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DELIRIUM AFTER MAJOR ABDOMINAL SURGERY: THE ROLE OF FRAILTY, ANESTHETIC MANAGEMENT, AND MULTIMODAL ANALGESIA

DELIRIUM APÓS CIRURGIA ABDOMINAL MAIOR: O PAPEL DA FRAGILIDADE, MANEJO ANESTÉSICO E ANALGESIA MULTIMODAL

DELIRIO DESPUÉS DE CIRUGÍA ABDOMINAL MAYOR: EL PAPEL DE LA FRAGILIDAD, MANEJO ANESTÉSICO Y ANALGESIA MULTIMODAL

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ABSTRACT

Introduction: Postoperative delirium (POD) is an acute and fluctuating disturbance of attention, awareness, and cognition that frequently affects older adults after major abdominal surgery. Its development reflects an interaction between pre-existing vulnerability and perioperative precipitating factors. Frailty, excessive anesthetic exposure, hemodynamic instability, uncontrolled pain, opioid burden, and sleep disruption are potentially relevant components of this interaction. Objective: To evaluate the association between frailty and POD after major abdominal surgery and to examine whether anesthetic management and multimodal analgesia modify its incidence. Methods: PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library were searched for studies published from January 2015 through August 31, 2026. Randomized trials, prospective or retrospective cohorts, and controlled before-and-after studies involving adults undergoing major abdominal surgery were eligible. Mixed major-surgery populations were included when they provided directly relevant evidence regarding anesthetic depth, anesthetic agents, regional techniques, or analgesic interventions. Risk of bias was assessed according to study design, and the certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation framework. Clinical and methodological heterogeneity precluded quantitative pooling. Results: Twenty-two publications representing 21 independent cohorts were included. Frailty was consistently associated with POD, although its predictive performance improved when combined with cognition, nutritional status, surgical complexity, and perioperative variables. A contemporary meta-analysis reported an odds ratio of 2.47 (95% confidence interval [CI] 2.04–2.99) for POD in frail surgical patients. In abdominal-specific cohorts, POD incidence ranged from 5.5% to 34%. Multimodal prehabilitation reduced delirium from 11.7% to 8.2% in a nonrandomized study, while multidisciplinary geriatric care was associated with a reduction from 29.2% to 11.3%. Evidence regarding anesthetic depth was inconsistent: the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes trial found no benefit from

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electroencephalography guidance, whereas a separate targeted-depth trial reported POD in 19% with lighter anesthesia versus 28% with deeper anesthesia. Combined epidural–general anesthesia reduced POD from 5.0% to 1.8% but increased intraoperative hypotension from 33% to 49%. Moderate-to-severe pain on postoperative day 1 was independently associated with delirium (adjusted odds ratio 1.63; 95% CI 1.27–2.08). A small colorectal trial reported less POD with preemptive multimodal analgesia, whereas opioid-free anesthesia, ketamine, and gabapentin did not demonstrate consistent preventive effects. Conclusion: Frailty is an important marker of vulnerability to delirium after major abdominal surgery but should be interpreted within a multidimensional assessment that includes cognition, nutrition, functional performance, and surgical stress. Anesthetic management should prioritize avoidance of excessive hypnotic exposure, prolonged electroencephalographic suppression, and hemodynamic instability rather than a single anesthetic drug or numerical depth target. Multimodal analgesia should provide effective pain control while limiting unnecessary opioid exposure, but neither complete opioid avoidance nor routine administration of a specific adjunct is supported. The most defensible preventive strategy is an individualized, multidisciplinary pathway combining frailty screening, geriatric optimization, physiologically tailored anesthesia, adequate analgesia, early mobilization, sleep preservation, and systematic delirium surveillance.

Keywords: Postoperative Delirium. Frailty. Abdominal Surgery. Anesthesia. Multimodal Analgesia.

RESUMO

Introdução: Delírio pós-operatório (DPO) é um distúrbio agudo e flutuante da atenção, consciência e cognição que afeta frequentemente adultos idosos após cirurgia abdominal maior. Seu desenvolvimento reflete uma interação entre vulnerabilidade pré-existente e fatores precipitantes perioperatórios. Fragilidade, exposição anestésica excessiva, instabilidade hemodinâmica, dor não controlada, sobrecarga de opioides e disrução do sono são componentes potencialmente relevantes dessa interação. Objetivo: Avaliar a associação entre fragilidade e DPO após cirurgia abdominal maior e examinar se o manejo anestésico e a analgesia multimodal modificam sua incidência. Métodos: PubMed/MEDLINE, Embase, Scopus, Web of Science e Cochrane Library foram pesquisadas para estudos publicados de janeiro de 2015 até 31 de agosto de 2026. Ensaios randomizados, coortes prospectivos ou retrospectivos e estudos controlados antes-e-depois envolvendo adultos submetidos a cirurgia abdominal maior eram elegíveis. Populações de cirurgia maior mista foram incluídas quando forneceram evidências diretamente relevantes regarding profundidade anestésica, agentes anestésicos, técnicas regionais ou intervenções analgésicas. O risco de viés foi avaliado de acordo com o desenho do estudo, e a certeza da evidência foi avaliada usando o framework de Grading of Recommendations Assessment, Development and Evaluation. Heterogeneidade clínica e metodológica impediram pooling quantitativo. Resultados: Vinte e duas publicações representando 21 coortes independentes foram incluídas. Fragilidade foi consistentemente associada com DPO, embora seu desempenho preditivo melhorasse quando combinado com cognição, estado nutricional, complexidade cirúrgica e variáveis perioperatórias. Uma meta-análise contemporânea relatou uma razão de chances de 2,47 (intervalo de confiança de 95% [IC] 2,04–2,99) para DPO em pacientes cirúrgicos frágeis. Em coortes específicas de abdômen, a incidência de DPO variou de 5,5% a 34%. Pré-reabilitação multimodal reduziu delírio de 11,7% para 8,2% em um estudo não randomizado, enquanto cuidado geriátrico multidisciplinar foi associado a uma redução de 29,2% para 11,3%. A evidência regarding profundidade anestésica foi inconsistente: o ensaio

Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes não encontrou benefício da orientação por eletroencefalografia, enquanto um ensaio separado de profundidade direcionada relatou DPO em 19% com anestesia mais leve versus 28% com anestesia mais profunda. Anestesia combinada epidural–geral reduziu DPO de 5,0% para 1,8% mas aumentou hipotensão intraoperatória de 33% para 49%. Dor moderada a grave no primeiro dia pós-operatório foi independentemente associada com delírio (razão de chances ajustada 1,63; IC de 95% 1,27–2,08). Um pequeno ensaio colorretal relatou menos DPO com analgesia multimodal preemptiva, enquanto anestesia sem opioides, cetamina e gabapentina não demonstraram efeitos preventivos consistentes. Conclusão: Fragilidade é um marcador importante de vulnerabilidade a delírio após cirurgia abdominal maior, mas deve ser interpretada dentro de uma avaliação multidimensional que inclua cognição, nutrição, desempenho funcional e estresse cirúrgico. O manejo anestésico deve priorizar a evitação de exposição hipnótica excessiva, supressão eletroencefalográfica prolongada e instabilidade hemodinâmica em vez de um único fármaco anestésico ou alvo numérico de profundidade. A analgesia multimodal deve fornecer controle eficaz da dor enquanto limita exposição desnecessária a opioides, mas nem a completa evitação de opioides nem a administração rotineira de um adjunto específico é apoiada. A estratégia preventiva mais defensável é uma via multidisciplinar individualizada que combina rastreamento de fragilidade, otimização geriátrica, anestesia fisiologicamente adaptada, analgesia adequada, mobilização precoce, preservação do sono e vigilância sistemática de delírio.

Palavras-chave: Delírio Pós-operatório. Fragilidade. Cirurgia Abdominal. Anestesia. Analgesia Multimodal.

RESUMEN

Introducción: El delirio postoperatorio (DPO) es un trastorno agudo y fluctuante de la atención, conciencia y cognición que afecta frecuentemente a adultos mayores después de cirugía abdominal mayor. Su desarrollo refleja una interacción entre vulnerabilidad preexistente y factores precipitantes perioperatorios. La fragilidad, la exposición anestésica excesiva, la inestabilidad hemodinámica, el dolor no controlado, la carga de opioides y la disrupción del sueño son componentes potencialmente relevantes de esta interacción. Objetivo: Evaluar la asociación entre fragilidad y DPO después de cirugía abdominal mayor y examinar si el manejo anestésico y la analgesia multimodal modifican su incidencia. Métodos: PubMed/MEDLINE, Embase, Scopus, Web of Science y Cochrane Library fueron buscados para estudios publicados desde enero de 2015 hasta el 31 de agosto de 2026. Ensayos aleatorios, cohortes prospectivos o retrospectivos y estudios controlados antes-después que involucraran adultos sometidos a cirugía abdominal mayor eran elegibles. Las poblaciones de cirugía mayor mixta se incluyeron cuando proporcionaban evidencia directamente relevante regarding profundidad anestésica, agentes anestésicos, técnicas regionales o intervenciones analgésicas. El riesgo de sesgo fue evaluado según el diseño del estudio, y la certeza de la evidencia fue evaluada utilizando el marco de Grading of Recommendations Assessment, Development and Evaluation. La heterogeneidad clínica y metodológica impidió la agrupación cuantitativa. Resultados: Veintidós publicaciones que representan 21 cohortes independientes fueron incluidas. La fragilidad se asoció consistentemente con DPO, aunque su desempeño predictivo mejoró cuando se combinó con cognición, estado nutricional, complejidad quirúrgica y variables perioperatorias. Un metanálisis contemporáneo reportó una razón de probabilidades de 2,47 (intervalo de confianza del 95% [IC] 2,04–2,99) para DPO en pacientes quirúrgicos frágiles. En cohortes específicas abdominales, la incidencia de DPO varió del 5,5% al 34%. La prehabilitación

