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Postoperative Cognitive Disorder- what do we know about risk factors and prevention?: A Systematic Review

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ABSTRACT
Introduction
Postoperative Cognitive Dysfunction (POCD) is a significant health complication that affects mental processes, particularly in elderly patients after surgery. It is characterized by impaired memory, attention, and executive functions, leading to prolonged hospitalization and increased mortality. The pathogenesis of POCD involves inflammation in the central nervous system, but the exact mechanisms remain unclear.
Aim of Study
This study aims to identify and analyze the risk factors and potential markers of POCD, focusing on preoperative, perioperative, and postoperative factors. The goal of our work is to increase knowledge about POCD, thereby improving care for patients affected by this disorder.
Materials
The study reviews existing literature on POCD and examines various risk factors, such as age, comorbidities, education level, and surgical procedures. It also explores potential markers like inflammatory cytokines and describes hypothetical prevention strategies.
Results
The study highlights that age, diabetes, and certain surgical types of operation are significant risk factors for POCD. Inflammatory markers like S-100β protein and interleukin-6 can be associated with POCD. The use of Enhanced Recovery After Surgery (ERAS) protocols and cognitive interventions shows promise in reducing POCD incidence.
Conclusion
Understanding POCD's risk factors and markers is crucial for developing effective prevention strategies. Further research is needed to establish a specific approach to POCD.

Keywords: postoperative cognitive disorder, risk factors, potential markers, prevention, age, cardiac surgery

1. INTRODUCTION

Postoperative Cognitive Disorder (POCD) is a significant health problem. It occurs after surgical operations, especially in elderly patients. Defined as impaired memory, attention, planning and decision-making skills. It can lead to serious consequences, such as prolonged hospitalization [1] and increased mortality [2]. Studies indicate that between 9% and 54% of elderly patients experience this condition within the first few weeks after surgery, but it can occur up to 12 months after surgery [3].
A key role in the mechanism of POCD is played by inflammation in the central nervous system, mediated by various cytokines (such as TNF, IL-1β) [4]. However, the exact mechanisms that lead to the disruption of synaptic plasticity as a result of inflammation, which is the neurobiological basis for cognitive decline, are still largely undiscovered.

Regions of the central nervous system whose disruption is responsible for POCD include the hippocampus and prefrontal cortex[5].
The diagnosis of POCD is made using neuropsychological tests such as the MMSE (Mental State Short Evaluation Scale) or MoCA (Montreal Cognitive Function Assessment Scale) performed after surgery. The ideal scenario would be to do these tests before surgery as well, for comparison of the aspects being assessed.
To date, no drug treatment regimen or specific technique has been developed to prevent POCD. The use of dexmedetomidine, cognitive training or physical activity has been raised. The best known treatment method is still prevention. This can be done by finding patients with risk factors for this complication and then minimizing them accordingly. The purpose of our work is to present risk factors and potential markers of POCD.
Understanding the risk factors for POCD is key to improving the care of patients undergoing surgery and provides an opportunity to introduce appropriate therapy before surgery. In the following sections, we will provide a detailed breakdown of preoperative, perioperative and postoperative factors, as well as discuss potential markers of this condition. This knowledge can contribute to better risk management and more effective prevention of POCD.

2. POCD RISK FACTORS:

In our work, we adopted a division into preoperative, perioperative, and postoperative risk factors with additional description of potential markers. We also looked at available methods of preventing POCD.

2.1 PREOPERATIVE FACTORS:

2.1.1 AGE. Aging is associated with neuronal damage, microglia and astrocyte disruption, and neuroinflammation. These are factors that favor the occurrence of POCD. Another potential explanation is the increasing risk of diseases with age, such as diabetes, atrial fibrillation and dementia. Not only the hippocampus and prefrontal cortex play a role in the pathogenesis of POCD, but also the insula, thalamus, and cerebellum, and inflammation in these regions, may explain the association between POCD and age. [5] It has been proven that old age affects the incidence of POCD regardless of the type of treatment. It has not been clearly established above which age the risk of POCD increases, the numbers mentioned are 60 [6] and 75 [7].

