REVIEW ARTICLE

Unveiling the Risk Factors for Postoperative Cognitive Dysfunction

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ABSTRACT

Postoperative cognitive decline (POCD), a concerning consequence of surgery, can significantly impact a patient's recovery and long-term well-being. This study gives insights into a multifaceted exploration of risk factors associated with POCD. It meticulously examines pre-operative patient characteristics such as age, educational background, and the presence of pre-existing cognitive decline. Intra-operative factors under investigation include the complexity and duration of the surgery, and the specific anesthetic agents employed. The study aims to shed light on the mechanisms underlying POCD. This comprehensive analysis has the potential to empower healthcare professionals in developing more targeted preventative measures. By identifying high-risk patients, clinicians can implement pre-operative interventions like cognitive training or medication adjustments. Additionally, optimizing surgical protocols to minimize blood flow disruptions and selecting the most neuroprotective anesthetic agents could further mitigate POCD risk.
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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a condition characterized by a decline in cognitive function following surgery, particularly in elderly patients. The term "peri-operative neurocognitive disorders" (PND) aligns with the clinical diagnostic criteria for neurocognitive impairment outlined in the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5), replacing the terms "post-operative delirium" (POD) and "post-operative coma disorder" (POCD). Although the term PND is increasingly being used, this study focuses on POCD due to the majority of scientific data supporting it (1,2). The definitive difference between POD and POCD remains elusive. It is suggested that POCD is more appropiate terminology and concept over the long period, while POD occurs commonly during the hospital stay (75).

The risk factors for POCD are multifactorial and can be categorized into patient-related, surgical, and anesthetic factors. Patient-related risk factors include advanced age, low educational level, pre-existing cognitive impairment, alcohol abuse, and severity of coexisting illness 1,2. Surgical factors such as the type and duration of surgery, as well as the use of cardiopulmonary bypass, have been associated with an increased risk of POCD (3). Additionally, anesthetic factors, including the choice of anesthetic agents and the depth of anesthesia, have been implicated in the development of POCD (4).

Furthermore, it is important to consider the impact of comorbidities such as cerebrovascular and systemic vascular disease, as well as undiagnosed mild cognitive dysfunction, which may contribute to the development of POCD (5). Additionally, genetic factors, such as the presence of an APOE4 allele, have been suggested to potentially confer a higher risk for developing POCD through the mechanism that release inflammatory mediatros that block nicotine and acetylcholinea receptors, although there are conflicting reports in the literature regarding this association (6, 75). The incidence of POCD varies depending on the population studied, the definition of POCD used, the timing of testing, and the choice of control group (7).

Prevention of POCD is crucial, especially in the elderly, as it is associated with increased mortality, risk of early workforce exit, and dependence on social security (8). Therefore, there is a need to improve knowledge around risk factors, prevention, and management of postoperative cognitive side effects (9). Additionally, the identification of high-risk populations for POCD, such as elderly patients with specific medical conditions, can aid in reducing long-term postoperative complications and improving postoperative quality of life (10). The purpose of this article is analysis the potential risk factors that contributes to increased incidence of POCD.

PATHOPHYSIOLOGY OF POCD

The pathologic mechanism of postoperative cognitive dysfunction (POCD) is not clearly known. However, the mechanism suggests a complex and multifactorial process that involves various neurobiological and inflammatory pathways. Several studies have highlighted the role of neuroinflammation as a key hallmark in the development of neurological complications (11). Inflammation that leads to the activation of cerebral microglia has been found to play a pivotal role in the etiology of POCD. The mechanism by which dexmedetomidine affects postoperative cognitive impairment has been associated with glucocorticoid receptors, particularly in the frontal cortex and hippocampus. Studies have demonstrated that hippocampal recruitment of bone marrow-derived macrophages is a necessary mechanism of developing POCD in mice, indicating the involvement of innate immune responses in the development of cognitive dysfunction post-surgery.(12).

Other mechanisms suggest that cholinergic dysfunction is a risk factor for the development of POCD by interfering with the resolution of the neuroinflammatory response (13). Furthermore, it has been suggested that inhibiting receptor-interacting protein kinase 1 (RIPK1) limits neuroinflammation and alleviates postoperative cognitive impairments in aged mice, indicating a potential therapeutic target for POCD (14). Postoperative cognitive dysfunction in old mice is associated with gliosis, beta-amyloid accumulation, and protein hyperphosphorylation in the hippocampus (15). By limiting the resolution of neuroinflammatory response thought to contribute to POCD, cholinergic dysfunction might lead to longer duration of POCD.

Other sedative agents, such as sevoflurane and dexmedetomidine, a sedative agent has been investigated for its effect on POCD, and their has been found to restore autophagic flux and modulate associated microRNAs and the cholinergic anti-inflammatory pathway, suggesting a potential role in mitigating neuroinflammation and cognitive dysfunction post-surgery (16).

