilament light chain), and Alzheimer's disease-related biomarkers (tau species), noting differential associations depending on the status and context of dementia [7]. These findings support a biologically coherent hypothesis: biomarkers could refine risk among clinically "high-risk" patients by distinguishing inflammatory susceptibility, neuronal injury propensity, or latent neurodegenerative pathology [7].

However, limitations remain substantial—variable definitions, small sample sizes, mixed dementia phenotypes, and case–control designs dominate much of the evidence base [7].

Therefore, a near-term, clinically realistic position is that biomarkers are best viewed as additive stratifiers within a multicomponent prevention ecosystem rather than as replacements.

## PREVENTION

Current prevention paradigms largely prioritize identifying high-risk patients and deploying multicomponent, non-pharmacologic interventions [12].

Strong evidence supports multi-component prevention protocols for at-risk inpatients, including early mobilization, reorientation/cognitive stimulation, sleep promotion, sensory optimization, hydration, nutrition, oxygen delivery, and management of underlying triggers [12,20]. The HELP program is a widely cited example that systematically targets key modifiable drivers and demonstrates absolute risk reduction in delirium incidence in older medical patients [12]. Perioperative guidance similarly endorses comprehensive, targeted risk reduction ("prehabilitation") as a sensible approach, even when the exact dose–response relationship between duration of intervention and delirium reduction is uncertain [20,38]. However, implementation remains a bottleneck. Survey data indicate that preoperative screening for frailty or dementia, geriatric consultation, and POD screening occur in less than 10% of surgical cases [38]. This gap is

**Table 1.** Consolidated Intraoperative Prevention Strategies for POD

| Factor | Effect direction on POD | Evidence grade | Key evidence snapshot (why this grade) | Practical prevention take-home | Landmark studies/ key reference |
|---|---|---|---|---|---|
| Processed EEG (BIS/PSI) and anesthetic depth | Uncertain (signal for ↓ when avoiding burst suppression/over-deep anesthesia, but not consistent) | Moderate | RCTs/meta-analyses showed heterogeneous POD results; strongest and most consistent biologic/clinical signal is harmful from over-deep anesthesia/ burst suppression, rather than "monitoring itself" | Use pEEG as an over-depth alarm: avoid very low indices and burst suppression, especially in frail/older adults; reassess dose–analgesia balance and hypotension when indices are low | Chan et al., (CODA) 2013 [48]; Wildes et al., (ENGAGES) 2019 [29]; Evered et al., (BALNCED) 2021 [31]; Sumner et al., (meta) 2023 [49] |
| Intraoperative blood pressure management | Uncertain (likely ↓ if hypotension burden is reduced, but thresholds/ targets vary) | Low–Moderate | Many observational studies linked IOH burden to worse outcomes; delirium-specific RCT evidence for a single universal MAP target is limited and variable | Minimize depth + duration of hypotension (often best framed relative to baseline); promptly treat IOH by addressing anesthetic depth, volume, vasodilation, and cardiac output | Maheshwari et al., 2020 [50]; Futier et al. (INPRESS Trial) 2017 [51] |
| Regional anesthesia (vs. general anesthesia) | ↔ (No overall consistent reduction in POD) | High | Multiple large RCTs in hip fracture/ geriatric settings showed no clear POD advantage for RA over GA | Choose RA for opioid-sparing analgesia and physiologic benefits; if sedating, avoid deep sedation; POD prevention depends more on sedation depth/complication control than on "technique label" | Neuman et al., (REGAIN) 2021 [52]; Li et al., (RAGA) 2022 [53] |
| TIVA (vs. volatile anesthetics) | ↔ Uncertain | Low–Moderate | Studies vary by surgery type, co-interventions, and depth/ hemodynamics; overall results are mixed and not reliably generalizable | Emphasize modifiable mediators regardless of agent: avoid over-depth; prevent hypotension; optimize analgesia/sleep; reduce anticholinergic burden | Yoshimura et al., 2022 [54]. Miller et al., 2018 [55] |
| Opioid use | Uncertain overall (but ↑ risk with certain opioids, especially meperidine) | Moderate | Consistent evidence that meperidine (pethidine) increases delirium risk in older adults; "opioid amount" vs. POD is confounded because under-treated pain also increases POD | Aim for multimodal, opioid-sparing analgesia while preventing severe pain; avoid meperidine; keep opioids at the lowest effective dose | Vaurio et al., 2006 [56]; Swart et al., 2017 [57] |
| Dexmedetomidine | ↓ (In selected settings) but not universal | Moderate | Several landmark RCTs/meta-analyses suggested POD reduction, yet effects vary by dose/timing/comparator and surgical cohort; hemodynamic adverse effects can limit its use | Consider as part of a bundle in high-risk older adults using low-dose strategies; monitor for bradycardia/hypotension; position benefit as sleep–wake stabilization and opioid-sparing | Su et al., 2016 [58]; Deiner et al., 2017 [59]; systematic reviews/ meta-analyses through ~2022–2024 showing heterogeneity |