2.1.2 COMORBIDITIES

Comorbidities have been proven to be important in the development of POCD. Diabetes, which triggers neurodegradation and inflammation in the body, is known as increasing the risk of POCD. Among patients who had diabetes, the risk of POCD increased commensurate with poorer HbA1C control[7].
A comparative analysis of three randomized control trials [8] involving more than a thousand patients estimated the risk of POCD associated with preoperative medical conditions such as diabetes, hypertension and obesity. Interestingly, only diabetes, regardless of the other conditions listed, was found to be associated with an increased risk of developing the disorder. Moreover there is another scientific paper where authors obtained inconclusive results in the case of coexisting hypertension [9].

The results of one meta-analysis [10] do not provide a clear answer regarding the impact of neurocognitive impairment on POCD. However, they correlate with a higher incidence of postoperative delirium, one of the postoperative risk factors for POCD.
It has been reported that inflammation in the central nervous system may be largely responsible for depression [11]. According to another meta-analysis [12], depression significantly increases the risk of POCD, which may explain the convergent mechanism of these two disorders .

2.1.3 EDUCATION LEVEL

The relationship between education level and the prevalence of POCD is increasingly recognized by researchers. Comparing patients of the same age but with different levels of education, the prevalence of POCD is higher in less educated patients. This difference may be due to greater cognitive resources in better educated individuals, as well as greater health awareness and neuroplasticity. Less educated individuals are also at greater risk for environmental hazards and unhealthy lifestyles [13].

2.1.4 GUT MICROBIOTA

Emerging work examining the correlation between POCD and the gut microbiota in an animal model. A potential mechanism for POCD is inflammation in the CNS, which may be regulated through the gut-brain axis. The influence of the gut microbiota on the occurrence of this phenomenon was investigated. It was noted that patients who developed POCD had poorer intestinal flora, increased colony counts of Firmicutes bacteria and decreased Proteobacteria [14].There are also reports suggesting a reduction in the incidence of POCD under the influence of probiotics [15]. These studies unfortunately have some limitations. Namely, they were conducted on a small group of patients. Further work in this direction is needed.

2.2 PERIOPERATIVE FACTORS:

2.2.1 TYPE OF SURGERY

The incidence of postoperative cognitive dysfunction is strongly associated with the type of surgery performed. POCD risk and severity rise with the duration and complexity of the surgical procedure, due to the release of endotoxins and cerebral emboli. Endotoxins stimulate the release of interleukins, which are responsible for the systemic inflammatory response [16]. Several studies show that POCD is particularly more common in cardiac surgeries [17] and orthopedic surgeries [18]. Authors suggest that potential mechanisms behind the higher incidence of POCD in these procedures include the length of the procedure, disturbances in blood supply to the brain during surgery with ECMO, or the prolonged effects of anesthetic drugs. A 2024 meta-analysis [19] indicates that patients undergoing cardiac surgery are at increased risk of mortality. In addition, patients diagnosed with POCD in less than 30 days have an increased risk of prolonged hospital stay. The results of a study [20] conducted on patients undergoing abdominal surgery revealed that the incidence of POCD was significantly higher in the group of patients who underwent laparotomy surgery compared to those who underwent laparoscopic surgery. This suggests that the use of minimally invasive surgical techniques may reduce the risk of developing POCD.

2.2.2 TYPE OF ANESTHESIA

A correlation was sought between POCD and the type of anesthesia used. The results obtained during the meta-analysis showed no difference in the incidence of POCD between general and regional anesthesia [21]. However, it should be noted that patients were not matched for other risk factors. Further studies in this direction are needed. Additionally, a clinical trial involving 180 participants [22] was conducted to explore this relationship further. Its main objective was to evaluate postoperative cognitive function in elderly patients undergoing laparoscopic inguinal hernia repair in relation to different rates of propofol dosage. Reducing the rate of intravenous propofol infusion did not reduce the incidence of POCD.