RISK FACTORS

Cardiac surgery

Postoperative cognitive dysfunction (POCD) is a well-recognized complication following cardiac surgery, affecting a significant proportion of patients. The incidence of POCD after cardiac surgery has been reported to be as high as 25-70%. Factors contributing to POCD include patient-specific factors, type of surgery, intraoperative and postoperative factors (17). It was thought that the process was due to immune priming, neuroinflammation aggravated by aging, and atherosclerosis as the main pathophysiology (33). An International Study of Postoperative Cognitive Dysfunction (ISPOCD1) found that cognitive dysfunction was present in 26% of older patients one week after major noncardiac surgery and in 10% three months after surgery (21, 22). In patients undergoing cardiac surgery with cardiopulmonary bypass, POCD has been reported to be evident in 53% at discharge and remains present in 36% of patients at 6 weeks after surgery (23).

Several factors have been associated with an increased risk of POCD following cardiac surgery. These include the high postoperative temperature after cardiac surgery, highlighting the importance of avoiding postoperative hyperthermia (18). Furthermore, a history of alcohol dependence has been linked to an increased incidence and severity of POCD in cardiac surgical patients (24). On the other hand, it was found that in cardiac surgery, the intraoperative cerebral oximetry values do not show any significance toward POCD (32).

While there is a high prevalence of POCD after cardiac surgery, it is important to note that current evidence exempts cardiac surgery as the primary causes of cognitive dysfunction (19). The lack of unequivocal associations between cardiac surgery and postoperative cognitive dysfunction suggests that cognitive decline following cardiac surgery may not be solely due to the surgery itself, but rather due to the progression of underlying vascular diseases (20).

Exisiting cognitive impairment

The relationship between existing cognitive impairment and postoperative cognitive dysfunction has been extensively studied in the literature. Several studies have consistently demonstrated a significant association between preoperative cognitive impairment and adverse postoperative outcomes in elderly surgical patients. It was found that impaired cognition was associated with the occurrence of POCD ranging from 2.401 (95% CI 1.185-4.865, p value= 0.015) to 8.35 (95% CI 4.25-16.38) (25-28). On the other hand, the association between lower animal fluency scores and POCD has an odds ratio of 1.08 (95%CI 1.01-1.51) for each point decrease in the number of animals named (29). The study also revealed that individuals who had POCD had lower mean preoperative MMSE scores than those who did not (30). Global cognitive performance, IQCODE score, and living alone are significantly associated with long-term cognitive decline after postoperative delirium in the older adult population (34).

These findings highlight the need for comprehensive preoperative cognitive screening in older surgical patients. Moreover, the other implications of preoperative cognitive impairment is linked to adverse outcomes such as longer hospital stays and functional decline This suggests that preoperative cognitive impairment not only affects immediate postoperative outcomes but also has long-term consequences for patients' recovery and functional status (31).

Duration of surgery

The association between the duration of surgery has not been studied well. However, several studies have tried to domenstrate the relationship between a longer duration of surgery with an increased risk of POCD. People who develop POCD 3 monts after surgery have 5 minutes longer anesthesia duration (215.0 ± 92.8) compared to those who did not develop POCD (211.5 ± 103.2), with no statistifically significant result (p value = 0.521) (21). Longer duration of surgery might trigger more oxidative stress thus leading to more profound inflammation. However, the sole relationship about the duration of surgery has not been shown clearly(35,36).

Age

POCD has been a significant concern, particularly in older patients undergoing surgery. Several risk factors have been identified in the literature that contribute to the development of POCD, with age being a prominent factor (38-40). Older age has consistently been associated with an increased risk of postoperative cognitive decline.

Studies have shown that advanced age is a predictor of cognitive decline after surgery, with up to 65% of patients aged 65 years and older experiencing delirium and 10% developing long-term cognitive decline (37). Additionally, older patients are at higher risk of preoperative cognitive impairment, which further elevates their susceptibility to postoperative cognitive decline (41).

Age-related decline in cerebral and cerebrovascular function contributes to the high prevalence of postoperative delirium and cognitive dysfunction in elderly patients, leading to delays in recovery and discharge (42). Preoperative cognitive optimization through activities like brain exercises has shown promise to reduce the incidence of postoperative delirium in elderly surgical patients (43).

Although there have been several arguments about the benefits, monitoring cerebral oxygen saturation was recommended during surgery, as cerebral desaturation can lead to early postoperative cognitive decline and prolonged hospital stays in elderly patients. The vulnerability of the elderly to postoperative cognitive decline has raised concerns, with research highlighting the need to address anesthetic neurotoxicity and its impact on cognitive function in the elderly population (44).

Gender

Gender has been identified as a potential risk factor for postoperative cognitive decline, with some studies highlighting its impact. While some research suggests that there are no significant differences in postoperative cognitive outcomes between men and women (6), other studies have indicated that the female sex can be a risk factor for postoperative impairments in specific cognitive domains (45). In a study with an elderly population, it was found that females might contribute as a risk factor for POCD, with age as the dominating factor contributing to it (47).

