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Chun Yang, Yiying Zhang, Jie Sun, Yasushi Satoh and Diansan Su

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Post-operative neuropsychiatric disorder, 2nd Edition

Topic editors
Chun Yang — Nanjing Medical University, China
Yiying Zhang — Massachusetts General Hospital, Harvard Medical School, United States
Jie Sun — Southeast University, China
Yasushi Satoh — National Defense Medical College, Japan
Diansan Su — Shanghai Jiao Tong University, China

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Effects of Sevoflurane and Propofol on Posttraumatic Stress Disorder After Emergency Trauma: A Double-Blind Randomized Controlled Trial

Junfeng Zhong [1†], ***Yan Li*** [2†], ***Lichao Fang*** [3†], ***Dan Han*** [4], ***Chuhao Gong*** [4], ***Shuangyan Hu*** [5], ***Rongguo Wang*** [6], ***Liwei Wang*** [6], ***Rui Yao*** [7], ***Beiping Li*** [7], ***Yangzi Zhu*** [6*] **and** ***Youjia Yu*** [2*]

[1] Department of Pain, Shaoxing People's Hospital, Shaoxing, China, [2] Department of Anesthesiology, Suzhou Xiangcheng People's Hospital, Suzhou, China, [3] Emergency and Critical Department, Suzhou Xiangcheng People's Hospital, Suzhou, China, [4] Department of Anesthesiology, Xuzhou Renci Hospital, Xuzhou, China, [5] Department of Anesthesiology, Shaoxing People's Hospital, Shaoxing, China, [6] Department of Anesthesiology, Xuzhou Central Hospital, Xuzhou, China, [7] Department of Anesthesiology, The First People's Hospital of Xuzhou, Xuzhou, China

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Edited by:
Chun Yang,
Nanjing Medical University, China

Reviewed by:
Shengtao Wang,
Shandong Provincial Hospital, China
He Liu,
Zhejiang University School of Medicine and Huzhou Central Hospital, China

****Correspondence:***
Yangzi Zhu
zhuyz@188.com
Youjia Yu
yuyoujia0717@163.com

† These authors have contributed equally to this work

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Objective: Posttraumatic stress disorder (PTSD) is a frequent and disabling consequence of traumatic events. A previous study found that early use of propofol was a potential risk factor for PTSD. This prospective study aimed to investigate the effect of propofol and sevoflurane on PTSD after emergency surgery in trauma patients.

Methods: A total of 300 trauma patients undergoing emergency surgery were randomly divided into two groups and anesthetized with propofol and/or sevoflurane. Perioperative clinical data were collected. The incidence of PTSD was evaluated with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) in the two groups 1 month after the operation. The relevance of the injury time and CAPS-5 scores was assessed by Spearman correlation analysis. Logistic regression analysis was used to analyze the risk factors for PTSD.

Results: The incidence of PTSD in the propofol group was higher than that in the sevoflurane group 1 month postoperatively (23.2 vs. 12.2%, $P = 0.014$). The injury time was negatively correlated with the CAPS-5 score in the propofol group ($r = -0.226$, $P < 0.001$). In the logistic regression analysis, the utilization of propofol was an independent risk factor for PTSD ($P = 0.017$).

Conclusion: Early use of propofol general anesthesia in emergency surgery for trauma patients may increase the risk of PTSD.

Clinical Trial Registration: www.chictr.org.cn, identifier: ChiCTR2100050202.

Keywords: trauma, posttraumatic stress disorder, propofol, sevoflurane, emergency surgery

INTRODUCTION

Posttraumatic stress disorder (PTSD) refers to a set of characteristic symptoms that occurs after an individual experiences an unusually threatening or catastrophic event: repeated recurrence of traumatic experiences, persistent increased alertness, and avoidance of situations similar to or related to stimuli that may persist for years or decades in trauma-exposed survivors (1–3). As a result, this mental state is highly debilitating and interferes with the patient's daily life and social activities (4, 5). In recent years, due to frequent traffic accidents, natural disasters, wars, terrorist violence and other events, the incidence of PTSD has been as high as 10–22% (6, 7). It has caused a large amount of harm and placed a large economic burden on patients, families and society (8). However, until now, prevention and treatment options for PTSD have been limited (9).

Patients who experience physical trauma in traumatic events such as car accidents, earthquakes and falls often need emergency surgical treatment or intensive care at an early stage. Studies have identified the prevalence of PTSD in intensive care unit (ICU) survivors to be more than twice that in the general population (10). Approximately 20% of patients develop PTSD after surgery or hospitalization (11). These trauma patients are inevitably treated with anesthetic sedatives that act on the central nervous system, propofol being the most commonly used (12). Once PTSD develops, it is difficult to cure (13). An important reason for this is that conditioned fear memory is abnormally strengthened and does not easily fade away (14, 15). One animal study suggested that early application of propofol has a significantly strengthens fear memory (16). A clinical retrospective analysis reported that early use of propofol in ICU patients who experienced car accident trauma was a risk factor for PTSD (17). However, there is no prospective clinical study on the effect of the use of different general anesthetics on PTSD in emergency trauma patients.

The purpose of this study was to investigate the effects of propofol and sevoflurane, two commonly used general anesthetics, on the incidence of postoperative PTSD in emergency trauma patients to lay a theoretical foundation for finding a more suitable general anesthetic for emergency trauma patients.

MATERIALS AND METHODS

Study Design and Participants

This study was registered at www.chictr.org.cn (ChiCTR2100050202). The study protocol was approved by the ethics committees of all participating hospitals. Written informed consent was obtained from all patients. Three hundred trauma patients who underwent emergency surgery under general anesthesia were selected. The inclusion criteria were as follows: emergency trauma due to a car accident, falling, engineering accident, etc., ASA I-III, and age 18–60. The exclusion criteria were craniocerebral or spinal cord injury, hemorrhagic shock decompensation, liver or renal dysfunction, history of alcohol abuse or drug dependence, history of neurological or psychiatric diseases, severe visual, hearing or language impairment, and significant past physical or mental trauma.

Anesthesia-Related Procedures

Patients were randomly divided into the propofol group and the sevoflurane group by the random number method. Anesthesia induction and endotracheal intubation were performed after admission to the operating room. Anesthesia induction was performed with midazolam (20–60 μg/kg), sufentanil (0.4–0.8 μg/kg), etomidate (0.3 mg/kg) and cisatracurium (0.2–0.4 mg/kg). After successful tracheal intubation and mechanical ventilation were achieved, the tidal volume was 6–10 mL/kg, and the respiratory rate was 11–14 times/min. The propofol group received 1% propofol at 0.1–0.15 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ for anesthesia maintenance. The sevoflurane group received 2–4% sevoflurane via inhalation for anesthesia maintenance. All patients received remifentanil continuously at 0.2∼0.4 μg·kg-1·min-1 during surgery to maintain analgesia, and cisatracurium was intermittently injected intravenously to maintain muscle relaxation. BP, ECG, HR, SpO_2, $PetCO_2$ and the Bispectral Index (BIS) were continuously monitored intraoperatively. The intraoperative SpO_2 was maintained above 98%, and the rate of propofol or sevoflurane inhalation was adjusted according to the BIS to maintain the BIS between 40 and 60 and the $PetCO_2$ between 35 and 45 mmHg. Intravenous analgesia was used in all patients after surgery. The analgesic fluid formulations in both groups were as follows: sufentanil combined with palonosetron hydrochloride (0.15 mg diluted to 200 ml. Sufentanil patient-controlled analgesia was infused at a rate of 0.04 $\mu g{\cdot}kg^{-1}{\cdot}h^{-1}$ and a 0.1 μg bolus every 15 min when needed *via* the pump for the first 2 days after surgery.

Observational Index

General demographic data were collected preoperatively, and patients were assessed with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and trauma severity score (TSS). The patient's clinical parameters, such as injury time (the time from injury to anesthesia induction), drug use, operation time, blood loss, transfusion and ICU admission, were recorded. Adverse reactions, such as pain, delirium, nausea, and pruritus, were observed 48 h after surgery, and visual analog scale (VAS) scores were recorded 6, 24, and 48 h after surgery. The occurrence of PTSD was assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) 1 month after surgery. Professionally trained nurses, blinded to treatment group assignments, carried out the neuropsychological tests at both times in tranquil surroundings. The data analyst also did not know the grouping. The CAPS-5 is a structured diagnostic interview and considered the gold standard in PTSD evaluation. The CAPS-5 provides a continuous measure of the severity of overall PTSD and of the four symptom clusters (intrusions, avoidance, negative alterations in cognition/mood, arousal and reactivity) and presence/absence of PTSD diagnosis, which can be administered by appropriately trained paraprofessionals (18).