2.2.3 LACK OF MONITORING OF DEPTH OF ANESTHESIA

The depth of sedation can be measured by BIS, or bispectral index. This parameter is formed from electronically converting the electroencephalogram into a numerical value in the range of 0-100, where 0-40 indicates deep anesthesia and 90-100 indicates wakefulness. The results of some works show that patients who did not have their depth of sedation monitored were more likely to develop POCD [23]. These results do not match the meta-analysis, which found no statistically significant reduction in the incidence of POCD in patients who were monitored with BIS [24]. Controlling with a bispectral index, may be a potential way to prevent the occurrence of POCD, and too shallow sedation. Further randomized studies and trials in this direction are needed.

A randomized clinical control trial [25] emphasized the importance of using other methods to monitor the depth of anesthesia, such as entropy and SPI- Surgical Plethysmographic Index. The authors, analyzing 95 patients with traumatic injuries undergoing emergency life-saving surgery, stressed that these methods can be used to prevent the development of POCD.

2.2.4 METHOD OF SUSTAINING ANESTHESIA

Maintenance of anesthesia, is a step whose goal is to maintain an adequate level of analgosedation throughout the procedure. A commonly used technique is maintenance with anesthetic gases such as Sevoflurane, Desflurane. Another method used is maintenance of anesthesia with propofol, the so-called TIVA (total intravenous anesthesia) method. Sevoflurane is used as one of the most common anesthetic gases. It has proven effects on inflammation in the nervous system, changes in neurotransmitters, a decrease in brain-derived neurotrophic factor, mitochondrial oxidative stress and changes in amyloid β levels. These changes could potentially predispose to POCD[26].

An analysis of 28 articles comparing the incidence of POCD when anesthesia is maintained with inhaled anesthetics and with the TIVA method, did not clearly show which method causes POCD more often. However, the authors emphasize that the quality of the results is low, and further studies are needed to definitively determine the effect of the type of anesthesia maintenance on POCD [27].

In a previously cited study [22], the authors suggest that sevoflurane, fentanyl and norepinephrine may be directly related to the occurrence of POCD within 48 hours after surgery. Nevertheless, confirmation of this thesis requires a larger group of patients.

2.3 POSTOPERATIVE RISK FACTORS AND POTENTIAL MARKERS:

2.3.1 POSTOPERATIVE RISK FACTORS

Postoperative risk factors are the most difficult to assess, as they cannot be separated from pre- and perioperative factors. Postoperative risk factors for POCD include conditions such as postoperative delirium, various types of arrhythmias, including atrial fibrillation, and prolonged time in the intensive care unit [12].Another paper showed a statistically significant correlation between POCD, and postoperative infection, subsequent surgery, and respiratory complications[6].It was shown [6] that early POCD was more likely to occur in patients affected by postoperative infections and respiratory complications. The authors indicated in their conclusions that only the risk factor we mentioned earlier, age, posed a risk for late POCD.

2.3.2 POTENTIAL MARKERS OF POC

2.3.2.1 Markers of inflammation

A meta-analysis that considered 13 studies on the correlation between inflammatory markers and POCD found that S-100β protein and interleukin-6 are significant markers associated with postoperative cognitive impairment. In the case of neuron-specific enolase, interleukin-1β and tumor necrosis factor-α, no correlation was found between their elevated levels and a higher incidence of POCD. Therefore, it is recommended that studies be conducted on a larger group of patients and that a cutoff point be established above which the risk of POCD significantly increases[28].

Data from a meta-analysis by Chunmei Fu et al [29] indicate that elevated levels of CRP, S-100B and IL-6 are associated with POCD after total hip arthroplasty (THA). According to the authors, regular monitoring of the levels of these markers may facilitate early identification of POCD in patients after THA, allowing timely interventions to mitigate cognitive complications.

2.3.2.2 Glial fibrillary acidic protein (GFAP)

Researchers who conducted a retrospective study on 56 patients after CABG surgery came to the following conclusions:

Postoperative GFAP levels in patients with POCD were significantly higher (12.95 ± 7.47) compared to patients without POCD (3.80 ± 2.77), indicating a strong association between elevated GFAP levels and cognitive impairment after CABG surgery[30]. The concentration of acidic fibrillary protein, which is found in astrocytes, among other things, appears to be a promising marker for the presence of POCD; however, it must be kept in mind that its elevation also occurs with other neurological diseases, which reduces the specificity of this protein as a marker. Further research is needed toward the use of GFAP as a marker of POCD.