multimodal redujo el delirio del 11,7% al 8,2% en un estudio no aleatorizado, mientras que la atención geriátrica multidisciplinaria se asoció con una reducción del 29,2% al 11,3%. La evidencia regarding profundidad anestésica fue inconsistente: el ensayo Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes no encontró beneficio de la orientación por electroencefalografía, mientras que un ensayo separado de profundidad dirigida reportó DPO en el 19% con anestesia más ligera versus 28% con anestesia más profunda. La anestesia combinada epidural-general redujo DPO del 5,0% al 1,8% pero aumentó la hipotensión intraoperatoria del 33% al 49%. El dolor moderado a severo en el primer día postoperatorio se asoció independientemente con delirio (razón de probabilidades ajustada 1,63; IC 95% 1,27–2,08). Un pequeño ensayo colorrectal reportó menos DPO con analgesia multimodal preventiva, mientras que la anestesia libre de opioides, la ketamina y la gabapentina no demostraron efectos preventivos consistentes. Conclusión: La fragilidad es un marcador importante de vulnerabilidad al delirio después de cirugía abdominal mayor pero debe interpretarse dentro de una evaluación multidimensional que incluya cognición, nutrición, desempeño funcional y estrés quirúrgico. El manejo anestésico debe priorizar la evitación de exposición hipnótica excesiva, supresión electroencefalográfica prolongada e inestabilidad hemodinámica en lugar de un único fármaco anestésico o objetivo numérico de profundidad. La analgesia multimodal debe proporcionar un control efectivo del dolor mientras limita la exposición innecesaria a opioides, pero ni la evitación completa de opioides ni la administración rutinaria de un adyuvante específico está respaldada. La estrategia preventiva más defensible es una vía multidisciplinaria individualizada que combine cribado de fragilidad, optimización geriátrica, anestesia fisiológicamente adaptada, analgesia adecuada, movilización temprana, preservación del sueño y vigilancia sistemática del delirio.

Palabras clave: Delirio Postoperatorio. Fragilidad. Cirugía Abdominal. Anestesia. Analgesia Multimodal.

1 INTRODUCTION

Postoperative delirium (POD) is an acute neuropsychiatric syndrome characterized by fluctuating disturbances in attention, awareness, and cognition. It usually develops during the first postoperative days and may present with hyperactive, hypoactive, or mixed motor features. Hypoactive delirium is particularly likely to remain unrecognized without structured and repeated assessment.[1]

Among older adults undergoing elective surgery, a systematic review estimated a pooled POD incidence of 18.4% (95% confidence interval [CI] 14.3–23.3%). Previous delirium, cognitive impairment, functional dependence, frailty, psychotropic medication use, and limited caregiver support were among the principal prognostic factors.[2] The incidence varies substantially according to patient vulnerability, type and urgency of surgery, diagnostic instrument, and duration of surveillance.

Major abdominal surgery combines several potent precipitating factors, including extensive tissue injury, systemic inflammation, prolonged anesthesia, fluid shifts, blood loss, postoperative pain, sleep disruption, immobility, fasting, and exposure to psychoactive medications. Delirium in this setting is associated with prolonged hospitalization, functional decline, institutionalization, increased costs, and mortality. It should therefore be understood as an organ dysfunction affecting a vulnerable brain rather than an unavoidable consequence of chronological age.[3]

The pathophysiology of POD is multifactorial. Surgical injury releases damage-associated molecular patterns and inflammatory mediators that may alter endothelial function, blood–brain barrier permeability, microglial activity, neurotransmission, and cerebral energy metabolism.[3] Cerebral hypoperfusion, hypoxemia, metabolic abnormalities, pain, sleep deprivation, and medication effects may amplify these changes.

Frailty describes diminished physiological reserve and reduced capacity to recover from acute stress. It is distinct from age, disability, and comorbidity, although these conditions frequently overlap. A 2025 meta-analysis including 43 studies and 14,441 participants found that preoperative physical frailty was associated with POD, with a pooled odds ratio (OR) of 2.47 (95% CI 2.04–2.99).[4] An earlier synthesis found a crude OR of 3.28 (95% CI 2.51–4.28) and an adjusted OR of 2.45 (95% CI 1.58–3.81).[5]

Frailty can be evaluated using phenotype-based instruments, deficit-accumulation indices, the Clinical Frailty Scale, the Fatigue–Resistance–Ambulation–Illnesses–Loss of Weight scale, the Risk Analysis Index, physical-performance measures, or comprehensive

geriatric assessment. These instruments do not identify identical populations. Consequently, frailty should be used to trigger more detailed evaluation and preventive care rather than as an isolated reason to deny surgery.

Anesthetic management may affect POD through hypnotic exposure, electroencephalographic suppression, cerebral perfusion, hemodynamic instability, opioid administration, and postoperative recovery. Randomized trials comparing lighter and deeper anesthesia have produced conflicting findings. A systematic review of six studies involving 7,736 older adults found no statistically significant difference between lighter and deeper anesthesia, with substantial heterogeneity and low certainty of evidence (OR 1.40; 95% CI 0.63–3.08).[6]

Pain management represents a similarly complex pathway. Severe pain activates sympathetic and inflammatory responses, disrupts sleep and mobilization, and independently correlates with delirium. In a multicenter abdominal-surgery cohort of 2,674 older adults, moderate-to-severe pain on postoperative day 1 was associated with POD after multivariable adjustment (OR 1.63; 95% CI 1.27–2.08).[7] Conversely, excessive opioid exposure can cause sedation, respiratory depression, sleep disruption, and impaired cognitive assessment.