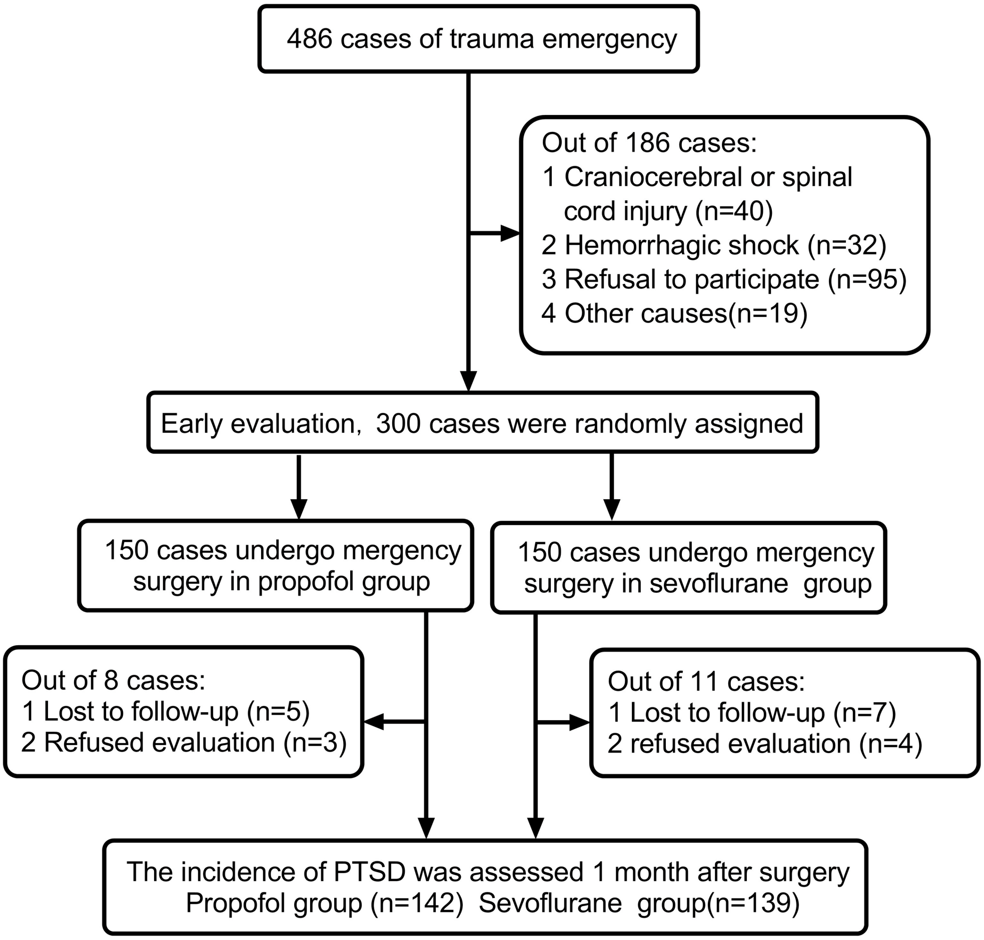

FIGURE 1 | Enrollment flowchart for patients in this study.

Statistics

PASS software was used to estimate the sample size. According to pretrial results, the prevalence of PTSD was 9% in the sevoflurane group and 23% in the propofol group. Hence, to detect a reduction in the PTSD rate from 23 to 9% and achieve a statistical efficacy of 90% ($\alpha = 0.05$, $\beta = 0.1$), 278 patients would be required.

SPSS 23.0 software was used for the statistical analysis. The data are expressed as the mean ± standard deviation, the independent sample *t* test was used for comparison of the means of the two groups, and the *t* test was used when the variance was not uniform. Enumeration data were compared by $\chi 2$ test. A logistic regression model was established to analyze the risk factors related to PTSD in emergency trauma patients. The Hosmer-Lemeshow test was used. When $P < 0.05$, the difference was statistically significant. Spearman's test was used to analyze the correlation between the CAPS-5 score and the time to anesthesia, i.e., the time from injury to the start of anesthesia; when the test level was $\alpha = 0.05$, $P < 0.05$ was considered statistically significant.

RESULTS

Demographic Information and Perioperative Clinical Data

A total of 300 patients were enrolled. Nineteen patients withdrew from the study due to refusal to return for follow-up, loss of follow-up and other reasons. Finally, 281 patients completed the follow-up and cognitive function assessments. The process is shown in **Figure 1**. There were no statistically significant differences in sex distribution, age, ASA grade, preoperative hypertension, smoking status, APACHE II score, ISS, injury time, operation, recovery time, blood loss, transfusion or ICU occupancy rate between the two groups, as shown in **Table 1**. Postoperative pain, delirium, nausea and pruritus between the two groups showed no statistical significance, as shown in **Table 2**.

Effects of General Anesthetic on PTSD

Comparison of the incidence of PTSD between the two groups showed that PTSD occurred in 33 of 142 patients in the propofol group (23.2%). PTSD occurred in 17 of 139 patients

TABLE 1 | Demographic and surgery characteristics.

Factor	Propofol group (*n* = 142)	Sevoflurane group (*n* = 139)	t/χ^2	*P*-value
Age (years)	40.3 ± 9.3	41.1 ± 8.7	0.776	0.438
BMI (kg/m^2)	27.7 ± 5.2	27.1 ± 4.8	0.932	0.352
Sex (male/female)	82/60	77/62	0.158	0.691
Hypertension (cases, %)	17 (12%)	14 (10.1%)	0.258	0.611
Diabetes (cases, %)	15 (10.6%)	16 (11.5%)	0.064	0.800
Smoking (cases, %)	27 (19%)	25 (18%)	0.049	0.824
ASA grade (II/III)	98/44	100/39	0.289	0.591
APACHE II score	7.68 ± 2.49	7.54 ± 2.70	0.463	0.643
ISS	14.3 ± 8.11	13.5 ± 8.32	0.786	0.433
Injury time (min)	53.3 ± 9.78	52.7 ± 8.19	0.528	0.598
Surgery time (min)	103 ± 40.7	99 ± 39.5	0.827	0.409
Awake time (min)	19.6 ± 9.30	20.2 ± 8.31	0.599	0.549
Intraoperative awareness (cases, %)	0	0		
ICU admission (cases, %)	16(11.3%)	11(7.9%)	0.910	0.340
Estimated blood loss (ml)	382 ± 210	414 ± 222	−1.243	0.215
Transfusion (cases, %)	10(7.0%)	12(8.6%)	0.246	0.620

Physiology and Chronic Health Evaluation; ISS, trauma severity score. Values are the mean ± SD or number (percentage).

TABLE 2 | Adverse characteristics in the two groups.

Factor	Propofol group (*n* = 142)	Sevoflurane group (*n* = 139)	t/χ^2	*P*-value
VAS score 6 h postoperation	3.1± 1.3	2.9 ± 1.4	0.930	0.353
VAS score 24 h postoperation	3.2 ± 1.6	3.1 ± 1.4	0.629	0.530
VAS score 48 h postoperation	1.8 ± 1.5	1.7 ± 1.4	0.794	0.428
Delirium (cases, %)	19 (13.4%)	17 (12.2%)	0.083	0.773
Nausea (cases, %)	21 (14.8%)	20 (14.4%)	0.009	0.924
Pruritus (cases, %)	13 (9.2%)	14 (10.1%)	0.068	0.794

VAS, visual analog scale for pain. Values are the mean ± SD or number (percentage).

in the sevoflurane group (12.2%). Comparing the CAPS-5 scores between the two groups, the CAPS-5 score in the propofol group was significantly higher than that in the sevoflurane group, as shown in **Table 3**.

Correlation Analysis for the Time to Anesthesia

Spearman analysis was performed on the correlation between the time to anesthesia and the CAPS-5 score in the two groups. The results showed that the time to anesthesia was negatively correlated with the CAPS-5 score in the propofol group ($r = 0.226$, $P < 0.001$). There was no significant negative correlation between the time to anesthesia and the CAPS-5 score in the sevoflurane group ($r = 0.002$, $P = 0.612$), as shown in **Figure 2**.

TABLE 3 | CAPS-5 scores and the incidence of adverse events in the two groups.

Factor	Propofol group (*n* = 142)	Sevoflurane group (*n* = 139)	t/χ^2	*P*-value
CAPS-5 score	34.1 ± 5.8	32.2 ± 6.8	2.46	0.014
PTSD (cases, %)	33 (23.2%)	17 (12.2%)	5.82	0.016

CAPS-5, Clinician-Administered PTSD Scale; PTSD, posttraumatic stress disorder. Values are the mean ± SD or number (percentage).

Risk Factors for PTSD in Emergency Trauma Patients

Risk factors associated with PTSD in emergency trauma patients were assessed by logistic regression analysis. Sex, age, operation time, trauma severity and other factors were not significantly correlated with the incidence of PTSD, but the use of propofol was significantly correlated with the incidence of PTSD ($P = 0.017$), as shown in **Table 4**.

DISCUSSION

Epidemiological studies have shown that the prevalence of PTSD in the general U.S. population is 6–8%, and it can be as high as 13–30% in the military (17, 19). More than 230 million patients worldwide undergo surgery each year, and 20% of patients develop PTSD after surgery or hospitalization (11, 20). In this study, among 281 patients who underwent emergency trauma surgery, 50 (17.8%) developed PTSD 1 month after surgery. The incidence of PTSD in the propofol anesthesia group was significantly higher than that in the sevoflurane anesthesia group. The above results show that the incidence of PTSD in emergency trauma patients is not low and that the occurrence of PTSD is affected by early anesthesia treatment.