2.3.2.3 Plasma mRNA-221-3p

Researchers from China showed that the relative plasma levels of microRNA-221-3p were 1.78 and 2.73 times higher in the group of patients with POCD compared to the group without the disorder. The study was conducted 1 day before and 7 days after surgery, respectively. Based on this, we hypothesized that the relative plasma content of microRNA-221-3p 7 days after surgery may be an independent risk factor for POCD. However, it should be noted that the study has some limitations, as all samples came from a single center in China.

Therefore, further studies in this direction are needed to confirm these results and determine the role of microRNA-221-3p as a marker for POCD [31].

3. PROTECTION AND PREVENTION STRATEGIES

As mentioned before, currently the best treatment method is considered to be prevention. Most preventive strategies are linked to the known risk factors that were discussed earlier. Several authors describe chronic illnesses such as diabetes [7] [9] as risk factors of POCD, which might suggest that management and control of ongoing health conditions plays an important role in preventing POCD. Choosing a possibly least invasive surgical procedure [20] and most adequate anesthesia have been described as preventive strategies as well [16]. Moreover, all of the above aim to minimize inflammation and optimize conditions for early recovery and are considered as a part of ERAS protocol.

Kotekar et al. point out that Enhanced Recovery After Surgery (ERAS), also referred to as "accelerated recovery," improves postoperative recovery, minimizes inpatient time and lowers perioperative complication rates. ERAS protocols, consisting of evidence-based treatment strategies, aim to reduce surgical stress, enhance postoperative recovery through comprehensive measures implemented before, during, and after surgery [16]. In a prospective observational study by Duran et. al, patients managed with the ERAS protocol showed improvement in cognitive functions, measured by the Mini-Mental Test (MMT). In conclusion, the study suggests that the ERAS protocol not only reduces complication rates and hospital stay durations but also enhances early postoperative cognitive recovery [32].

Another interesting course of research was studied in a systematic review by Bowden et al. (2022) [33]. The aim was to assess postoperative cognitive interventions as a strategy to enhance cognitive function following surgery. Although the review did not directly evaluate POCD prevention, it indicated that cognitive interventions showed some efficacy in enhancing cognitive function after surgery, especially in memory-related aspects. This presents a promising course for further research and approach to postoperative cognitive disorder.

As mentioned before, several markers of POCD have been investigated, yet none were proven specific. Identification of potential markers and their correlation with postoperative cognitive disorder creates a promising course for future prevention strategies and development of innovative protocols. The case appears to be similar to monitoring anesthetic depth. Monitoring anesthetic depth using BIS could serve as a strategy for preventing POCD; however, current research findings are inconclusive, and further exploration of this topic is necessary. It is worth emphasizing that until further advancements in therapeutic interventions occur, preventive strategies, early identification, and management of perioperative risk factors appear to be the most effective approach for addressing POCD. Therefore, further investigation in this area appears to be indispensable.

4. SUMMARY

Post-operative cognitive impairment is still a little-studied condition that particularly frequently affects elderly people undergoing cardiac surgery. More and more attention is being paid to its incidence and the complications it brings. There are only a few certain risk factors for POCD. Unfortunately, the others are either insufficiently studied or the results of analyses from different centers differ. We need extensive multicenter work to be able to state unequivocally what can be considered determinants of the described disorder. Moreover, markers that could help estimate the occurrence of this complication are also not clearly defined. The ones we have listed show promise, but we need more research on their utility. In addition, the availability and price of some of them is limited in a physician's daily practice. Work on POCD would definitely be facilitated by a questionnaire to estimate its risk. This would allow efforts to minimize preoperative risk factors. In addition, increased vigilance would make it possible to try to eliminate perioperative and postoperative risk factors in advance. POCD is a complication that requires a multispecialty approach, the basis for its control should be a multispecialty collaboration between geriatricians, anesthesiologists, surgeons and psychiatrists. We hope that our work will contribute to increased awareness of POCD and provide a better understanding of the issue.