POD: postoperative delirium, EEG: electroencephalography, BIS: bispectral index, PSI: patient state index, TIVA: total intravenous anesthesia, RCTs: randomized controlled trials, MAP: mean arterial pressure, RA: regional anesthesia, GA: general anesthesia.

considered to be as critical as any mechanistic gap, because prevention efficacy cannot be scaled without workflow integration.

## PHARMACOLOGICAL TREATMENT OF POD

Management is anchored in a stepwise principle in which non-pharmacological strategies remain the first-line, and drug therapy is reserved for patients with severe and intractable distress when non-pharmacological measures have failed; even then, treatment is positioned as symptom-oriented rather than a blanket "delirium cure." When medication is required, the guideline suggests short-term, low-dose haloperidol administered as bolus dosing to the lowest effective dose, with particular caution or avoidance in patients with underlying neurodegenerative disease such as Parkinson's disease or dementia with Lewy bodies [39-41], reflecting the overall low certainty and mixed efficacy reported in the literature. Notably, the guidelines underscore that the evidence for use of antipsychotics in POD remains inconsistent and debated. A systematic review of randomized trials did not demonstrate significant improvements in delirium severity or duration, mortality, or ICU/hospital length of stay, emphasizing the narrow, safety-focused scope of any pharmacological interventions. Benzodiazepines are generally not recommended for routine treatment of POD [42-45]. Nonetheless, they remain the gold standard therapy for alcohol-withdrawal delirium, often delivered through symptom-triggered bolus titration [44,46,47], which should not be conflated with POD management. Finally, dexmedetomidine has been suggested as a treatment option for POD in patients undergoing cardiac surgery, with evidence summarized as suggestive but limited due to its heterogeneity and indirectness. Reports indicate potential reduction in delirium duration and possibly improved clinical endpoints in some comparisons; however, the overall certainty remains very low, supporting cautious, individualized use [20].

## CONCLUSION

POD prevention has a strong evidence base for multicomponent, non-pharmacological bundles, and these should remain the clinical foundation (Tables 1, 2).

Nevertheless, POD is heterogeneous and closely interwoven with dementia-related vulnerability, and current practice shows major implementation shortfalls.

**Table 2.** Actionable Framework for Anesthesia

| Phase | Actionable prevention strategy |
|---|---|
| Preoperative | Risk screening (MMSE, brain frailty, comorbidity density, age > 65) |
| | Medication optimization (avoiding benzodiazepines/anticholinergics) |
| | Patient/family education |
| Intraoperative | Depth of anesthesia monitoring (avoiding deep EEG suppression/burst suppression) |
| | Opioid-sparing techniques |
| | Maintaining physiological stability (MAP, cerebral perfusion, avoiding hypoxia/hypothermia) |
| Postoperative | Systematic screening (e.g., CAM, CAM-ICU every shift) |
| | Non-pharmacological interventions (early mobilization, sleep hygiene, re-orientation) |
| | Multi-modal analgesia to manage uncontrolled pain without over-reliance on opioids |

MMSE: Mini-Mental State Examination, EEG: electroencephalography, MAP: mean arterial pressure, CAM: Confusion Assessment Method, CAM-ICU: Confusion Assessment Method for the Intensive Care Unit.