Enhanced Recovery After Surgery (ERAS) protocols favor multimodal analgesia, early mobilization, timely oral intake, avoidance of prolonged fasting, and reduction of unnecessary tubes and sedatives.[8] Multimodal analgesia combines interventions acting through different pathways to improve analgesia while reducing the dose-dependent adverse effects of any single agent. It does not necessarily mean opioid-free anesthesia, and the inclusion of additional medications does not automatically confer protection against delirium.

Current perioperative consensus therefore emphasizes preoperative risk identification, medication review, adequate pain control, avoidance of deliriogenic exposure, physiological stability, sensory aids, sleep preservation, early mobilization, hydration, nutrition, and structured postoperative screening.[9] The relative contribution of frailty, anesthetic management, and analgesic strategy remains uncertain because these factors interact and have frequently been studied in different populations. A focused synthesis is required to translate the available evidence into a coherent approach for major abdominal surgery.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To evaluate the association between preoperative frailty and the incidence of delirium after major abdominal surgery and to determine how anesthetic management and multimodal analgesia influence that relationship.

2.2 SECONDARY OBJECTIVES

1. To compare the predictive value of frailty instruments with cognitive, nutritional, functional, and conventional perioperative assessments.
2. To evaluate the effects of anesthetic depth, electroencephalographic monitoring, anesthetic agents, hemodynamic management, and neuraxial techniques on POD.
3. To assess the association between postoperative pain, opioid exposure, regional analgesia, and POD.
4. To examine the effectiveness of prehabilitation, comprehensive geriatric assessment, and multicomponent perioperative pathways.
5. To identify clinically relevant benefits, adverse effects, methodological limitations, and priorities for future research.

3 METHODOLOGY

3.1 DESIGN AND REPORTING

This systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[10] A protocol defining the population, exposures, outcomes, and analytical approach was prepared before eligibility assessment but was not prospectively registered.

3.2 INFORMATION SOURCES AND SEARCH STRATEGY

PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library were searched for publications from January 1, 2015, through August 31, 2026. Reference lists of relevant systematic reviews, clinical guidelines, and eligible studies were also evaluated.

Controlled vocabulary and free-text terms combined concepts related to postoperative delirium, abdominal surgery, gastrointestinal surgery, colorectal surgery, hepatobiliary

surgery, pancreatic surgery, frailty, geriatric assessment, anesthetic depth, electroencephalography, bispectral index, dexmedetomidine, remimazolam, hypotension, postoperative pain, opioids, epidural analgesia, regional anesthesia, multimodal analgesia, enhanced recovery, and prehabilitation.

3.3 ELIGIBILITY CRITERIA

Eligible studies enrolled adults undergoing major elective or urgent abdominal surgery and evaluated at least one of the following:

- Preoperative frailty, functional performance, nutritional vulnerability, or comprehensive geriatric assessment.
- Anesthetic depth, processed electroencephalography, anesthetic agents, or hemodynamic management.
- Regional, neuraxial, opioid-sparing, opioid-free, preemptive, or multimodal analgesia.
- Multidisciplinary prehabilitation or geriatric perioperative care.

Randomized trials, prospective cohorts, retrospective cohorts, and controlled before-and-after studies were included. Mixed major-surgery populations were eligible when the intervention was directly relevant to abdominal surgery and POD was assessed with a recognized diagnostic instrument.

Studies evaluating only emergence agitation, delayed neurocognitive recovery, or long-term cognitive decline without a distinct POD outcome were excluded. Case reports, small case series, conference abstracts, trial protocols, pediatric studies, and studies without an analyzable perioperative exposure were also excluded.

3.4 OUTCOMES

The primary outcome was POD diagnosed during the first seven postoperative days using the Confusion Assessment Method (CAM), three-minute CAM, CAM for the Intensive Care Unit, Diagnostic and Statistical Manual of Mental Disorders criteria, or another validated instrument.

Secondary outcomes included delirium duration and severity, pain intensity, opioid consumption, electroencephalographic suppression, hypotension, bradycardia,

postoperative complications, intensive care admission, length of stay, functional recovery, and mortality.

3.5 DATA EXTRACTION AND SYNTHESIS

Study design, surgical population, sample size, eligibility criteria, frailty instrument, intervention, comparator, delirium assessment, effect estimate, precision, adverse events, and methodological limitations were extracted into a standardized evidence matrix.

Quantitative pooling was not undertaken because the studies differed substantially in surgical procedures, frailty definitions, anesthetic protocols, analgesic regimens, comparators, and delirium-surveillance periods. Results were synthesized narratively across three principal domains: vulnerability and frailty, anesthetic management, and analgesia.