Disclosure

Authors' contribution:

Conceptualization: Antonina Drzewiecka, Anna Krysińska
Data collection and analysis: Aleksandra Rudzka, Monika Gaszyńska
Investigation:Antonina Drzewiecka, Maria Madejska
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Resources: Wiktor Korczak, Weronika Woźniak
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REFERENCES
[1] Sturm, H., Wildermuth, R., Stolz, R., Bertram, L., Eschweiler, G., Thomas, C., Rapp, M., & Joos, S. (2019). Diverging Awareness of Postoperative Delirium and Cognitive Dysfunction in German Health Care Providers. Clinical Interventions in Aging, 14, 2125 - 2135.
[2] Relander, K., Hietanen, M., Nuotio, K., Ijäs, P., Tikkala, I., Saimanen, E., Lindsberg, P., & Soinne, L. (2021). Cognitive Dysfunction and Mortality After Carotid Endarterectomy. *Frontiers in Neurology*, 11. https://doi.org/10.3389/fneur.2020.593719.
[3] Bhushan S, Li Y, Huang X, Cheng H, Gao K, Xiao Z. Progress of research in postoperative cognitive dysfunction in cardiac surgery patients: A review article. Int J Surg. 2021 Nov;95:106163. doi: 10.1016/j.ijsu.2021.106163. Epub 2021 Nov 4. PMID: 34743049.
[4] Terrando, N., Eriksson, L. I., Kyu Ryu, J., Yang, T., Monaco, C., Feldmann, M., ... & Maze, M. (2011). Resolving postoperative neuroinflammation and cognitive decline. *Annals of neurology*, *70*(6), 986-995.
[5]Xianyi Lin, Yeru Chen, Piao Zhang, Gang Chen, Youfa Zhou, Xin Yu,
The potential mechanism of postoperative cognitive dysfunction in older people,
Experimental Gerontology,
Volume 130,2020,110791,ISSN 0531-5565, https://doi.org/10.1016/j.exger.2019.110791.
[6] Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet. 1998 Mar 21;351(9106):857-61. doi: 10.1016/s0140-6736(97)07382-0. Erratum in: Lancet 1998 Jun 6;351(9117):1742. PMID: 9525362.
[7] Arefayne NR, Berhe YW, van Zundert AA. Incidence and Factors Related to Prolonged Postoperative Cognitive Decline (POCD) in Elderly Patients Following Surgery and Anaesthesia: A Systematic Review. *J Multidiscip Healthc*. 2023;16:3405-3413
https://doi.org/10.2147/JMDH.S431168
[8] Lachmann G, Feinkohl I, Borchers F, Ottens TH, Nathoe HM, Sauer AM, Dieleman JM, Radtke FM, van Dijk D, Spies C, Pischon T. Diabetes, but Not Hypertension and Obesity, Is Associated with Postoperative Cognitive Dysfunction. Dement Geriatr Cogn Disord. 2018;46(3-4):193-206. doi: 10.1159/000492962. Epub 2018 Oct 16. PMID: 30326480.

[9] Insa, Feinkohl., Georg, Winterer., Tobias, Pischon., Tobias, Pischon. (2017). Hypertension and Risk of Post-Operative Cognitive Dysfunction (POCD): A Systematic Review and Meta-Analysis. Clinical Practice & Epidemiology in Mental Health, 13(1):27-42. doi: 10.2174/1745017901713010027

[10] N. Travica, M. Lotfaliany, Andrew Marriott, Seyed A Safavynia, M. Lane, L. Gray, N. Veronese, Michael Berk, D. Skvarc, Hajara Aslam, E. Gamage, M. Formica, Katie Bishop and W. Marx. "Peri-Operative Risk Factors Associated with Post-Operative Cognitive Dysfunction (POCD): An Umbrella Review of Meta-Analyses of Observational Studies." *Journal of Clinical Medicine*, 12 (2023). https://doi.org/10.3390/jcm12041610.

[11] Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., … Camus, V. (2020). Neuroinflammation and depression: A review. European Journal of Neuroscience. doi:10.1111/ejn.14720

[12] Greaves D, Psaltis PJ, Davis DHJ, Ross TJ, Ghezzi ES, Lampit A, Smith AE, Keage HAD. Risk Factors for Delirium and Cognitive Decline Following Coronary Artery Bypass Grafting Surgery: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2020 Nov 17;9(22):e017275. doi: 10.1161/JAHA.120.017275. Epub 2020 Nov 7. PMID: 33164631; PMCID: PMC7763731.