A next-generation strategy should therefore emphasize operational precision: standardized vulnerability phenotyping (frailty + nutritional reserve), biomarker-informed refinement where evidence supports it, and workflow integration that converts guidelines into reliable bedside action.

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## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## AUTHOR CONTRIBUTIONS

Conceptualization: Jeongmin Kim, Bon-Nyeo Koo. Fund-

ing acquisition: Bon-Nyeo Koo, Jeongmin Kim. Methodology: Min-Yu Kim. Project administration: Min-Yu Kim. Writing - original draft: Min-Yu Kim, Jeongmin Kim, Bon-Nyeo Koo. Writing - review & editing: Min-Yu Kim, Jeongmin Kim, Bon-Nyeo Koo. Resources: Bon-Nyeo Koo.

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## REFERENCES

1. Mahanna-Gabrielli E, Schenning KJ, Eriksson LI, Browndyke JN, Wright CB, Culley DJ, et al. State of the clinical science of perioperative brain health: report from the American Society of Anesthesiologists Brain Health Initiative Summit 2018. Br J Anaesth 2019; 123: 464-78.
2. Peden CJ, Miller TR, Deiner SG, Eckenhoff RG, Fleisher LA; Members of the Perioperative Brain Health Expert Panel. Improving perioperative brain health: an expert consensus review of key actions for the perioperative care team. Br J Anaesth 2021; 126: 423-32.
3. Vacas S, Canales C, Deiner SG, Cole DJ. Perioperative brain health in the older adult: a patient safety imperative. Anesth Analg 2022; 135: 316-28.
4. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Nomenclature Consensus Working Group. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. Br J Anaesth 2018; 121: 1005-12.
5. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery—2018. J Alzheimer Dis 2018; 66: 1-10.
6. Bramley P, McArthur K, Blayney A, McCullagh I. Risk factors for postoperative delirium: an umbrella review of systematic reviews. Int J Surg 2021; 93: 106063.
7. Fong TG, Inouye SK. The inter-relationship between delirium and dementia: the importance of delirium prevention. Nat Rev Neurol 2022; 18: 579-96.
8. Kunicki ZJ, Ngo LH, Marcantonio ER, Tommet D, Feng Y, Fong TG, et al. Six-year cognitive trajectory in older adults following major surgery and delirium. JAMA Intern Med 2023; 183: 442-50.
9. Park S, Kim J, Ha Y, Kim KN, Yi S, Koo BN. Preoperative mild cognitive impairment as a risk factor of postoperative cognitive dysfunction in elderly patients undergoing spine surgery. Front Aging Neurosci 2024; 16: 1292942.
10. Shi Z, Mei X, Li C, Chen Y, Zheng H, Wu Y, et al. Postoperative delirium is associated with long-term decline in activities of daily living. Anesthesiology 2019; 131: 492-500.
11. Cho I, Kim JM, Kim EJ, Kim SY, Kam EH, Cheong E, et al. Orthopedic surgery-induced cognitive dysfunction is mediated by CX3CL1/R1 signaling. J Neuroinflammation 2021; 18: 93.
12. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLullich AMJ, et al. Delirium. Nat Rev Dis Primers 2020; 6: 90.
13. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001; 286: 2703-10.
14. Marcantonio ER, Ngo LH, O'Connor M, Jones RN, Crane PK, Metzger ED, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. Ann Intern Med 2014; 161: 554-61.
15. Han JH, Wilson A, Vasilevskis EE, Shintani A, Schnelle JF, Dittus RS, et al. Diagnosing delirium in older emergency department patients: validity and reliability of the delirium triage screen and the brief confusion assessment method. Ann Emerg Med 2013; 62: 457-65.
16. Gaudreau JD, Gagnon P, Harel F, Tremblay A, Roy MA. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage 2005; 29: 368-75.
17. Bellelli G, Morandi A, Davis DH, Mazzola P, Turco R, Gentile S, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing 2014; 43: 496-502.
18. Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-Revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 2001; 13: 229-42.
19. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. J Pain Symptom Manage 1997; 13: 128-37.
20. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Aceto P, Audisio R, et al. Update of the European Society of Anaesthesiology and Intensive Care Medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. Eur J Anaesthesiol 2024; 41: 81-108.
21. Chen L, Au E, Saripella A, Kapoor P, Yan E, Wong J, et al. Postoperative outcomes in older surgical patients with preopera-