3.6 RISK OF BIAS AND CERTAINTY ASSESSMENT

Randomized trials were assessed using the revised Cochrane risk-of-bias framework. Nonrandomized intervention and prognostic studies were evaluated with attention to confounding, participant selection, exposure classification, missing data, outcome measurement, and selective reporting.

Particular concerns included variable frailty definitions, unblinded treatment assignment, historical controls, inadequate adjustment for baseline cognition, postoperative delirium assessed as a secondary outcome, and insufficient multiplicity control. Certainty was graded separately for frailty as a prognostic marker, frailty-directed interventions, anesthetic management, and multimodal analgesia.

4 RESULTS

4.1 STUDY SELECTION AND CHARACTERISTICS

Twenty-two publications representing 21 independent cohorts were included. The evidence comprised 11 randomized trials, one prospective anesthetic-depth comparison, six prospective observational cohorts, two retrospective cohorts, and one uncontrolled before-and-after intervention with a subsequent long-term report.

Thirteen cohorts were restricted to abdominal, gastrointestinal, colorectal, gastric, or pancreatic surgery. The remaining studies enrolled mixed major noncardiac populations that included abdominal procedures or evaluated interventions directly applicable to abdominal surgery. Sample sizes ranged from 133 to 2,674 participants.

POD incidence ranged from 1.8% in a combined epidural–general anesthesia group to 34% in an older gastroenterological-cancer cohort. Surveillance varied from three to seven postoperative days. Differences in baseline vulnerability and assessment frequency contributed materially to the observed variation.

Table 1

Principal studies evaluating frailty, anesthetic management, and analgesia

Domain and study	Design and population	N	Exposure or comparison	Principal delirium result
Sánchez Acedo et al.[11]	Prospective cohort; patients ≥65 years undergoing urgent abdominal surgery	446	Frailty and perioperative predictors	POD occurred in 13.6%. Frailty was not independently associated after adjustment; cognitive impairment OR 5.80, physiological severity OR 5.80, and American Society of Anesthesiologists status OR 3.15.
Tsai et al.[12]	Prospective cohort; older adults undergoing elective abdominal cancer surgery	345	Comprehensive geriatric assessment-defined frailty	POD occurred in 8.1% of frail versus 2.5% of fit patients. Incidence increased from 1.6% with no frailty conditions to approximately 10%–12% with three or more conditions.
Sugi et al.[13]	Retrospective cohort; patients ≥75 years undergoing gastroenterological -cancer surgery	158	Geriatric, physical, nutritional, and cognitive assessments	POD occurred in 34%. Short Physical Performance Battery ≤9, Mini Nutritional Assessment Short-Form ≤11, Mini-Mental State Examination ≤24, and regular benzodiazepine use were

Domain and study	Design and population	N	Exposure or comparison	Principal delirium result
				independent predictors.
Ni et al.[14]	Prospective cohort; older adults undergoing major thoracic or abdominal surgery	299	Frailty and cognitive impairment	POD occurred in 25.6% of frail versus 14.6% of nonfrail patients. Frailty alone had an area under the curve (AUC) of 0.657; an integrated model achieved an AUC of 0.814.
Zhao et al.[15]	Prospective cohort; elective abdominal surgery in patients ≥65 years	163	Revised Risk Analysis Index, nutritional risk, and metabolic variables	Revised Risk Analysis Index, Nutrition Risk Screening 2002, and triglycerides were independently associated with POD. The frailty index achieved an AUC of 0.790.
Xia et al.[16]	Prospective cohort; pancreatic-cancer surgery	293	Nutrition, FRAIL score, and perioperative factors	POD occurred in 19.5%. Frailty score OR 2.45 (95% CI 1.44–4.16) and intraoperative hypotension OR 2.87 (95% CI 1.16–7.12). Frailty AUC was 0.829.
Janssen et al.[17],[18]	Uncontrolled before-and-after study; colorectal cancer or abdominal aortic aneurysm surgery	627	Multimodal prehabilitation versus historical care	POD decreased from 11.7% to 8.2%; adjusted OR 0.56 (95% CI 0.32–0.98). Prehabilitation did not reduce one-year mortality; POD was associated with mortality, HR 4.36 (95% CI 2.45–7.75).

Domain and study	Design and population	N	Exposure or comparison	Principal delirium result
Tarazona-Santabalbina et al.[19]	Retrospective cohort; elective colorectal-cancer surgery in adults ≥70 years	310	Daily multidisciplinary geriatric care versus usual care	POD occurred in 11.3% with geriatric care versus 29.2% with usual care, despite greater baseline vulnerability in the intervention group.
Wildes et al.; Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes trial[20]	Randomized trial; adults ≥60 years undergoing major surgery	1,232	Electroencephalography-guided anesthetic administration versus usual care	POD occurred in 26.0% versus 23.0%; absolute difference 3.0% (95% CI −2.0 to 8.0), P=.22. Guidance reduced anesthetic concentration and suppression time but not delirium.
Evered et al.; BALANCED anesthesia substudy[21]	Multicenter randomized trial; at-risk adults undergoing major surgery	655	Bispectral Index target 50 versus target 35	POD occurred in 19% with lighter versus 28% with deeper anesthesia; OR 0.58 (95% CI 0.38–0.88).
Chen et al.[22]	Prospective depth-comparison trial; pre-frail older adults undergoing abdominal surgery	150	Cerebral State Index 50–59 versus 40–49	Lighter anesthesia produced an approximately 14-percentage-point reduction in POD and higher Quality of Recovery-15 scores; exact group incidences were incompletely reported in the abstract.
Zhang et al.[23]	Randomized trial; major abdominal surgery in adults 65–89 years	370	Remimazolam-based versus propofol-based anesthesia	POD occurred in 17.1% versus 19.7%; OR 1.19 (95% CI 0.69–2.06), P=.578. Hypotension was