Education profile

Lower educational levels are associated with an increased risk of postoperative cognitive decline. Individuals with lower levels of education are more likely to experience cognitive impairment following surgery compared to those with higher educational level profiles (48,49). Some specified that high school education compared to lower than high school education level does not differ to the relation with POCD, suggesting that a minimum high school of education and further/higher education level is essential to reduce the risk of developing POCD (50). The incidence of POCD in lower educational levels might be found until the duration of 3 months after surgery (21,45). People with Higher educational levels are associated with a reduced risk of POCD with RR per education year increment of 0.90 (50).

Mode of anesthesia

There has been no agreement over the results with some leaning toward general anesthesia and the other favors spinal anesthesia. Some even found no significant difference in the occurrence of postoperative delirium between spinal and general anesthesia in hip fracture surgery patients, as both contribute to POCD(51). It was in line with studies that compare spinal and general anesthesia in elective spine surgery and assessed postoperative fatigue, cognitive dysfunction, and quality of life, with no clear superiority between the two anesthesia types (52).

A retrospective cohort study on elderly patients undergoing intertrochanteric fracture surgeries and concluded that general anesthesia with laryngeal mask airway and nerve block was associated with better postoperative cognitive function compared to other anesthesia methods (53). On the other hand, some suggested that spinal anesthesia may lead to lower disturbance in cognitive function after surgery than general anesthesia. (54). It was further elaborated that combined spinal-epidural anesthesia (CSEA) shows a better cognitive outcome than general anesthesia in elderly patients undergoing hip surgery (55).

Agents of aneshtesia

Sevoflurane, a commonly used inhalation anesthetic, has been a subject of interest concerning its impact on postoperative cognitive function. Several studies have investigated the effects of sevoflurane on cognitive outcomes, shedding light on its potential role as a risk factor for postoperative cognitive decline. The incidence of postoperative cognitive dysfunction was significantly lower in the sevoflurane group compared to the total intravenous anesthesia group. Another study also suggests that sevoflurane-based anesthesia was associated with better short-term postoperative cognitive performance than propofol-based anesthesia. This finding suggests that sevoflurane may have a favorable impact on postoperative cognitive outcomes compared to other anesthesia modalities (56,57).

Potential mechanisms underlying sevoflurane-induced cognitive impairment were demonstrated to correlate with the inhibition of the mTOR signaling pathway, in addition to inflammatory reactions caused by sevoflurane and surgical procedures, which may contribute to cognitive decline (58). In rats, it was also found that sevoflurane-induced working memory impairment may depend on advanced age and anesthetic concentration and may be related to decreased functional connectivity between PFC excitatory neurons (60). Moreover, the neuroprotective effects of certain interventions have been explored in mitigating sevoflurane-induced cognitive dysfunction. For example, studies have shown that honokiol-mediated mitophagy and exogenous recombinant Hsp70 can ameliorate sevoflurane-induced cognitive impairment (59). These findings suggest that targeting specific pathways involved in cognitive function may offer protective effects against the cognitive decline associated with sevoflurane anesthesia. Regardless of the favorable cognitive outcomes and several studies done on sevoflurane, in clinical practice, there have been conflicting results on the use of sevoflurane in correlation with POCD. This variability underscores the importance of considering individual differences in response to sevoflurane when evaluating its effects on postoperative cognitive outcomes.

Studies demonstrated that dexmedetomidine can effectively reduce the incidence of postoperative cognitive impairment in patients undergoing coronary artery bypass grafting. Another study found that the use of dexmedetomidine has a positive effect on preventing and reducing the incidence of postoperative cognitive disturbance (61-63).

Dexmedetomidine may inhibit hippocampal inflammation induced by surgical trauma, thereby improving postoperative cognitive function in rats. Additionally, the anti-inflammatory effects of dexmedetomidine relieve cognitive decline by reducing inflammatory responses (64-66). These findings suggest that dexmedetomidine's anti-inflammatory properties may play a crucial role in protecting cognitive function postoperatively. However, there are still some conflicting studies showing that dexmetomidine might not show any effect. This indicates that the effects of dexmedetomidine on postoperative cognitive function may vary depending on the specific patient population or type of surgery.

Research has shown that fentanyl, commonly used for pain management in surgical settings, can have implications for cognitive function. While studies have indicated that POCD is less common found with fentanyl compared to other opioid agents such as moprhine and hydromorphone (71). it is important to note that fentanyl has been associated with immediate postoperative cognitive dysfunction (72). Furthermore, the impact of fentanyl on cognitive function extends beyond the immediate postoperative period. Long-term use of opioids, including fentanyl, has been associated with cognitive impairment in patients with chronic noncancer pain (73). This suggests that the cognitive effects of fentanyl may persist beyond the acute postoperative phase.

Chronic exposure to fentanyl can lead to neuronal and glial alterations, further emphasizing the potential long-term consequences on cognitive function (74). Other mechanism for long-term consequences on cognitive function was elaborated on sensorimotor function, particularly concerning driving performance (46).