The pathogenesis of PTSD is complex, and its exact neurobiological mechanism is still unclear (21). Recurrent traumatic experiences, one of the core symptoms of PTSD, have been found to be associated with abnormal enhancement of fear memory (22, 23). Anesthetics are commonly thought to have an amnestic effect (24, 25), but the most recent studies found not only that propofol was relatively ineffective at inhibiting activation of the amygdala-dependent fear system but also that it had an unusual strengthening effect on emotional memories (26, 27). In an animal experiment, it was found that propofol anesthesia could significantly enhance fear memory in experimental animals within 1 h after receiving the conditioned fear stimulus. However, after 1 h, propofol had no significant effect on fear memory, and it was thought that propofol might enhance memory traces in the early consolidation stage of fear memory (16). To this end, this study independently analyzed the correlation between the time to anesthesia and the CAPS-5 score 1 month after propofol and sevoflurane anesthesia. The results showed that the time to anesthesia was negatively correlated with the CAPS-5 score in the propofol group, while there was not a significant negative correlation between the time to anesthesia and the CAPS-5 score in the sevoflurane group. This finding

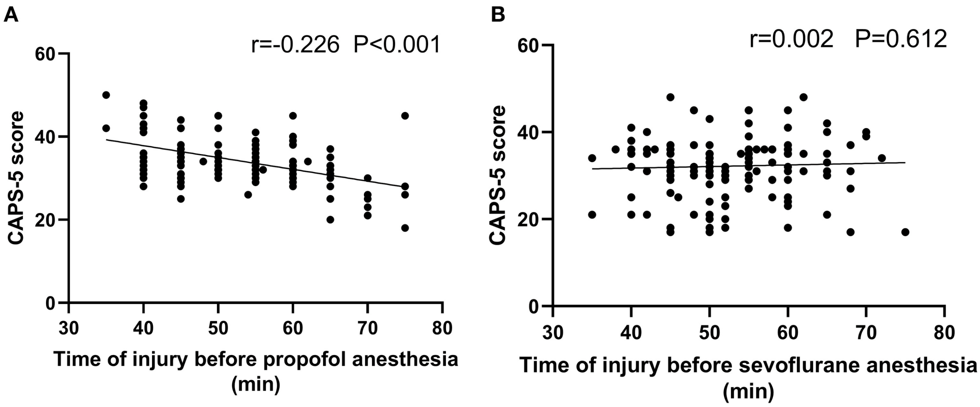

FIGURE 2 | Correlation analysis for the time from injury to admission and the CAPS-5 score 1 month after surgery. **(A)** shows the propofol general anesthesia group ($n = 142$), and **(B)** shows the sevoflurane general anesthesia group ($n = 139$). Scatter plot **(A)** shows a significant negative correlation between the time from injury to admission and the CAPS-5 score 1 month after surgery ($r = -0.226$; $p < 0.001$), and **(B)** shows no significant correlation between the time from injury to admission and the CAPS-5 score 1 month after surgery ($r = 0.002$; $p = 0.612$).

TABLE 4 | Logistic regression analysis for factors related to postoperative PTSD in patients with emergency trauma.

Factor	OR	95% credibility interval	*P*-value
Gender	0.711	0.342∼1.475	0.359
BMI	0.984	0.921∼1.051	0.625
Age	0.997	0.962∼1.033	0.857
Hypertension	1.336	0.450∼3.970	0.602
Diabetes	0.683	0.263∼1.776	0.435
Smoking	0.516	0.220∼1.210	0.128
Injury time	0.968	0.934∼1.004	0.083
Delirium	1.007	0.382∼2.655	0.989
Postoperation 6 h VAS	0.914	0.714∼1.169	0.473
Postoperation 24 h VAS	0.966	0.777∼1.202	0.759
Postoperation 48 h VAS	0.842	0.656∼1.081	0.176
Anesthetics (propofol)	2.236	1.152∼4.340	0.017
ICU admission	0.409	0.162∼1.032	0.058

is consistent with animal experiments, suggesting that earlier application of propofol in the early stage of trauma may enhance the degree of traumatic memory reinforcement and thus promote the occurrence of PTSD.

PTSD may be associated with a variety of factors, such as sex, pain, trauma severity, and smoking (28, 29). To identify additional related risk factors, logistic regression analysis was performed on all participants to evaluate the risk factors related to PTSD in emergency trauma patients. Sex, age, operation time, trauma severity and other factors were not significantly correlated with the incidence of PTSD, but the use of propofol was significantly correlated with the incidence of PTSD. These results provide further evidence that propofol use is associated with an increased risk of PTSD.

Nevertheless, this study had several limitations that deserve mention. First, the 6.3% of patients lost by the 1-month follow-up may have resulted in statistical limitations of the PTSD incidence at the 1-month follow-up. Second, surgery itself may have an effect on PTSD. However, animal studies have suggested that surgery itself had no effect on fear memories in PTSD (30). Third, the population in this study was relatively narrow due to the use of strict inclusion and exclusion criteria. Patients with psychiatric or neurological disorders, such as depression or insomnia, were excluded to decrease the likelihood that the disease itself would interfere with the evaluation of PTSD (31, 32). Four, some studies suggested that PTSD was bound up with chronic pain (33). The lack of data on chronic postsurgical pain may be a limitation in this research. Finally, this study evaluated emergency department trauma patients after only 1 month, and a systematic review of traumatic brain injury showed changes in the prevalence of PTSD after 3, 6, 12, and 24 months (34). Our follow-up studies will extend the duration of follow-up.

In conclusion, early use of propofol general anesthesia in emergency surgery for trauma patients has a certain risk of PTSD. Compared with propofol anesthesia, sevoflurane anesthesia may have certain value in reducing postoperative PTSD in trauma patients undergoing early emergency surgery. Therefore, anesthesia should be carefully selected for patients with trauma requiring emergency surgery as soon as possible, and further research on this issue is needed in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Suzhou Xiangcheng

People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZ formulated the design of the studies. JZ, YL, and LF performed the experiments and analysis of the studies and drafted the manuscript. DH, CG, SH, RW, LW, RY, and BL performed the experiments and collected data. YY and YZ conceived the study, completed its design and coordination, and secured funding for the project. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Koirala R, Søegaard EGI, Thapa SB. Updates on pharmacological treatment of post-traumatic stress disorder. *JNMA J Nepal Med Assoc.* (2017) 56:274–80. doi: 10.31729/jnma.3108
2. He M, Wei JX, Mao M, Zhao GY, Tang JJ, Feng S, et al. Synaptic plasticity in PTSD and associated comorbidities: the function and mechanism for diagnostics and therapy. *Curr Pharm Des.* (2018) 24:4051–9. doi: 10.2174/1381612824666181120094749
3. Qi W, Gevonden M, Shalev A. Prevention of post-traumatic stress disorder after trauma: current evidence and future directions. *Curr Psychiatry Rep.* (2016) 18:1–11. doi: 10.1007/s11920-015-0655-0
4. McCleery JM, Harvey AG. Integration of psychological and biological approaches to trauma memory: implications for pharmacological prevention of PTSD. *J Trauma Stress.* (2004) 17:485–96. doi: 10.1007/s10960-004-5797-5
5. Palgi S, Klein E, Shamay-Tsoory S. The role of oxytocin in empathy in PTSD. *Psychol Trauma.* (2017) 9:70–5. doi: 10.1037/tra0000142
6. Bisson JI, Cosgrove S, Lewis C, Robert NP. Post-traumatic stress disorder. *BMJ.* (2015) 351:h6161. doi: 10.1136/bmj.h6161
7. Chin WS, Shiao JS, Liao SC, Kuo CY, Chen CC, Guo YL. Depressive, anxiety and post-traumatic stress disorders at six years after occupational injuries. *Eur Arch Psychiatry Clin Neurosci.* (2017) 267:507–16. doi: 10.1007/s00406-016-0762-x
8. Abraham CM, Obremskey WT, Song Y, Jackson JC, Ely EW, Archer KR. Hospital delirium and psychological distress at 1 year and health-related quality of life after moderate-to-severe traumatic injury without intracranial hemorrhage. *Arch Phys Med Rehabil.* (2014) 95:2382–9. doi: 10.1016/j.apmr.2014.08.005
9. Friedman MJ, Bernardy NC. Considering future pharmacotherapy for PTSD. *Neurosci Lett.* (2016) 649:181–5. doi: 10.1016/j.neulet.2016.11.048
10. Jackson J, Pandharipande P, Girard T, Brummel N, Thompson J, Hughes C et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med.* (2014) 25:369–79. doi: 10.1016/S2213-2600(14)70051-7
11. Whitlock EL, Rodebaugh TL, Hassett AL, Shanks AM, Kolarik E, Houghtby J, et al. Psychological sequelae of surgery in a prospective cohort of patients from three intraoperative awareness prevention trials. *Anesth Analg.* (2015) 120:87–95. doi: 10.1213/ANE.0000000000000498
12. Kate MK, Perry CM. Propofol: a review of its use in intensive care sedation of adults. *CNS Drugs.* (2003) 17:235–72. doi: 10.2165/00023210-200317040-00003
13. Alexander KS, Nalloor R, Bunting KM, Vazdarjanova A. Investigating individual pre-trauma susceptibility to a PTSD-like phenotype in animals. *Front Syst Neurosci.* (2020)13:85. doi: 10.3389/fnsys.2019.00085
14. Bowers ME, Ressler KJ. An overview of translationally informed treatments for posttraumatic stress disorder: animal models of pavlovian fear conditioning to human clinical trials. *Biol Psychiatry.* (2015) 78:E15–27. doi: 10.1016/j.biopsych.2015.06.008
15. Molina CSP, Berry S, Nielsen A, Winfield R. PTSD in civilian populations after hospitalization following traumatic injury: a comprehensive review. *Am J Surg.* (2018) 216:745–53. doi: 10.1016/j.amjsurg.2018.07.035
16. Hauer D, Ratano P, Morena M, Scaccianoce S, Briegel I, Palmery M, et al. Propofol enhances memory formation via an interaction with the endocannabinoid system. *Anesthesiology.* (2011) 114:1380–8. doi: 10.1097/ALN.0b013e31821c120e
17. Usuki M, Matsuoka Y, Nishi D, Yonemoto N, Matsumura K, Otomo Y, et al. Potential impact of propofol immediately after motor vehicle accident on later symptoms of posttraumatic stress disorder at 6-month follow up: a retrospective cohort study. *Crit Care.* (2012) 16:R196. doi: 10.1186/cc11681
18. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The clinician-administered PTSD scale for DSM-5 (CAPS-5): development and initial psychometric evaluation in military veterans. *Psychol Assess.* (2018) 30:383–95. doi: 10.1037/pas0000486
19. Kok BC, Herrell RK, Thomas JL, Hoge CW. Posttraumatic stress disorder associated with combat service in Iraq or Afghanistan: reconciling prevalence differences between studies. *J Nerv Ment Dis.* (2012) 200:444–50. doi: 10.1097/NMD.0b013e3182532312
20. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry.* (2005) 62:593–602. doi: 10.1001/archpsyc.62.6.593
21. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet.* (2008) 372:139–44. doi: 10.1016/S0140-6736(08)60878-8
22. Sbarski B, Akirav I. Cannabinoids as therapeutics for PTSD. *Pharmacol Ther.* (2020) 211:107551. doi: 10.1016/j.pharmthera.2020.107551
23. Kida S. Reconsolidation/destabilization, extinction and forgetting of fear memory as therapeutic targets for PTSD. *Psychopharmacology.* (2019) 236:49–57. doi: 10.1007/s00213-018-5086-2
24. Wicking M, Steiger F, Nees F, Diener SJ, Grimm O, Ruttorf M, et al. Deficient fear extinction memory in posttraumatic stress disorder. *Neurobiol Learn Mem.* (2016) 136:116–26. doi: 10.1016/j.nlm.2016.09.016
25. Veselis RA, Reinsel RA, Feshchenko VA, Wroński M. The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. *Anesthesiology.* (1997) 87:749–64. doi: 10.1097/00000542-199710000-00007
26. Vallejo AG, Kroes MCW, Rey E, Acedo MV, Moratti S, Fernández G, et al. Propofol-induced deep sedation reduces emotional episodic memory reconsolidation in humans. *Sci Adv.* (2019) 5:eaav3801. doi: 10.1126/sciadv.aav3801
27. Pryor KO, Root JC, Mehta M, Stern E, Pan H, Veselis RA, et al. Effect of propofol on the medial temporal lobe emotional memory system: a functional magnetic resonance imaging study in human subjects. *Br J Anaesth.* (2015) 115:i104–13. doi: 10.1093/bja/aev038
28. Morena M, Berardi A, Peloso A, Valeri D, Palmery M, Trezza V, et al. Effects of ketamine, dexmedetomidine and propofol anesthesia on emotional memory consolidation in rats: consequences for the development of post-traumatic stress disorder. *Behav Brain Res.* (2017) 329:215–20. doi: 10.1016/j.bbr.2017.04.048
29. Gilliam WP, Craner JR, Schumann ME, Gascho K. The mediating effect of pain catastrophizing on PTSD symptoms and pain outcome. *Clin J Pain.* (2019) 35:583–8. doi: 10.1097/AJP.0000000000000713