Domain and study	Design and population	N	Exposure or comparison	Principal delirium result
				less frequent with remimazolam.
Peng et al.[24]	Randomized trial; older adults undergoing major abdominal surgery	203 analyzed	Intraoperative dexmedetomidine 0.3 or 0.6 μg/kg/h versus saline	Both doses markedly improved first-night sleep, but no between-group difference was found in POD, hypotension, bradycardia, or 30-day mortality.
Su et al.[25]	Randomized trial; older adults admitted to intensive care after noncardiac surgery	700	Low-dose postoperative dexmedetomidine versus placebo	POD occurred in 9% versus 23%; OR 0.35 (95% CI 0.22–0.54). Applicability depends on postoperative monitoring and infusion setting.
Deiner et al.[26]	Randomized trial; older adults undergoing major elective noncardiac surgery	404	Intraoperative dexmedetomidine versus placebo	POD occurred in 12.2% versus 11.4%, P=.94. No cognitive or functional benefit was demonstrated.
Li et al.[27]	Multicenter randomized trial; major thoracic or abdominal surgery	1,802 randomized; 1,720 analyzed	Combined epidural–general anesthesia with epidural analgesia versus general anesthesia with intravenous analgesia	POD occurred in 1.8% versus 5.0%; relative risk (RR) 0.351 (95% CI 0.197–0.627); number needed to treat 31. Hypotension occurred in 49% versus 33%; RR 1.47.
Ma et al.[7]	Secondary analysis of multicenter prospective data; elective abdominal surgery in adults ≥65 years	2,674	Moderate-to-severe versus absent-to-mild pain on postoperative day 1	POD occurred in 16.3% versus 9.6%. Adjusted OR 1.63 (95% CI 1.27–2.08); propensity-matched OR 1.44 (95% CI 1.11–1.88).

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Domain and study	Design and population	N	Exposure or comparison	Principal delirium result
Sun et al.[28]	Single-center randomized trial; laparoscopic colorectal surgery	133	Preemptive multimodal analgesia versus the same principal components initiated later	POD occurred in 8.98% versus 24.24%, P<.05. The intervention included preinduction transversus abdominis plane block, dexmedetomidine, flurbiprofen, and oxycodone-based postoperative analgesia.
Zhao et al.[29]	Randomized trial; laparoscopic abdominal surgery in adults ≥60 years	195 analyzed	Opioid-free anesthesia with dexmedetomidine, esketamine, and lidocaine versus opioid-based anesthesia	POD was similar between groups. Opioid-free anesthesia reduced nausea and opioid consumption but prolonged emergence and post-anesthesia care unit stay.
Avidan et al.; Prevention of Delirium and Complications Associated with Surgical Treatments trial[30]	International randomized trial; major surgery in adults >60 years	672	Ketamine 0.5 mg/kg, ketamine 1 mg/kg, or placebo	POD occurred in 19.45% with ketamine versus 19.82% with placebo; difference 0.36% (95% CI −6.07 to 7.38). Hallucinations and nightmares increased with dose.
Leung et al.[31]	Randomized trial; older adults undergoing major surgery	697	Perioperative gabapentin versus placebo	POD occurred in 24.0% versus 20.8%, P=.30. Gabapentin reduced opioid use but did not reduce delirium or hospital stay.

Source: Prepared by the authors.

4.2 RISK OF BIAS AND CERTAINTY

The large randomized trials generally had low risk of bias for treatment allocation and delirium assessment, although abdominal-specific applicability was sometimes indirect. Smaller single-center trials had concerns regarding limited precision, secondary delirium outcomes, incomplete reporting, multiple comparisons, or nonstandard implementation of diagnostic scores.

Frailty cohorts had moderate-to-serious risk of confounding. Frailty was associated with age, cognitive impairment, malnutrition, comorbidity, functional dependence, and surgical complexity, and adjustment strategies varied considerably.

The certainty of evidence was considered moderate for frailty as a prognostic marker but low for the proposition that modifying frailty itself prevents POD. Certainty was low for anesthetic-depth targeting because of conflicting randomized results and heterogeneous targets. Evidence for epidural–general anesthesia was moderate but required consideration of hypotension. Evidence supporting any specific multimodal drug combination was low.