Biomarkers

Biomarkers of neurological damage might have the ability to predict postoperative cognitive outcomes. Brain fatty acid binding protein (BFABP), Neuron-specific enolase (NSE), and astroglial S100 Calcium-binding proteinb (S100b) are frequently studied with cognitive decline (67). A co-founding problem is that, while these biomarkers are released in response to injury, it is unclear whether they are secreted in reaction to harmful neuroprotective or neuronal healing processes. A recent study has shown that BFABP, NSE, and S100b do not have any correlation with POCD over 3 months after surgery(68).

Another neuronal cerebrospinal fluid(CSF) biomarker that has been identified to correlate with POCD is CSF amyloid β (Aβ1-42). Some studies have indicated that low levels of CSF amyloid β (Aβ1-42) may predict POCD in the elderly with preexisting Alzheimer's disease (69). However, other studies show otherwise, CSF amyloid β (Aβ1-42), NSE, total tau (T-tau), and neurofilament light (NFL) were found to be released after major surgery indicating neuronal injury, but were not found to have a long-term association with POCD (70).

PREOPERATIVE COGNITIVE TRAINING

Several studies have explored the potential benefits of preoperative cognitive training in mitigating the risk of POCD. Study for a blinded randomized controlled trial to assess the effects of computerized cognitive training on cognitive outcomes following coronary artery bypass grafting surgery highlight the interest in utilizing cognitive interventions before surgery to improve postoperative cognitive function (76). Other RCT focusing on increasing preoperative cognitive reserve through cognitive training to prevent postoperative delirium and cognitive decline in cardiac surgical patients emphasizing the importance of implementing structured cognitive training programs 2-3 weeks before surgery to optimize cognitive function and reduce the risk of postoperative complications (77). Similar insights are reported in other study with patients undergoing gastrointestinal surgery (78).

CONCLUSION

Postoperative cognitive dysfunction (POCD) is a common complication after surgery, affecting a significant proportion of patients. While the exact mechanisms underlying POCD remain unclear, several risk factors have been identified. These factors can be broadly categorized into patient-related, surgery-related, and anesthesia-related factors. Patient-related factors include age, pre-existing cognitive dysfunction, and education level. Surgery-related factors encompass the type of surgery, duration of surgery, and other factors. Anesthesia-related factors include the type and depth of anesthesia, as well as the use of certain medications. Understanding these risk factors is crucial for developing strategies to prevent or mitigate POCD. By identifying patients at high risk, clinicians can implement preventive measures such as preoperative cognitive training and optimization of anesthetic techniques. Further research is needed to elucidate the pathophysiology of POCD and develop more effective interventions, including studies about combination of preventive measures and cognitive screening as a preventive outcomes for POCD.

REFERENCES

1. Hu R, Huang D, Tong J, Liao Q, Hu Z, Ouyang W. Aspartic acid in the hippocampus: a biomarker for postoperative cognitive dysfunction. Neural Regeneration Research. 2014;9(2):143. doi:10.4103/1673-5374.125343