30. Kolltveit S, Lange-Nielsen II, Thabet AA, Dyregrov A, Pallesen S, Johnsen TB, et al. Risk factors for PTSD, anxiety, and depression among adolescents in Gaza. *Trauma Stress.* (2012) 25:164–70. doi: 10.1002/jts.21680
31. Cox RC, Taylor S, Strachan E, Olatunji BO. Insomnia and posttraumatic stress symptoms: evidence of shared etiology. *Psychiatry Res.* (2020) 286:112548. doi: 10.1016/j.psychres.2019.112548
32. Kline AC, Cooper AA, Rytwinski NK, Feeny NC. The effect of concurrent depression on PTSD outcomes in trauma-focused psychotherapy: a meta-analysis of randomized controlled trials. *Behav Ther.* (2021) 52:250–66. doi: 10.1016/j.beth.2020.04.015
33. Gasperi M, Panizzon M, Goldberg J, Buchwald D, Afari N. Posttraumatic stress disorder and chronic pain conditions in men: a twin study. *Psychosom Med.* (2021) 83:109–17. doi: 10.1097/PSY.0000000000000899
34. Iljazi A, Ashina H, Al-Khazali HM, Lipton RB, Ashina M, Schytz HW, et al. Post-traumatic stress disorder after traumatic brain injury-a systematic review and meta-analysis. *Neurol Sci.* (2020) 41:2737–46. doi: 10.1007/s10072-020-04458-7

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Preoperative Status of Gut Microbiota Predicts Postoperative Delirium in Patients With Gastric Cancer

Hu Liu[1†], Gao Cheng[2†], Yuan-ling Xu[1†], Qi Fang[1], Lei Ye[3], Chun-hui Wang[2] and Xue-sheng Liu[1*]*

[1] *Department of Anesthesiology, Key Laboratory of Anesthesiology and Perioperative Medicine of Anhui Higher Education Institutes, First Affiliated Hospital of Anhui Medical University, Anhui Medical University, Hefei, China,* [2] *Department of Anesthesiology, Fourth Affiliated Hospital of Anhui Medical University, Hefei, China,* [3] *Department of Neurosurgery, First Affiliated Hospital of Anhui Medical University, Hefei, China*

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***Correspondence:**
*Chun-hui Wang
wangchhaymz@163.com
Xue-sheng Liu
liuxuesheng@ahmu.edu.cn*

† These authors have contributed equally to this work

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Introduction: Post-operative delirium (POD) is a serious complication which occurs after surgery, especially in the elderly undergoing abdominal surgery. Increasing evidence has revealed an association between the gut microbiota and psychological disorders involving the "brain-gut" axis. However, the association between the pathogenesis of POD after abdominal surgery in aging and composition of the gut microbiota remains unclear.

Methods: Forty patients (≥65 years old) who underwent abdominal surgery were included in the study. Twenty patients had POD, whereas 20 patients did not. POD was diagnosed and assessed using the confusion assessment method (CAM) during the postoperative period. Total DNA fractions were extracted from all fecal samples of patients. 16S rRNA sequencing was performed to determine the composition of the gut microbiota. The quality of the samples was determined by calculating the α- and β-diversities.

Results: The α- and β-diversities indicated that the samples were eligible for detection and comparison. We observed multiple differentially abundant bacteria in patients with and without POD. Generally, *Proteobacteria, Enterbacteriaceae*, *Escherichia shigella*, *Klebsiella*, *Ruminococcus*, *Roseburia*, *Blautia*, *Holdemanella*, *Anaerostipes*, *Burkholderiaceae*, *Peptococcus*, *Lactobacillus*, and *Dorea* were abundant in the POD cohort, whereas *Streptococcus equinus* and *Blautia hominis* were abundant in the control cohort. The results of receiver operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) of *Escherichia shigella* was 0.75. Phenotype prediction showed that the gut microbiota may influence POD by altering the tolerance to oxidative stress.

Conclusion: There were significant associations between the pathogenesis of POD and composition of the gut microbiota. *Escherichia shigella* are promising diagnostic bacterial species for predicting POD onset after abdominal surgery in elderly people.

Clinical Trial Registration: http://www.chictr.org.cn/index.aspx, Chinese Clinical Trial Registry ChiCTR200030131.

Keywords: surgery, aging, gut microbiota, post-operative delirium, prediction, *Shigella*

INTRODUCTION

Post-operative delirium (POD) is a neurobehavioral symptom characterized by changes in consciousness and unfocused attention (1). POD tends to occur in elderly patients with longer hospital stays and leads to a higher lethality and a lower quality of life (2, 3). As a common complication after surgery, the incidence of POD varies among surgical types and age (4, 5). POD shows a lower incidence among patients undergoing out-patient surgery (6) but a relatively higher incidence in those undergoing abdominal surgery and in elderly people (7–9). Considering the high incidence (10) and negative effects of POD, studies are needed to identify effective predictive markers and mechanisms for surgical patients in clinical practice.

The gut bacteria of adults are composed of around 10^{12}–10^{14} microbes, of which the number is much higher than that of microbes on the skin and cells in the body (11). The gut microbiota participates in numerous signal transduction, metabolic pathways and the regulation of immune-inflammatory axis in the host (12, 13). Thus, it has been considered as a functional organ or second human genome in recent years (14). The gut bacteria is a promising target for investigating markers or the underlying pathogenesis of diseases. Ding et al. (15) found that gastrointestinal symptoms in children were significantly associated with the symptoms of autism spectrum disorder (ASD), and the bacteria *Actinobacteria* and *Firmicutes* may play a role in ASD pathogenesis. Recently, increasing evidence has indicated an association between the gut microbiota and neuropsychiatric diseases, termed as the "brain-gut" axis (16, 17). Although POD was shown to be significantly associated with age and inflammatory status of patients (18–20), the mechanisms of POD are still unclear.