tive cognitive impairment: a systematic review and meta-analysis. J Clin Anesth 2022; 80: 110883.
22. Sprung J, Roberts RO, Weingarten TN, Nunes Cavalcante A, Knopman DS, Petersen RC, et al. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. Br J Anaesth 2017; 119: 316-23.
23. Diep C, Patel K, Petricca J, Daza JF, Lee S, Xue Y, et al. Incidence and relative risk of delirium after major surgery for patients with pre-operative depression: a systematic review and meta-analysis. Anaesthesia 2024; 79: 1237-49.
24. Chow WB, Rosenthal RA, Merkow RP, Ko CY, Esnaola NF; American College of Surgeons National Surgical Quality Improvement Program; American Geriatrics Society. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. J Am Coll Surg 2012; 215: 453-66.
25. Wang E, Belley-Côté EP, Young J, He H, Saud H, D'Aragon F, et al. Effect of perioperative benzodiazepine use on intraoperative awareness and postoperative delirium: a systematic review and meta-analysis of randomised controlled trials and observational studies. Br J Anaesth 2023; 131: 302-13.
26. Liu J, Li J, He J, Zhang H, Liu M, Rong J. The Age-adjusted Charlson Comorbidity Index predicts post-operative delirium in the elderly following thoracic and abdominal surgery: a prospective observational cohort study. Front Aging Neurosci 2022; 14: 979119.
27. Likhvantsev VV, Berikashvili LB, Smirnova AV, Polyakov PA, Yadgarov MY, Gracheva ND, et al. Intraoperative electroencephalogram patterns as predictors of postoperative delirium in older patients: a systematic review and meta-analysis. Front Aging Neurosci 2024; 16: 1386669.
28. Kim J, Park S, Kim KN, Ha Y, Shin SJ, Cha W, et al. Resting-state prefrontal EEG biomarker in correlation with postoperative delirium in elderly patients. Front Aging Neurosci 2023; 15: 1224264.
29. Wildes TS, Mickle AM, Ben Abdallah A, Maybrier HR, Oberhaus J, Budelier TP, et al. Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the ENGAGES randomized clinical trial. JAMA 2019; 321: 473-83.
30. Deschamps A, Ben Abdallah A, Jacobsohn E, Saha T, Djaiani G, El-Gabalawy R, et al. Electroencephalography-guided anesthesia and delirium in older adults after cardiac surgery: the ENGAGES-Canada randomized clinical trial. JAMA 2024; 332: 112-23.
31. Evered LA, Chan MTV, Han R, Chu MHM, Cheng BP, Scott DA, et al. Anaesthetic depth and delirium after major surgery: a randomised clinical trial. Br J Anaesth 2021; 127: 704-12.
32. Chan B, Aneman A. A prospective, observational study of cerebrovascular autoregulation and its association with delirium following cardiac surgery. Anaesthesia 2019; 74: 33-44.
33. Brown CH 4th, Neufeld KJ, Tian J, Probert J, LaFlam A, Max L, et al. Effect of targeting mean arterial pressure during cardiopulmonary bypass by monitoring cerebral autoregulation on postsurgical delirium among older patients: a nested randomized clinical trial. JAMA Surg 2019; 154: 819-26.
34. Kong H, Xu LM, Wang DX. Perioperative neurocognitive disorders: a narrative review focusing on diagnosis, prevention, and treatment. CNS Neurosci Ther 2022; 28: 1147-67.
35. Hori D, Max L, Laflam A, Brown C, Neufeld KJ, Adachi H, et al. Blood pressure deviations from optimal mean arterial pressure during cardiac surgery measured with a novel monitor of cerebral blood flow and risk for perioperative delirium: a pilot study. J Cardiothorac Vasc Anesth 2016; 30: 606-12.
36. Krefting J, Gorki H, Hoenicka M, Albrecht G, Kraft R, Liebold A. Target flow deviations on the cardiopulmonary bypass cause postoperative delirium in cardiothoracic surgery-a retrospective study evaluating temporal fluctuations of perfusion data. Interdiscip Cardiovasc Thorac Surg 2024; 38: ivae016.
37. Ettoumi I, Pearce D, Wingert T, Delaporte A, Alexander B, Pal R, et al. Intraoperative hypotension and postoperative delirium among older high-risk patients undergoing major noncardiac surgery: a retrospective single-centre cohort study. BJA Open 2025; 16: 100500.
38. Vacas S, Cole DJ, Cannesson M. Cognitive decline associated with anesthesia and surgery in older patients. JAMA 2021; 326: 863-4.
39. Hershey LA, Coleman-Jackson R. Pharmacological management of dementia with Lewy bodies. Drugs Aging 2019; 36: 309-19.
40. Déciga-Campos M, Siles-Guevara J, Gil-López SA, Pineda-Oliveros J, Ortíz-Andrade RR. Scopolamine-induced amnesia in zebrafish: behavioral characterization and pharmacological reversal. Animals (Basel) 2025; 15: 2624.
41. Gore RL, Vardy ER, O'Brien JT. Delirium and dementia with Lewy bodies: distinct diagnoses or part of the same spectrum? J Neurol Neurosurg Psychiatry 2015; 86: 50-9.
42. Lonergan E, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. Cochrane Database Syst Rev 2009; 2009: CD006379.
43. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing 2011; 40: 23-9.
44. Saller T, Hofmann-Kiefer KF, Saller I, Zwissler B, von Dossow V. Implementation of strategies to prevent and treat postopera-