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington: 2013;American psychiatric association. Available from : https://repository.poltekkes-kaltim.ac.id/657/1/Diagnostic%20and%20statistical%20manual%20of%20mental%20disorders%20_%20DSM-5%20(%20PDFDrive.com%20).pdf
3. Steinmetz J, Rasmussen L. Peri-operative cognitive dysfunction and protection. Anaesthesia. 2015;71(S1):58-63. doi:10.1111/anae.13308
4. Peng X, Liu R, Zhu Y, Xu Q, Li J. Sevoflurane versus isoflurane for postoperative cognitive dysfunction of patients undergoing major cardiac surgeries: a prospective cohort study. Indian Journal of Pharmaceutical Education and Research. 2019;53(4):710-715. doi:10.5530/ijper.53.4.135
5. Strøm C, Rasmussen L, Sieber F. Should general anaesthesia be avoided in the elderly?. Anaesthesia. 2013;69(s1):35-44. doi: 10.1111/anae.12493
6. Schenning K, Murchison C, Mattek N, Kaye J, Quinn J. Sex and genetic differences in postoperative cognitive dysfunction: a longitudinal cohort analysis. Biology of Sex Differences. 2019;10(1). doi:10.1186/s13293-019-0228-8.
7. Daiello LA, Racine AM, Gou YR, Marcantiono ER, Xie Z, Kunze LJ, et al. Postoperative delirium and postoperative cognitive dysfunction. Anesthesiology. 2019;131(3):477-491. doi:10.1097/aln.0000000000002729
8. Takazawa T, Horiuchi T, Orihara M, Nagumo K, Tomioka A, Ideno Y, et al. Prevention of postoperative cognitive dysfunction by minocycline in elderly patients after total knee arthroplasty: a randomized, double-blind, placebo-controlled clinical trial. Anesthesiology. 2022;138(2):172-183. doi:10.1097/aln.0000000000004439
9. Jildenstål P, Rawal N, Hallén J, Berggren L, Jakobsson J. Perioperative management in order to minimise postoperative delirium and postoperative cognitive dysfunction: results from a swedish web-based survey. Annals of Medicine and Surgery. 2014;3(3):100-107. doi:10.1016/j.amsu.2014.07.001
10. Li L, Luo Y, Liu M, Xue H. Clinical characteristics of postoperative cognitive dysfunction after local balloon compression for trigeminal neuralgia: a retrospective study. Research square. 2023;1. doi:10.21203/rs.3.rs-2649508/v1
11. Subramaniyan S, Terrando N. Neuroinflammation and perioperative neurocognitive disorders. Anesthesia & Analgesia. 2019;128(4):781-788. doi:10.1213/ane.0000000000004053.
12. Degos V, Vacas S, Han Z, Rooijen N, Gressèns P, Su H, et al. Depletion of bone marrow–derived macrophages perturbs the innate immune response to surgery and reduces postoperative memory dysfunction. Anesthesiology. 2013;118(3):527-536. doi:10.1097/aln.0b013e3182834d94.
13. Terrando N, Eriksson L, Ryu J, Yang T, Monaco C, Feldmann M, et al. Resolving postoperative neuroinflammation and cognitive decline. Annals of Neurology. 2011;70(6):986-995. doi:10.1002/ana.226647.
14. Duan S, Wang X, Chen G, Quan C, Qu S, Tong J. Inhibiting ripk1 limits neuroinflammation and alleviates postoperative cognitive impairments in d-galactose-induced aged mice. Frontiers in Behavioral Neuroscience. 2018;12. doi:10.3389/fnbeh.2018.00138.
15. Wan Y, Xu J, Meng F, Bao Y, Ge Y, Lobo N, et al. Cognitive decline following major surgery is associated with gliosis, β-amyloid accumulation, and τ phosphorylation in old mice. Critical Care Medicine. 2010;38(11): 2190-2198. doi:10.1097/CCM.0b013e3181f17bcb.
16. Kho W, Haefen C, Paeschke N, Nasser F,