In a previous study of POD, Zhang et al. (21) detected an association between an abnormal composition of the gut microbiota and delirium-like behaviors after abdominal surgery in mice. Additionally, Maekawa et al. (22) observed a clinical association between pseudopsia and the gut microbiota among patients who underwent cardiac surgery. However, the relationship between POD and the gut microbiota in various surgery types and the relationship with aging has not been widely examined.

Abdominal surgery dramatically alters the composition of the gut microbiota and leads to POD, at a higher incidence rate compared to other types of surgery. However, the alterations of gut bacteria after surgery may be influenced by the applications of antibiotics (23, 24), which would confound the onset of POD. We hypothesized that the preoperative gut microbiota creates a certain gut or even systemic microenvironment, and surgery-induced alterations to the gut microbiota may lead to pathological changes in the "brain-gut" axis, subsequently leading to POD.

In this study, we investigated the association between the gut microbiota composition and POD in elderly patients who underwent abdominal surgeries to identify predictive markers of POD.

MATERIALS AND METHODS

Patients

This observational study was conducted from March 2020 to December 2020. Patients, aged 65 years and older and scheduled to undergo radical surgery for gastric cancer, with an American Society of Anesthesiologists (ASA) score of I–III and anticipated surgery time of 1.5–6 h, were included. All patients were screened with a mini-mental state examination (MMSE), and patients with scores of <20 were not enrolled because of dementia concerns. Patients were excluded if they met any of the following criteria: history of severe mental illness or dementia; extant factors that may affect cognition assessment, such as language, visual and auditory dysfunction, an unstable mental status or mental illness; and known or suspected abuse of an analgesic drug. Patients with severe adverse events during the operation (such as bleeding, anaphylactic shock, etc.) that led to death, life-threatening, irreversible damage to organ function, or prolonged hospital stay were also excluded. This study was approved by the Ethics Committee of First Affiliated Hospital of Anhui Medical University (Ethical Committee No. PJ2019-15-18), and registered in the Chinese Clinical Trial Registry (registration number ChiCTR200030131). Informed consent was obtained from all individuals, and all procedures conformed to the standards in the Declaration of Helsinki.

Anesthetic Management

All participants underwent radical gastrectomy for gastric cancer. All surgeries were performed under general anesthesia with midazolam, sufentanil, etomidate, and cisatracurium. Anesthesia was maintained by inhalation anesthetics or intravenous anesthesia. Bispectral index values of 40–60 were consistent with general anesthesia. A titration of 0.1–0.2 μg/kg sufentanil was given intravenously before the end of surgery, and intravenous controlled analgesia was used for postoperative analgesia. Medications were used to prevent postoperative nausea and vomiting.

Delirium Assessment

Assessment of delirium with confusion assessment method (CAM) was performed preoperatively (baseline) twice daily at 8 a.m. and 2 p.m. after the surgery until day 7. Patients were rendered as either CAM-positive (delirium present) or CAM-negative (delirium absent). The diagnosis of delirium was confirmed by psychiatrist consultation and consisted of four clinical criteria: (1) acute change and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. A diagnosis of delirium requires the presence of features 1 and 2 and either 3 or 4. Patients with hyperactive delirium were intravenously administered haloperidol in increments of 1–5 mg every 4 h as first-line treatment, which was repeated every 60 min as necessary.

Fecal Sample Collection and Preparation

Fecal samples were collected from all patients before surgery using sterile swabs and stored at −80°C. None of the patients had been administered antibiotics within the past 6 months before sampling. Bacterial DNA was extracted using an E.Z.N.A. ®Stool DNA Kit (D4015, Omega, Inc., Norcross, GA, USA) according to the manufacturer's protocol. The total DNA was eluted in 50 μl of elution buffer and stored at −80°C until measurement using PCR by LC-BioTechnology Co., Ltd. (Hang Zhou, Zhejiang Province, China).

PCR Amplification and 16S rDNA Sequencing

The V3-V4 region of the bacterial 16S rRNA gene was amplified with primers 341F (5′-CCTACGGGNGGCWGCAG-3′) and 805R (5′-GACTACHVGGGTATCTAATCC-3′). PCR was performed according to a previously published study (25). The amplicon pools were prepared for sequencing, and the size and quantity of the amplicon library were assessed on an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA) and using a Library Quantification Kit for Illumina (Kapa Biosciences, Woburn, MA, USA), respectively. The libraries were sequenced on NovaSeq PE250 platform (Illumina, San Diego, CA, USA).

Data Analysis

Demographic information and intraoperative data were analyzed using SPSS 23.0 software (version 23; SPSS, Inc., Chicago, IL, USA). The normal distribution of the data was evaluated using one-sample Kolmogorov–Smirnov test. Normally distributed continuous variables were presented as the means ± standard deviations and analyzed using independent sample *t*-tests. Categorical variables were presented as numbers (frequencies) and analyzed using Pearson's chi-square or Fisher's exact tests. *P*-values were two-sided, and $P < 0.05$ was considered to indicate significant results.

An Illumina NovaSeq platform was used for sample sequencing according to the manufacturer's recommendations, provided by LC-Bio. Paired-end reads were assigned to samples based on their unique barcode and truncated by cutting off the barcode and primer sequence. Paired-end reads were merged by using FLASH. Quality filtering of the raw reads was conducted under specific filtering conditions to obtain high-quality clean tags according to fqtrim (v0.94). Chimeric sequences were filtered using Vsearch software (v2.3.4). After dereplication using DADA2, we obtained feature table and feature sequences. The α- and β-diversity were calculated using QIIME2, with the same number of sequences extracted randomly by reducing the number of sequences to the minimum of some samples, and relative abundance (X bacteria count/total count) was used in bacteria taxonomy analysis. Images were drawn by R software (v3.5.2; The R Project for Statistical Computing, Vienna, Austria). Sequence alignment for species annotation was performed using BLAST with the SILVA and NT-16S alignment databases.

RESULTS

Baseline and Intra-Operative Data

The baseline demographics characteristics of the 40 patients in the POD and control group were similar in terms of age, sex, and body mass index (**Table 1**). Similarly, there were no significant differences in intra-operative data such as the operation time or ASA fitness grade ($P > 0.05$) (**Table 1**). The surgical types for the patients included laparotomy operation and endoscopic surgery, which were decided to be performed by the primary diseases and the physical condition of the patients. We reviewed some studies and found that there was no difference in the incidence of POD between the two surgical types (26, 27). Therefore, the surgical types could not be regarded as a confounding factor in our study.

Abundance of Gut Microbiota Between Patients With and Without POD

The original contributions presented in the study are publicly available. This data can be found at: http://www.ncbi.nlm.nih.gov/bioproject/797529. We illustrated the top 30 abundant gut bacteria with using taxonomy graphics according to the patient samples (**Figure 1A**) and groups (**Figure 1B**) at the genus level. There were 283 common bacterial categories at the genus level between the POD and control cohorts. However, 44 and 79 categories of bacteria were specific in the POD and control cohorts, respectively (**Figure 1C**). Furthermore, we depicted correlations between the 5 top abundant microbiota (*Streptococcus*, *Bifidobacterium*, *Faecalibacterium*, *Akkermansia*, and *Escherichia shigella*) and the cohort in a Circos graph (**Figure 1D**).

TABLE 1 | Patient characteristics.

	Control group	POD group	*P*-value
Age (years)	70.90 ± 3.48	71.35 ± 4.08	0.710
Sex (M/F)	12/8	11/9	0.749
BMI (kg/m^2)	21.25 ± 2.86	21.41 ± 2.73	0.858
ASA physical status			0.519
I	0 (0%)	0 (0%)	
II	11 (55%)	13 (65%)	
III	9 (45%)	7 (35%)	
Duration of surgery, min	171.5 ± 56.85	188.6 ± 73.39	0.414

Continuous variables are presented as the mean ± SD; categorical variables are presented as numbers. ASA, American Society of Anesthesiologists; BMI, body mass index; F, female; M, male; SD, standard deviation.