[13]Feinkohl I, Winterer G, Spies CD, Pischon T. Cognitive Reserve and the Risk of Postoperative Cognitive Dysfunction. Dtsch Arztebl Int. 2017 Feb 17;114(7):110-117. doi: 10.3238/arztebl.2017.0110. PMID: 28302254; PMCID: PMC5359463.

[14] Wang P, Yin X, Chen G, Li L, Le Y, Xie Z, Ouyang W, Tong J. Perioperative probiotic treatment decreased the incidence of postoperative cognitive impairment in elderly patients following non-cardiac surgery: A randomised double-blind and placebo-controlled trial. Clin Nutr. 2021 Jan;40(1):64-71. doi: 10.1016/j.clnu.2020.05.001. Epub 2020 May 11. PMID: 32451125.

[15]Wei X, Xing F, Xu Y, Zhang F, Cheng D, Zhou Y, Zheng F, Zhang W. Preoperative gut microbiota of POCD patients induces pre- and postoperative cognitive impairment and systemic inflammation in rats. J Neuroinflammation. 2024 Sep 12;21(1):221. doi:

[16] Kotekar N, Shenkar A, Nagaraj R. Postoperative cognitive dysfunction - current preventive strategies. Clin Interv Aging. 2018 Nov 8;13:2267-2273. doi: 10.2147/CIA.S133896. PMID: 30519008; PMCID: PMC6233864.

10.1186/s12974-024-03220-6. PMID: 39267080; PMCID: PMC11396237.

[17] Gao L, Taha R, Gauvin D, Othmen LB, Wang Y, Blaise G. Postoperative cognitive dysfunction after cardiac surgery. Chest. 2005 Nov;128(5):3664-70. doi: 10.1378/chest.128.5.3664. PMID: 16304328.

[18] Li X, Lai H, Wang P, Feng S, Feng X, Kong C, Wu D, Yin C, Shen J, Yan S, Han R, Liu J, Ren X, Li Y, Tang L, Xue D, Zhao Y, Huang H, Li X, Zhang Y, Wang X, Wang C, Jin P, Lu S, Wang T, Zhao G, Wang C; APPLE-MDT Research Team, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Diseases. Risk Factors for Postoperative Cognitive Decline After Orthopedic Surgery in Elderly Chinese Patients: A Retrospective Cohort Study. Clin Interv Aging. 2024 Mar 19;19:491-502. doi: 10.2147/CIA.S436349. PMID: 38525317; PMCID: PMC10960540.

[19] Suraarunsumrit P, Srinonprasert V, Kongmalai T, Suratewat S, Chaikledkaew U, Rattanasiri S, McKay G, Attia J, Thakkinstian A. Outcomes associated with postoperative cognitive dysfunction: a systematic review and meta-analysis. Age Ageing. 2024 Jul 2;53(7):afae160. doi: 10.1093/ageing/afae160. Erratum in: Age Ageing. 2024 Aug 6;53(8):afae198. doi: 10.1093/ageing/afae198. PMID: 39058915; PMCID: PMC11277860.

[20] Gong, G.-L., Liu, B., Wu, J.-X., Li, J.-Y., Shu, B.-Q., & You, Z.-J. (2018). Postoperative Cognitive Dysfunction Induced by Different Surgical Methods and Its Risk Factors. *American Surgeon*, *84*(9), 1531–1537. https://doi.org/10.1177/000313481808400963

[21] Sandeep Bhushan, Xin Huang, Yuanqiong Duan, Zongwei Xiao,
The impact of regional versus general anesthesia on postoperative neurocognitive outcomes in elderly patients undergoing hip fracture surgery: A systematic review and meta-analysis,
International Journal of Surgery,Volume 105,2022,106854,ISSN 1743-9191,https://doi.org/10.1016/j.ijsu.2022.106854.