Endesfelder S, Sifringer M, et al. Dexmedetomidine restores autophagic flux, modulates associated micrornas and the cholinergic anti-inflammatory pathway upon lps-treatment in rats. Journal of Neuroimmune Pharmacology. 2021;17(1-2):261-276. doi:10.1007/s11481-021-10003-w9.
17. Nair AS, Christopher A, Pulipaka SK, Suvvari P, Kodisharapu PK, Rayani BK. Efficacy of xenon anesthesia in preventing postoperative cognitive dysfunction after cardiac and major non-cardiac surgeries in elderly patients: a topical review. Medical Gas Research. 2021;11(3):110. doi:10.4103/2045-9912.3143302.
18. Berger M, Terrando N, Smith S, Browndyke J, Newman M, Mathew J. Neurocognitive function after cardiac surgery. Anesthesiology. 2018;129(4):829-851. doi:10.1097/aln.0000000000002194
19. Kapoor MC. Neurological dysfunction after cardiac surgery and cardiac intensive care admission: a narrative review part 1: the problem; nomenclature; delirium and postoperative neurocognitive disorder; and the role of cardiac surgery and anesthesia. Annals of Cardiac Anaesthesia. 2020;23(4):383. doi:10.4103/aca.aca_138_19
20. Okonkwo OC, Cohen RA, Gunstad J, Tremont G, Alosco ML, Poppas A. Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease. Cerebrovascular Diseases. 2010;30(4):362-373. doi:10.1159/000319564
21. Monk TG, Weldon BC, Garvan CW, Dede DE, Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008;108(1):18-30. doi:10.1097/01.anes.0000296071.19434.1e
22. Rudolph JL, Marcantonio ER, Culley DJ, Silverstein JH, Rasmussen LS, Crosby GJ, et al. Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia. 2008;63(9):941-947. doi:10.1111/j.1365-2044.2008.05523.x
23. Klinger RY, James OG, Wong TZ, Newman MF, Doraiswamy PM, Mathew JP. Cortical β-amyloid levels and neurocognitive performance after cardiac surgery. BMJ Open. 2013;3(9):e003669. doi:10.1136/bmjopen-2013-003669
24. Hudetz JA, Patterson KM, Byrne AJ, Iqbal Z, Gandhi SD, Warltier DC, et al. A history of alcohol dependence increases the incidence and severity of postoperative cognitive dysfunction in cardiac surgical patients. International Journal of Environmental Research and Public Health. 2009;6(11):2725-2739. doi:0.3390/ijerph6112725
25. Robinson TN, Wu DS, Pointer LF, Dunn CL, Moss M. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. Journal of the American College of Surgeons. 2012;215(1):12-17. doi:10.1016/j.jamcollsurg.2012.02.007
26. Culley DJ, Flaherty D, Fahey MC, Rudolph JL, Javedan H, Huang CC, et al. Poor performance on a preoperative cognitive screening test predicts postoperative complications in older orthopedic surgical patients. Anesthesiology. 2017;127(5):765-774. doi:10.1097/aln.0000000000001859
27. Au E, Thangathurai G, Saripella A, Yan E, Englesakis M, Nagappa M, et al. Postoperative outcomes in elderly patients undergoing cardiac surgery with preoperative cognitive impairment: a systematic review and meta-analysis. Anesthesia & Analgesia. 2023;136(6):1016-1028. doi:10.1213/ane.0000000000006346
28. Weiss Y, Zac L, Refaeli E, Ben-Yishai S, Zegerman A, Cohen B, et al. Preoperative cognitive impairment and postoperative delirium in elderly surgical patients. Annals of Surgery. 2022;278(1):59-64. doi:10.1097/sla.0000000000005657
29. Susano MJ, Grasfield RH, Friese M, Rosner B, Crosby G, Bader AM, et al. Brief preoperative screening for frailty and cognitive impairment predicts delirium after spine surgery. Anesthesiology. 2020;133(6):1184-1191. doi:10.1097/aln.0000000000003523
30. O' Brien H, Mohan H, Hare CO, Reynolds JV, Kenny RA. Mind over matter? the hidden epidemic of cognitive dysfunction in the older surgical patient. Annals of Surgery. 2017;265(4):677-691. doi:10.1097/sla.0000000000001900
31. Zietlow K, McDonald S, Sloane R, Browndyke J, Lagoo-Deenadayalan S, Heflin M. Preoperative cognitive impairment as a predictor of postoperative outcomes in a collaborative care model. Journal of the American Geriatrics Society. 2018;66(3):584-589. doi:10.1111/jgs.15261
32. Holmgaard F, Vedel AG, Rasmussen LS, Paulson OB, Nilsson JC, Ravn HB. The association between postoperative cognitive dysfunction and cerebral oximetry during cardiac surgery: a secondary analysis of a randomised trial. Br J Anaesth. 2019;123(2):196-205. doi: 10.1016/j.bja.2019.03.045.
33. van Harten AE, Scheeren TW, Absalom AR. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. Anaesthesia, 2012;67 doi:10.1111/j.1365-2044.2011.07008.x.
34. Devore EE, Fong TG, Marcantonio ER, Schmitt EM, Travison TG, Jones RN, et al. Prediction of Long-term Cognitive Decline Following Postoperative Delirium in Older Adults. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2017: 1697–1702. doi:10.1093/gerona/glx030.
35. Tzimas P, Samara E, Petrou A, Korompilias A, Chalkias A, Papadopoulos G. The influence of anesthetic techniques on postoperative cognitive function in elderly patients undergoing hip fracture surgery: General vs spinal anesthesia. Injury. 2018;49(12):2221–6. DOI: 10.1016/j.injury.2018.09.023