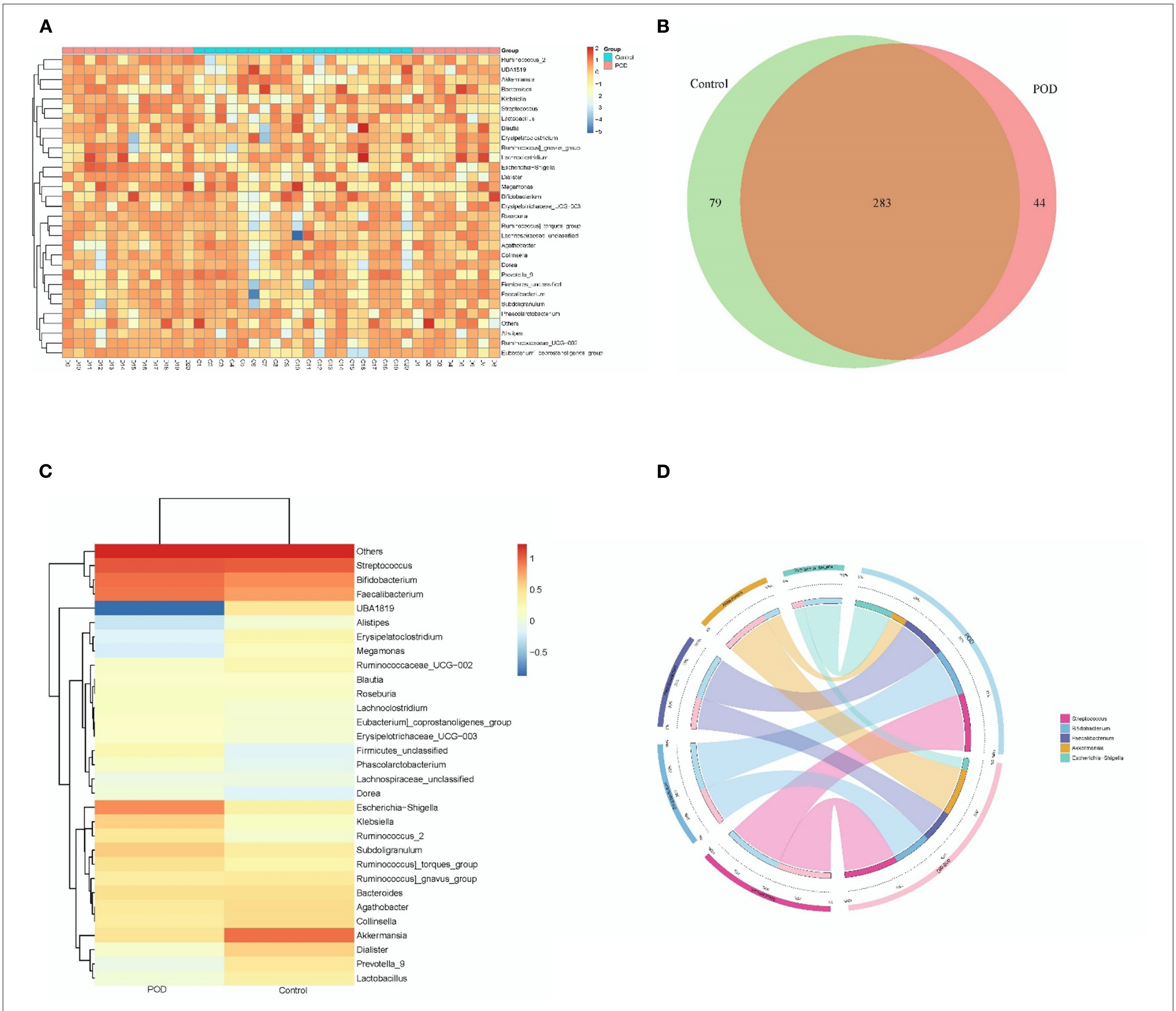

FIGURE 1 | Bacterial composition analysis in different samples **(A)** and cohorts **(B)**. Venn plot depicting common and specific microbes in different cohorts **(C)**. Circos plot showing the corresponding relation between cohorts and bacterial species81**(D)**.

Diversity Analysis

We analyzed the diversity for quality control of the samples in detecting the gut microbiota. **Supplementary Figure 1A** shows the observed operational taxonomic units between the POD and control cohorts, which did not significantly differ ($P = 0.31$). Good's coverage index indicated an excellent sequencing depth (**Supplementary Figure 1B**). We also calculated the Chao, Shannon, and Simpson indices to evaluate the abundance and homogeneity of the samples (**Supplementary Figures 1C,E**). The results indicated good sequencing quality. Principal Component Analysis (PCA) and Principal Co-ordinates Analysis (PCoA) were performed to determine the characteristics of the samples (**Figures 2A,B**). The results indicated that samples from two groups had comparable characteristics.

Differential Abundance of Gut Microbiota and Diagnostic Efficacy in POD

We investigated the differential abundance of the gut microbiota to identify specific bacterial types that may be involved in the pathogenesis and useful for the diagnosis of POD. Analysis using linear discriminant analysis effect size (LEfSe) indicated that multiple bacterial types differed in abundance between the POD and control cohorts, with a characteristics of linear discriminant value >3 (**Figures 3A,B**). *Proteobacteria, Enterbacteriaceae, E. shigella, Klebsiella, Ruminococcus, Roseburia, Blautia, Holdemanella, Anaerostipes, Burkholderiaceae, Peptococcus, Lactobacillus*, and *Dorea* were more abundant in the POD cohort, whereas *Streptococcus equinus* and *Blautia hominis* were more abundant in the control cohort. Meanwhile, the

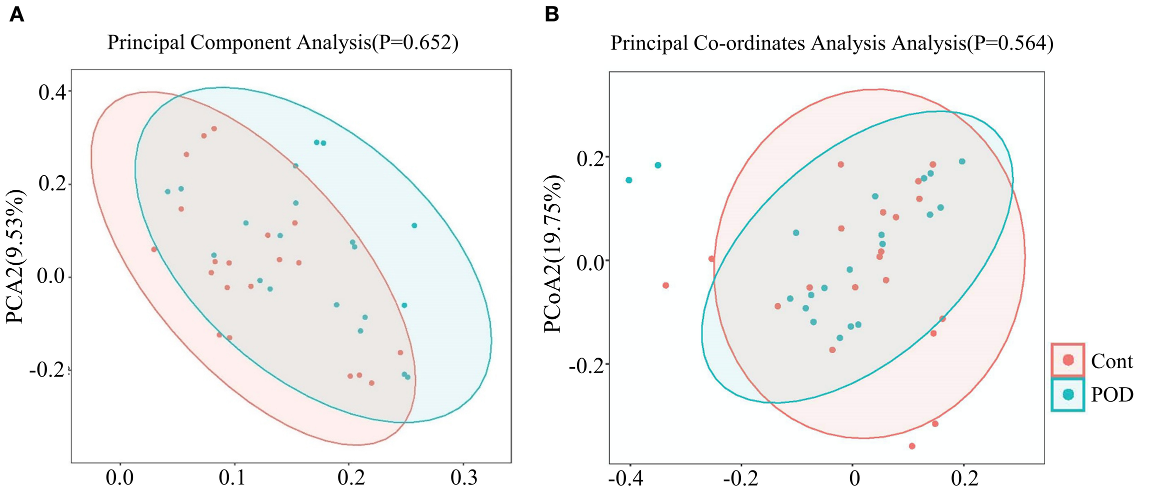

FIGURE 2 | β-diversity analyses of data. **(A)** Principal component analysis (PCA). **(B)** Principal Co-ordinates Analysis (PCoA).

difference of abundance of gut bacteria in Genus level between the POD and control cohorts was shown in **Figure 3E**. Moreover, a receiver operating characteristic (ROC) curve was drawn to identify bacteria useful for diagnosing POD. The area under the curve (AUC) of *Eubacterium hallii* (0.7675), *Oxyphotobacteria* (0.745), and *E. shigella* (0.75) showed areas of higher than 0.7 (**Figure 3C**). Based on these results, *E. shigella* was a promising predictive bacteria for diagnosing POD. No obvious correlations were observed among the different bacterial types (**Figure 3D**).

Functional and Phenotype Predictions

We also conducted bacterial gene functional prediction through Gene Ontology (GO) and pathway prediction analyses, as illustrated in **Figures 4A,B**. We predicted the potential phenotypes of the gut microbiota, including aerobic, oxygen-utilizing (anaerobic and facultatively anaerobic), mobile element-containing, biofilm-forming, gram-negative, gram-positive, pathogenic, and oxidative stress-tolerant bacteria (**Figures 5A–I**). We found a positive association between the phenotype of oxidative stress-tolerant and POD with borderline significance ($P = 0.044$).

DISCUSSION

We explored the association between the composition of the gut microbiota and POD. Interestingly, we found differential abundances of the gut microbiota between the POD and control cohorts. *Proteobacteria, Enterbacteriaceae, E. shigella*, *Klebsiella*, *Ruminococcus*, *Roseburia*, *Blautia*, *Holdemanella*, *Anaerostipes*, *Burkholderiaceae, Peptococcus*, *Lactobacillus*, and *Dorea* were more abundant in the POD cohort, whereas *S. equinus* and *B. hominis* were more abundant in the control cohort.

In recent decades, the "brain-gut" axis has received considerable attentions in clinical association and mechanism studies of neuropsychiatric disorders. Dysregulation of the gut microbiota was reportedly associated with various neuropsychiatric diseases, such as Alzheimer's disease (28), Parkinson's disease (29), ASD (30), and depression (31). Previous studies suggested that the gut microbiota influences the physiological functions of the brain through several pathways. For example, dysregulation of the gut microbiota leads to abnormal activation of systemic and neuro-inflammation (32, 33). It has been reported that 70–80% of immunocytes reside at the gut-associated lymphoid tissue (34), and the gut microbiota is closely related to the inflammatory status. Surgery may induce alterations in the composition of gut bacteria which subsequently secrete endotoxin, leading to endotoxemia and excessive intestinal inflammation, as well as aggravating systemic and neuro-inflammation (35, 36). Kawano et al. (37) have been found that the neuro-inflammation was significantly correlated with delirium. Seo et al. (38) also suggested that neutrophil-lymphocyte ratio could be deserved as a biomarker in delirium. We speculated that the alteration of gut bacteria related neuro-inflammation after abdominal surgery would be a potential influencing factor in the incidence of POD. Additionally, deregulation of the gut microbiota regulates brain function by altering bacterial metabolites. Some neurotransmitters, such as γ-aminobutyric acid, serotonin and dopamine, are produced in the gastrointestinal tract by gut bacteria (39) and reach the central nervous system bypassing the blood-brain-barrier (40, 41). Furthermore, studies have found that anticholinergic medications and dopaminergic medications instigated delirium, indicating that neurotransmitters might play important roles in POD (42, 43). Dysregulation of the gut microbiota in mice using antibiotics led to neural pathological changes, with some neurological diseases more severe than in the non-dysregulation mice cohort (34). Thus, the gut microbiota is important in the pathogenesis of neuropsychiatric disorders. However, few studies have focused on POD.