[22] Li T, Han W, Yang X, Wang Y, Peng L, He L, Hu L, Liu J, Xia M, Wang S. Effects of Different Injection Rates of Propofol on Postoperative Cognition in Elderly Patients Undergoing Laparoscopic Inguinal Hernia Repair. Drug Des Devel Ther. 2023 Jun 13;17:1741-1752. doi: 10.2147/DDDT.S407905. PMID: 37333962; PMCID: PMC10276595.

[23] Chen X, Li L, Yang L, Li A, Wu M, Yu D. A randomized trial: bispectral-guided anesthesia decreases incidence of delayed neurocognitive recovery and postoperative neurocognitive disorder but not postoperative delirium. Am J Transl Res. 2022 Mar 15;14(3):2081-2091. PMID: 35422948; PMCID: PMC8991109.

[24] Miao, M., Xu, Y., Sun, M., Chang, E., Cong, X., & Zhang, J. (2019). *BIS index monitoring and perioperative neurocognitive disorders in older adults: a systematic review and meta-analysis. Aging Clinical and Experimental Research, 32(12), 2449–2458.* doi:10.1007/s40520-019-01433-x

[25] Cotae AM, Ţigliş M, Cobilinschi C, Băetu AE, Iacob DM, Grinţescu IM. The Impact of Monitoring Depth of Anesthesia and Nociception on Postoperative Cognitive Function in Adult Multiple Trauma Patients. Medicina (Kaunas). 2021 Apr 23;57(5):408. doi: 10.3390/medicina57050408. PMID: 33922552; PMCID: PMC8146673.

[26] Wang CM, Chen WC, Zhang Y, Lin S, He HF. Update on the Mechanism and Treatment of Sevoflurane-Induced Postoperative Cognitive Dysfunction. Front Aging Neurosci. 2021 Jul 8;13:702231. doi: 10.3389/fnagi.2021.702231. PMID: 34305576; PMCID: PMC8296910.

[27] Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, Smith AF. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. Cochrane Database Syst Rev. 2018 Aug 21;8(8):CD012317. doi: 10.1002/14651858.CD012317.pub2. PMID: 30129968; PMCID: PMC6513211.

[28] Linying, Peng., Liwei, Xu., Wen, Ouyang. (2013). Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis.. PLOS ONE, 8(11):1-1. doi: 10.1371/JOURNAL.PONE.0079624

Postoperative cognitive dysfunction and neuroinflammation; Cardiac surgery and abdominal surgery are not the same - ScienceDirect

[29] Fu C, Lin J, Gong G, Zhong W, Chen H, Luo X. Inflammatory markers in postoperative cognitive dysfunction for patients undergoing total hip arthroplasty: a meta-analysis. Aging Clin Exp Res. 2022 Feb;34(2):277-288. doi: 10.1007/s40520-021-01919-7. Epub 2021 Jun 27. PMID: 34176086.
[30] (2022). Difference in GFAP Levels in POCD and Non-POCD Patients After on Pump CABG. Vascular Health and Risk Management, Volume 18:915-925. doi: 10.2147/vhrm.s386791
[31] Fan D, Chen X, Zhou H, Hu N, Chen C, Yao Y, Bai Y, Feng J, Jia J, Wang X. Plasma microRNA-221-3p as a biomarker for POCD after non-cardiac surgery. PLoS One. 2022 Oct 11;17(10):e0275917. doi: 10.1371/journal.pone.0275917. PMID: 36219614; PMCID: PMC9553040.
[32] Duran Yakar N, Yakar MN, Polat C, Akdas Tekin E, Sivriköz E, Turgut N. Effect of the Enhanced Recovery After Surgery Protocol on Postoperative Cognitive Functions in Colorectal Surgery. *Clin Sci Nutr*. 2022;4(1):20-27. doi:10.54614/ClinSciNutr.2022.210309
[33] Bowden T, Hurt CS, Sanders J, Aitken LM. Effectiveness of cognitive interventions for adult surgical patients after general anaesthesia to improve cognitive functioning: A systematic review. J Clin Nurs. 2023 Jul;32(13-14):3117-3129. doi: 10.1111/jocn.16423. Epub 2022 Jun 22. PMID: 35733323; PMCID: PMC10946716.