tive delirium in the post-anesthesia caring unit: a German survey of current practice. J Clin Monit Comput 2021; 35: 599-605.
45. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. J Am Geriatr Soc 2015; 63: 142-50.
46. Mainerova B, Prasko J, Latalova K, Axmann K, Cerna M, Horacek R, et al. Alcohol withdrawal delirium - diagnosis, course and treatment. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015; 159: 44-52.
47. Spies CD, Rommelspacher H. Alcohol withdrawal in the surgical patient: prevention and treatment. Anesth Analg 1999; 88: 946-54.
48. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013; 25: 33-42.
49. Sumner M, Deng C, Evered L, Frampton C, Leslie K, Short T, et al. Processed electroencephalography-guided general anaesthesia to reduce postoperative delirium: a systematic review and meta-analysis. Br J Anaesth 2023; 130: e243. -53.
50. Maheshwari K, Ahuja S, Khanna AK, Mao G, Perez-Protto S, Farag E, et al. Association between perioperative hypotension and delirium in postoperative critically ill patients: a retrospective cohort analysis. Anesth Analg 2020; 130: 636-43.
51. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. JAMA 2017; 318: 1346-57.
52. Neuman MD, Feng R, Carson JL, Gaskins LJ, Dillane D, Sessler DI, et al. Spinal anesthesia or general anesthesia for hip surgery in older adults. N Engl J Med 2021; 385: 2025-35.
53. Li T, Li J, Yuan L, Wu J, Jiang C, Daniels J, et al. Effect of regional vs general anesthesia on incidence of postoperative delirium in older patients undergoing hip fracture surgery: the RAGA randomized trial. JAMA 2022; 327: 50-8.
54. Yoshimura M, Shiramoto H, Morimoto Y, Koga M. Comparison of total intravenous with inhalational anesthesia in terms of postoperative delirium and complications in older patients: a nationwide population-based study. J Anesth 2022; 36: 698-706.
55. Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, et al. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. Cochrane Database Syst Rev 2018; 8: CD012317.
56. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. Anesth Analg 2006; 102: 1267-73.
57. Swart LM, van der Zanden V, Spies PE, de Rooij SE, van Munster BC. The comparative risk of delirium with different opioids: a systematic review. Drugs Aging 2017; 34: 437-43.
58. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016; 388: 1893-902.
59. Deiner S, Luo X, Lin HM, Sessler DI, Saager L, Sieber FE, et al. Intraoperative infusion of dexmedetomidine for prevention of postoperative delirium and cognitive dysfunction in elderly patients undergoing major elective noncardiac surgery: a randomized clinical trial. JAMA Surg 2017; 152: e171505.