In a clinical study of the relationship between the gut microbiota and pseudopsia after cardiac surgery, Maekawa et al. (22) reported that surgery lowered the total bacterial

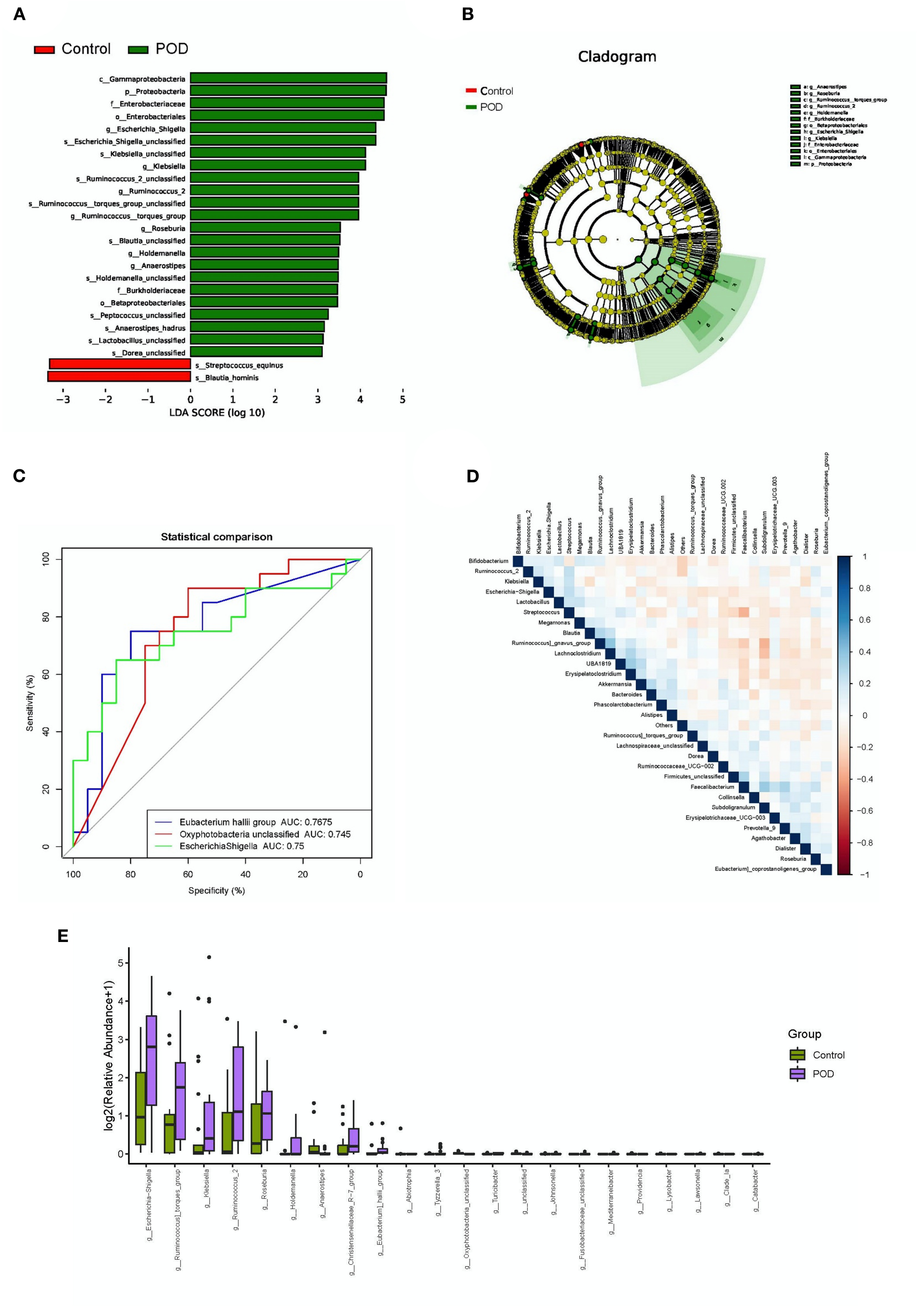

FIGURE 3 | Differential abundance and diagnostic efficacy of gut bacterial between POD and control cohorts. **(A)** Linear discriminant analysis effect size (LEfSe) of differentially abundant bacteria; **(B)** Cladogram of differentially abundant bacteria; **(C)** Receiver operating characteristic curve analysis of the diagnostic efficacies of bacteria (AUC > 0.7); **(D)** Correlation analysis among bacteria; **(E)** Differentially abundant bacteria in Genus level.

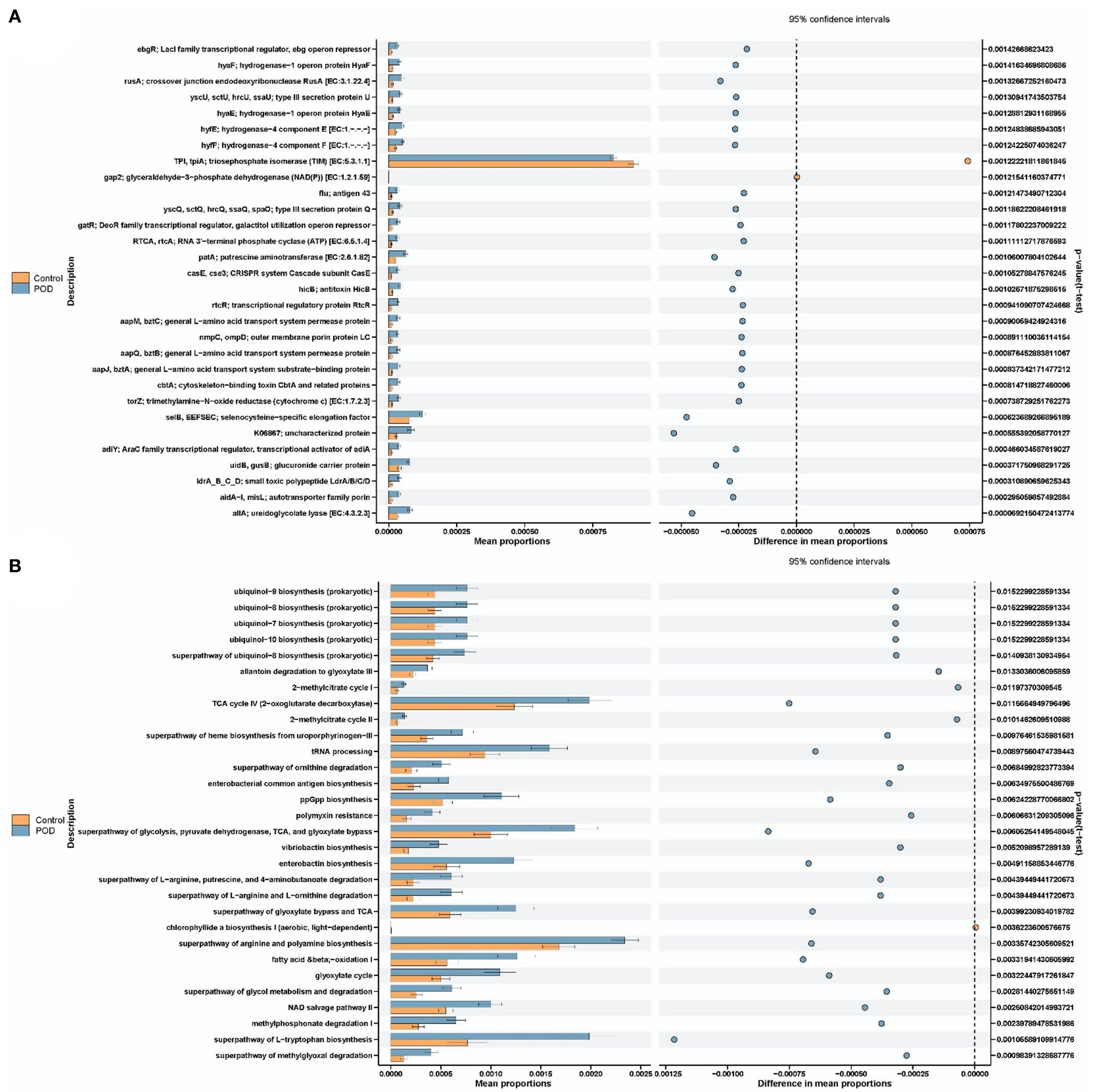

FIGURE 4 | Functional prediction by phylogenetic investigation of communities by reconstruction of unobserved states. **(A)** KO prediction. **(B)** Pathway abundance prediction.