5 DISCUSSION

The evidence supports a vulnerability–stress model of delirium after major abdominal surgery. Frailty, cognitive impairment, malnutrition, physical limitation, and cerebrovascular disease reduce the amount of surgical and physiological stress that a patient can tolerate. Anesthetic exposure, inflammation, pain, hypotension, sleep disruption, and medication effects then determine whether that vulnerability becomes clinically apparent as delirium.

Frailty is one of the most consistent markers of risk, approximately doubling to tripling the odds of POD in broad surgical meta-analyses.[4,5] The abdominal-specific studies showed a clear gradient: frail patients had more delirium than fit patients, and POD became increasingly frequent as frailty deficits accumulated.[12,16] Nevertheless, urgent abdominal surgery data demonstrated that frailty can lose statistical independence when cognition, acute physiological severity, anesthetic risk, and diagnosis are considered together.[11] Frailty is therefore clinically informative but is not a complete causal explanation.

Performance-based, nutritional, and cognitive variables appear to refine frailty assessment. In gastroenterological cancer surgery, low Short Physical Performance Battery, Mini Nutritional Assessment Short-Form, and Mini-Mental State Examination scores independently identified high-risk patients.[13] Frailty or cognitive screening alone showed limited discrimination in another cohort, whereas a model incorporating age, body mass

index, American Society of Anesthesiologists status, surgical duration, morphine exposure, surgical risk, frailty, and cognition achieved an AUC of 0.814.[14] The Revised Risk Analysis Index and FRAIL scale also demonstrated useful discrimination in abdominal and pancreatic surgery.[15],[16]

These findings favor a brief initial frailty screen followed by targeted assessment rather than reliance on a single instrument. Patients with an abnormal screen should undergo evaluation of cognition, medication burden, nutrition, mobility, sensory impairment, depression, anemia, hydration, and social support. The result should be communicated to surgeons, anesthesiologists, nurses, physiotherapists, nutrition professionals, and family members before surgery.

Evidence that vulnerability-directed care prevents delirium is promising but not definitive. Multimodal prehabilitation addressing physical capacity, nutrition, anemia, and frailty reduced POD from 11.7% to 8.2%, corresponding to an adjusted OR of 0.56.[17] The same program did not reduce one-year mortality, but POD itself was associated with more than fourfold higher one-year mortality and worse functional recovery.[18] Daily multidisciplinary geriatric assessment was associated with a reduction in delirium from 29.2% to 11.3%, despite greater baseline vulnerability in the intervention group.[19] Because both comparisons were nonrandomized, the magnitude of benefit requires confirmation in controlled trials.

Anesthetic depth is clinically relevant, but the evidence does not support a universal numerical target. In the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes trial, guidance reduced volatile-anesthetic exposure and electroencephalographic suppression but did not reduce POD.[20] Conversely, the BALANCED substudy reported a nine-percentage-point absolute reduction when a Bispectral Index target of 50 was compared with a target of 35.[21] An abdominal-specific study in pre-frail patients also favored lighter anesthesia.[22] The pooled evidence remains heterogeneous and of low certainty.[6]

These apparently conflicting results can be reconciled clinically. Processed electroencephalography is most useful when interpreted alongside the raw waveform, burst suppression, anesthetic concentration, nociceptive stimulation, neuromuscular blockade, age, and blood pressure. A single index cannot distinguish every cause of low cortical activity. The practical objective is adequate unconsciousness without avoidable anesthetic excess or prolonged suppression, particularly in frail patients whose pharmacodynamic sensitivity may be increased.

No general anesthetic agent has demonstrated sufficiently consistent superiority to be selected solely for delirium prevention. Remimazolam produced a POD incidence similar to propofol in major abdominal surgery, although it caused less hypotension.[23] Intraoperative dexmedetomidine improved sleep but did not reduce POD in a recent abdominal trial.[24] A postoperative low-dose dexmedetomidine infusion reduced POD from 23% to 9% in monitored older patients, whereas intraoperative administration in another large trial was neutral.[25],[26] Timing, dose, postoperative care environment, baseline risk, bradycardia, and hypotension probably contribute to this heterogeneity.

Hemodynamic management is an essential part of brain-oriented anesthesia. In pancreatic surgery, intraoperative hypotension was independently associated with POD, with an OR of 2.87.[16] However, the optimal pressure target is unlikely to be identical for every patient. Longstanding hypertension, carotid or intracranial vascular disease, baseline blood pressure, blood loss, anemia, and vasoactive requirements should inform an individualized target.

The epidural trial illustrates the importance of evaluating benefits and harms together. Combined epidural–general anesthesia with postoperative epidural analgesia reduced POD from 5.0% to 1.8%, an absolute reduction of 3.2 percentage points and a number needed to treat of 31.[27] It simultaneously increased systolic hypotension below 80 mmHg from 33% to 49% and increased vasopressor administration. Epidural analgesia may be appropriate for selected open abdominal procedures, but its use should consider cardiovascular reserve, anticoagulation, surgical approach, expected pain, and institutional expertise.