36. Vacas S, Cole DJ, Cannesson M. Cognitive decline associated with anesthesia and surgery in older patients. JAMA. 2021;326(9):863. doi:10.1001/jama.2021.47732.
37. Weerink LBM, van Leeuwen BL, Gernaat SAM, Absalom AR, Huisman MG, van der Wal-Huisman H, et al. Vitamin status and the development of postoperative cognitive decline in elderly surgical oncologic patients. Annals of Surgical Oncology. 2017;25(1):231-238. doi:10.1245/s10434-017-6118-63.
38. Norkienė I, Samalavičius R, Misiūrienė I, Paulauskienė K, Budrys V, Iva kevičius J. Incidence and risk factors for early postoperative cognitive decline after coronary artery bypass grafting. Medicina. 2010;46(7):460. doi:10.3390/medicina460700664.
39. Požgain Z, Dulić G, Kondža G, Bogović S, Šerić I, Hil D, et al. Is postoperative cognitive decline after cardiac surgery associated with plasma beta amyloid 1–42 levels?. Journal of Cardiothoracic Surgery. 2022;17(1). doi:10.1186/s13019-022-01755-45.
40. Anderson K, Ziegler O, Shi G, Sodha N, Ikeda I, Feng J, et al. Younger age is associated with greater early neurocognitive decline postcardiopulmonary bypass. JTCVS Open. 2020;1:1-9. doi:10.1016/j.xjon.2020.02.0016.
41. Griffiths R, Beech F, Brown A, Dhesi J, Foo I, Goodall J, et al. Peri-operative care of the elderly 2014. Anaesthesia. 2013;69(s1):81-98. doi:10.1111/anae.12524
42. Ishizawa Y. Does preoperative cognitive optimization improve postoperative outcomes in the elderly?. Journal of Clinical Medicine. 2022;11(2):445. doi:10.3390/jcm11020445
43. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Montanini S, et al. Monitoring cerebral oxygen saturation in elderly patients undergoing general abdominal surgery: a prospective cohort study. European Journal of Anaesthesiology. 2006;24(01):59. doi:10.1017/s0265021506001025
44. Oldham MA, Vachon J, Yuh D, Lee HB. Cognitive outcomes after heart valve surgery: a systematic review and meta-analysis. Journal of the American Geriatrics Society. 2018;66(12):2327-2334. doi:10.1111/jgs.15601
45. Kotekar N, Kuruvilla CS, Murthy V. Postoperative cognitive dysfunction in the elderly: a prospective clinical study. Indian J Anaesth. 2014; 58: 263–8. DOI: 10.4103/0019-5049.135034
46. Bilel S, Giorgetti A, Tirri M, Arfи R, Cristofori V, Marchetti B, et al. Sensorimotor alterations induced by novel fentanyl analogs in mice: possible impact on human driving performances. Current Neuropharmacology. 2023;21(1):87-104. doi:10.2174/1570159x21666221116160032
47. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. Survey of Anesthesiology. 2012;56(6):286-287. doi:10.1097/01.sa.0000422670.97733.97
48. Rachman A, Sauriasari R, Syafhan N, Prawiroharjo P, Risni H. Cognitive function in type 2 diabetes mellitus patients taking metformin and metformin-sulfonylurea. Kesmas National Public Health Journal. 2022;17(4):270. doi:10.21109/kesmas.v17i4.6303
49. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. The Lancet. 1998 Mar;351(9106):857–61. doi:10.1016/S0140-6736(97)07382-0.
50. Feinkohl I, Winterer G, Spies CD, Pischon T. Cognitive Reserve and the Risk of Postoperative Cognitive Dysfunction. Deutsches Arzteblatt international. 2017: 110-117 . doi:10.3238/arztebl.2017.0110.
51. O'Brien K, Feng R, Sieber F, Marcantonio ER, Tierney A, Magaziner J, et al. Outcomes with spinal versus general anesthesia for patients with and without preoperative cognitive impairment: secondary analysis of a randomized clinical trial. Alzheimer S & Dementia. 2023;19(9):4008-4019. doi:10.1002/alz.13132
52. Kundu M, Abdulla E, Rahman MM. Letter: spine surgery under spinal vs general anesthesia: prospective analysis of quality of life, fatigue, and cognition. Neurosurgery. 2022;92(1):e9-e9. doi:10.1227/neu.0000000000002217
53. Liu Y, Su M, Li W, Yuan H, Yang C. Comparison of general anesthesia with endotracheal intubation, combined spinal-epidural anesthesia, and general anesthesia with laryngeal mask airway and nerve block for intertrochanteric fracture surgeries in elderly patients: a retrospective cohort study. BMC Anesthesiology. 2019;19(1). doi:10.1186/s12871-019-0908-2
54. Efstathiou G, Batistaki C, Soulioti E, Roungeris L, Matsota P. Opioid-free anesthesia and postoperative cognitive dysfunction after minor urological surgery: a case series study. Anesthesiology and Pain Medicine. 2022;12(1). doi:10.5812/aapm.122094
55. Jeenger L, Jeenger J, Dulara SC, Joshi A. A comparative study of postoperative cognitive dysfunction in elderly patients undergoing hip surgery after general anaesthesia and combined spinal and epidural anaesthesia. Indian Journal of Clinical Anaesthesia. 2016: 362-367. doi:10.5958/2394-4994.2016.00063.9.
56. Duan GY, Duan ZX, Chen H, Chen F, Chen F, Du ZY, et al. Cognitive function and delirium following sevoflurane or propofol anesthesia for valve replacement surgery: a multicenter randomized controlled trial. The Kaohsiung Journal of Medical Sciences. 2022;39(2):166-174. doi:10.1002/

kjm2.12618
57. Schoen J, Husemann L, Tiemeyer C, Lueloh A, Sedemund-Adib B, Berger KU, et al. Cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. British journal of anaesthesia. 2011: 840-50. doi:10.1093/bja/aer091.
58. Liu Y, Ma L, Jiao L, Gao M, Guo W, Chen L, et al. Mammalian target of rapamycin/p70 ribosomal s6 protein kinase signaling is altered by sevoflurane and/or surgery in aged rats. Molecular Medicine Reports. 2012;12(6):8253-8260. doi:10.3892/mmr.2015.4444
59. Ye JS, Chen L, Lu YY, Lei SQ, Peng M, Xia ZY. Honokiol-mediated mitophagy ameliorates postoperative cognitive impairment induced by surgery/sevoflurane via inhibiting the activation of nlrp3 inflammasome in the hippocampus. Oxidative Medicine and Cellular Longevity. 2019:1-13. doi:10.1155/2019/8639618
60. Xu X, Tian X, Wang G. Sevoflurane reduced functional connectivity of excitatory neurons in prefrontal cortex during working memory performance of aged rats. Biomedicine & pharmacotherapy. 2018:106;1258-1266. doi:10.1016/j.biopha.2018.07.043.
61. Gong Z, Li J, Zhong Y, Guan X, Huang A, Ma L. Effects of dexmedetomidine on postoperative cognitive function in patients undergoing coronary artery bypass grafting. Experimental and Therapeutic Medicine. 2018. doi:10.3892/etm.2018.6778
62. Bi X, Wei J, Zhang X. Effects of dexmedetomidine on neurocognitive disturbance after elective non-cardiac surgery in senile patients: a systematic review and meta-analysis. Journal of International Medical Research. 2021;49(5):030006052110142. doi:10.1177/03000605211014294
63. Feng M, Chen X, Liu T, Zhang C, Wan L, Yao W. Dexmedetomidine and sufentanil combination versus sufentanil alone for postoperative intravenous patient-controlled analgesia: a systematic review and meta-analysis of randomized controlled trials. BMC Anesthesiology. 2019;19(1). doi:10.1186/s12871-019-0756-0
64. Chen N, Chen X, Xie J, Wu C, Qian J. Dexmedetomidine protects aged rats from postoperative cognitive dysfunction by alleviating hippocampal inflammation. Molecular Medicine Reports. 2019. doi:10.3892/mmr.2019.10438
65. Li R, Lai IK, Pan JZ, Zhang P, Maze M. Dexmedetomidine exerts an anti-inflammatory effect via α2 adrenoceptors to prevent lipopolysaccharide-induced cognitive decline in mice. Anesthesiology. 2020;133(2):393-407. doi:10.1097/aln.0000000000003390
66. Luo SM, Li LY, Guo LZ, Wang L, Wang YF, Chen N, et al. Dexmedetomidine exerts an anti-inflammatory effect via □2 adrenoceptors to alleviate cognitive dysfunction in 5xfad mice. Frontiers in Aging Neuroscience. 2022;14. doi:10.3389/fnagi.2022.9787687.
67. Kilminster S, Treasure T, McMillan T, Holt DW. Neuropsychologi-cal change and S-100 protein release in 130 unselected patients undergoing cardiac surgery. Stroke. 1999;30: 1869–74. DOI: 10.1161/01.str.30.9.1869
68. Kok WF, Koerts J, Tucha O, Scheeren TW, Absalom AR. Neuronal damage biomarkers in the identification of patients at risk of long-term postoperative cognitive dysfunction after cardiac surgery. Anaesthesia. 2017. 72: 359-369. doi:10.1111/anae.13712
69. Evered L, Silbert B, Scott DA, Ames D, Maruff P, Blennow K. Cerebrospinal Fluid Biomarker for Alzheimer Disease Predicts Postoperative Cognitive Dysfunction. Survey of Anesthesiology. 2016. doi:10.1097/01.sa.0000489968.05224.a9.
70. Danielson M, Wiklund A, Granath F, Blennow K, Mkrtchian S, Nellgerd B, et al. Association between cerebrospinal fluid biomarkers of neuronal injury or amyloidosis and cognitive decline after major surgery. British journal of anaesthesia. 2020. doi:10.1016/j.bja.2020.09.043.
71. Clark MR. Pharmacological treatments for chronic non-malignant pain. International Review of Psychiatry. 2000;12(2):148-156. doi:10.1080/09540260050007453
72. Kudoh A, Takase H, Takazawa T. A comparison of anesthetic quality in propofol-spinal anesthesia and propofol-fentanyl anesthesia for total knee arthroplasty in elderly patients. Journal of Clinical Anesthesia. 2004;16(6):405-410. doi:10.1016/j.jclinane.2003.10.003
73. Allegri N, Mennuni S, Rulli E, Vanacore N, Corli O, Floriani I, et al. Systematic review and meta-analysis on neuropsychological effects of long-term use of opioids in patients with chronic noncancer pain. Pain Practice. 2018;19(3):328-343. doi:10.1111/papr.12741
74. Lam D, Sebastian A, Bogguri C, Hum NR, Ladd A, Cadena J, et al. Dose-dependent consequences of sub-chronic fentanyl exposure on neuron and glial co-cultures. Frontiers in Toxicology. 2022;4. doi:10.3389/ftox.2022.983415
75. Figueiredo S, Devezas CM. Bridging the Gaps in Understanding POD and POCD: A Thorough Examination of Genetic and Clinical Biomarkers. Perioperative care and operating room management. 2024;35(5):100401–1. DOI:10.1016/j.pcorm.2024.100401
76. Greaves D, Psaltis PJ, Lampit A, Davis DHJ, Smith AE, Bourke A, et al. Computerised cognitive training to improve cognition including delirium following coronary artery bypass grafting surgery: protocol for a blinded randomised controlled trial. BMJ Open. 2020;10(2):e034551. doi:10.1136/

bmjopen-2019-034551

77. Butz M, Meyer R, Gerriets T, Sammer G, Doerr JM, El-Shazly J, et al. Increasing preoperative cognitive reserve to prevent postoperative delirium and postoperative cognitive decline in cardiac surgical patients (incore): study protocol for a randomized clinical trial on cognitive training. Frontiers in Neurology. 2022;13. doi:10.3389/fneur.2022.1040733
78. Saleh AJ, Tang GX, Hadi SM, Yan L, Chen MH, Duan KM, et al. Preoperative cognitive intervention reduces cognitive dysfunction in elderly patients after gastrointestinal surgery: a randomized controlled trial. Medical Science Monitor. 2015;21:798-805. doi:10.12659/msm.893359