Pain is not merely a symptom occurring alongside delirium. Moderate-to-severe pain on the first postoperative day was associated with a 63% increase in adjusted odds of POD in the largest abdominal-specific analysis.[7] Effective analgesia may reduce sympathetic activation, sleep disturbance, respiratory restriction, immobility, and inflammatory stress. At the same time, escalating opioids without addressing the cause of pain may worsen sedation, ventilation, bowel function, and cognition.

The colorectal trial of preemptive multimodal analgesia reported POD in 8.98% of treated patients versus 24.24% of controls.[28] Its regimen combined a preinduction transversus abdominis plane block, dexmedetomidine, flurbiprofen, perioperative oxycodone, and standardized postoperative patient-controlled analgesia. The study supports early, mechanism-based pain prevention, but POD was a secondary outcome and the sample was

small. The result should be replicated before this exact combination is treated as a standard delirium-prevention protocol.

Multimodal analgesia should not be equated with the complete elimination of opioids. In older adults undergoing laparoscopic abdominal surgery, opioid-free anesthesia modestly reduced nausea, opioid consumption, and time to gastrointestinal recovery but did not reduce POD and prolonged emergence and post-anesthesia care unit stay.[29] Small, carefully titrated opioid doses may remain appropriate when combined with acetaminophen, selected nonsteroidal anti-inflammatory drugs, local anesthetic infiltration, fascial-plane blocks, or epidural analgesia.[8] Drug selection should reflect renal function, bleeding risk, gastrointestinal risk, hepatic function, sedation susceptibility, and the type of incision.

Adding an analgesic adjunct is also not necessarily protective. The Prevention of Delirium and Complications Associated with Surgical Treatments trial found no reduction in POD with either of two ketamine doses and demonstrated more hallucinations and nightmares with increasing dose.[30] Gabapentin reduced opioid exposure but did not reduce POD or length of stay.[31] These results argue against routine prophylactic ketamine or gabapentin solely to prevent delirium in older adults.

The most coherent clinical strategy is a continuous pathway rather than an isolated intraoperative intervention. Before surgery, the pathway should identify frailty, cognitive impairment, malnutrition, anemia, medication risks, sensory limitations, and previous delirium. During surgery, it should avoid unnecessary benzodiazepines and anticholinergic exposure, titrate anesthesia to patient sensitivity, treat pain, maintain oxygenation and physiological stability, and minimize prolonged electroencephalographic suppression.[1,9]

Postoperatively, patients should receive scheduled delirium surveillance, frequent orientation, glasses and hearing aids, sleep protection, early removal of unnecessary devices, mobilization, hydration, nutrition, and regular assessment for pain, urinary retention, constipation, hypoxemia, infection, and metabolic disorders. Opioid requirements and sedation should be reviewed repeatedly rather than assessed only during the immediate recovery period. Pharmacological restraint or antipsychotic treatment should be reserved for severe distress or immediate risk after reversible causes have been addressed.

This review has limitations. Frailty instruments, abdominal procedures, anesthetic strategies, and delirium-assessment schedules were heterogeneous. Several intervention studies enrolled mixed surgical populations, limiting direct abdominal-specific inference. Most frailty studies were observational, while some apparently favorable pathway studies used

historical controls. The evidence supports risk-guided multicomponent care more strongly than any single medication, monitor, or regional technique.

6 CONCLUSION

Postoperative delirium after major abdominal surgery results from the interaction between baseline cerebral and physiological vulnerability and perioperative stress. Frailty is one of the most consistent markers of this vulnerability, but its interpretation is strengthened by simultaneous assessment of cognition, nutrition, mobility, comorbidity, medication exposure, and surgical complexity.

Frailty screening should not be used as an isolated exclusion criterion for surgery. Its principal value is to identify patients who require more detailed assessment, shared decision-making, preoperative optimization, closer physiological monitoring, and structured postoperative prevention. Evidence that prehabilitation and multidisciplinary geriatric care reduce delirium is encouraging, although adequately controlled abdominal-surgery trials remain necessary.

Anesthetic management should prioritize individualized dosing, avoidance of unnecessary hypnotic exposure and prolonged electroencephalographic suppression, and preservation of hemodynamic and respiratory stability. Processed electroencephalography can support this strategy, but a single index or universal depth target cannot replace clinical and physiological interpretation. No anesthetic agent has shown sufficiently consistent superiority to be recommended solely for POD prevention.

Multimodal analgesia should achieve effective pain control while limiting excessive opioid exposure and drug-related sedation. Regional or neuraxial techniques may reduce delirium in selected procedures, but their benefits must be weighed against hypotension, bleeding risk, technical feasibility, and surgical approach. Complete opioid avoidance, routine ketamine, and routine gabapentin are not supported as universal delirium-prevention strategies.

The most defensible approach is an individualized perioperative pathway integrating frailty and cognitive screening, nutritional and functional optimization, physiologically tailored anesthesia, balanced multimodal analgesia, early mobilization, sleep preservation, and repeated delirium assessment. Future trials should stratify participants by frailty, use validated delirium assessments at least twice daily, report delirium severity and duration, and evaluate functional and cognitive recovery in addition to incidence.

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