counts and species numbers. *Staphylococcus* and *Pseudomonas* counts were significantly higher postoperatively, and may be associated with the pathogenesis of pseudopsia. However, we did not conduct a longitudinal investigation to explore whether differences in the abundance of bacterial species occurred pre- and post-operatively. Numerous studies have suggested that the composition of the gut microbiota changes dramatically after abdominal surgery (44). Localized inflammation and antibiotics administration during abdominal surgery influences the gut microbiota composition. As different surgical methods and diverse antibiotics may confound the postoperative results, we only analyzed the association of the pre-operative gut microbiota status with the onset of POD. Zhang et al. (21) conducted a preliminary study of the association of delirium-like behavior with gut microbiota in an abdominal surgical mouse model. They found that multiple bacterial types were significantly associated with delirium, such as *Gammaproteobacteria, Bifidobacteriales, Ruminococcaceae*, *Butyricimonas*, *E. shigella*, and others. These

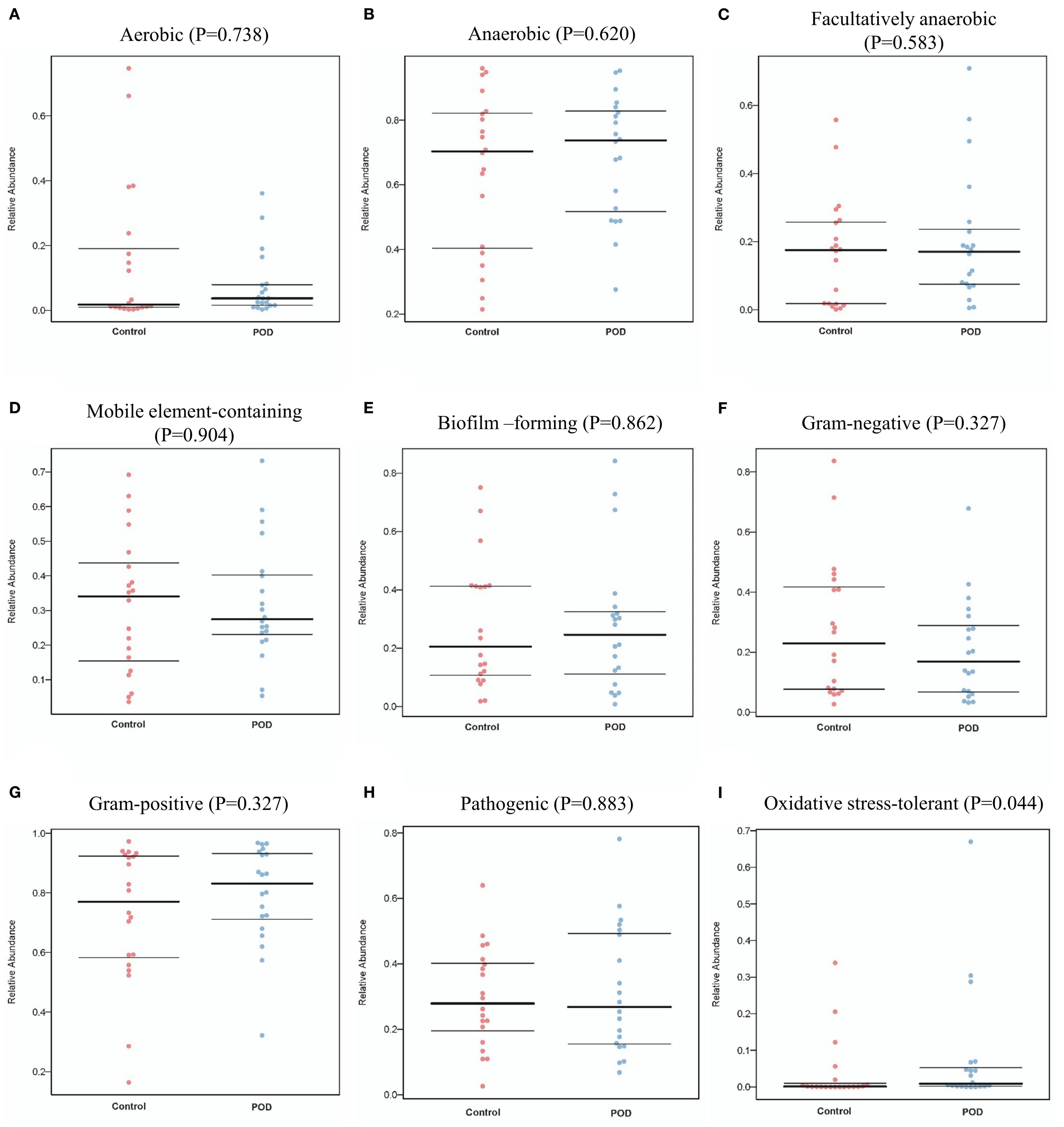

FIGURE 5 | Bacterial phenotype prediction for **(A)** Aerobic, **(B)** Anaerobic, **(C)** Facultatively anaerobic, **(D)** Mobile element-containing, **(E)** Biofilm-forming, **(F)** Gram-negative, **(G)** Gram-positive, **(H)** Pathogenic, and **(I)** Oxidative stress-tolerant.

results are partly consistent with our results and indicate that gut microbiota-induced psychological alterations are derived from a common bacterial cohort both in humans and mice. *Gammaproteobacteria* and *E. shigella* are both pathogenic and can colonize the gastrointestinal tract, leading to abnormal activation of gut inflammation. In reviewing previous studies, we did not find the clinical association between of post-operative diarrhea which could be induced by *E. shigella* with the incidence of POD. However, a previous study suggested that Shige toxin from *Shigella* contributed to the pathogenesis of delirium (45). Although *E. shigella* in our study might be a kind of colonized bacterial species and would not cause diarrhea, we speculated that the Shige toxin derived from the colonized *E. shigella* plays a role in the pathogenesis of POD after abdominal surgeries. This might provide clues in the prevention or treatment of POD by the intervention of gut bacteria, such as *E. shigella.* Animal experiments have shown that surgery significantly increased levels of *Gammaproteobacteria* (21), the correlation between the differential abundance of *Gammaproteobacteria* before surgery and POD has not been reported in clinical studies. Some studies suggested that higher proportions of *Gammaproteobacteria* were significantly associated with major depressive disorder (46) and ASD (47). Therefore, there may also be a connection between *Gammaproteobacteria* and POD. Although *Gammaproteobacteria* was found associated with POD in our study, the mechanisms need further analysis. Furthermore, *Ruminococcaceae* was previously reported to be correlated with the anti-depressant effects of R-ketamine in mice (48), however, some *Ruminococcaceae* at the genus level showed higher abundance in POD than in control. These results are different from previous studies of *Ruminococcaceae* in psychological disorders. As we could not find other related references to POD and *Ruminococcaceae*, a more comprehensive investigation of a larger cohort is required to confirm our results regarding the association between *Ruminococcaceae* and POD. We have also developed a model to predict the diagnostic efficacy of bacterial types in POD. Considering the results of differential abundance analysis, that *E. shigella* may predict POD based on its area under the curve of 0.75.

Finally, we performed phenotype prediction based on the differentially abundant bacterial types. The results indicated that oxidative stress tolerance was involved in the pathogenesis of POD. Oxidative stress has been widely reported to be involved in the pathogenesis of POD (49, 50). A detailed mechanism study is needed to investigate whether the production of oxidative stress-related metabolites is correlated with the gut microbiota.

Our study had some limitations. First, we only evaluated the association of POD with the gut microbiota. The detailed mechanisms through which the gut microbiota leads to the pathogenesis of POD were not examined. Secondly, the sample size in our study was relatively small, which may led to bias in statistical analysis. Therefore, additional samples should be evaluated in order to confirm our results in delirium clinical prediction.

CONCLUSION

In summary, we found significant associations between the pathogenesis of POD and composition of the gut microbiota. *E. shigella* is a promising diagnostic bacterial species for predicting POD onset after abdominal surgery. Phenotype prediction revealed that the gut microbiota may influence POD through oxidative stress tolerance.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories, accession number(s) can be found at: NCBI BioProject, PRJNA797529.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of Anhui Medical University, Hefei, Anhui, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL, C-hW, and X-sL contributed to conception and design of the study. GC and Y-lX organized the database. QF performed the statistical analysis. HL wrote the first draft of the manuscript. LY wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.852269/full#supplementary-material

REFERENCES

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* (2014) 383:911–22. doi: 10.1016/S0140-6736(13)60688-1
2. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet.* (2016) 388:1893–902. doi: 10.1016/S0140-6736(16)30580-3
3. Brown CH, Laflam A, Max L, Lymar D, Neufeld KJ, Tian J, et al. The Impact of Delirium After Cardiac Surgical Procedures on Postoperative Resource Use. *Ann Thorac Surg.* (2016) 101:1663–9. doi: 10.1016/j.athoracsur.2015.12.074
4. Kang SY, Seo SW, Kim JY. Comprehensive risk factor evaluation of postoperative delirium following major surgery: clinical data warehouse analysis. *Neurol Sci.* (2019) 40:793–800. doi: 10.1007/s10072-019-3730-1
5. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. *Nat Rev Neurosci.* (2016) 17:705–17. doi: 10.1038/nrn.2016.128
6. Fong TG, Hshieh TT, Wong B, Tommet D, Jones RN, Schmitt EM, et al. Neuropsychological profiles of an elderly cohort undergoing elective surgery and the relationship between cognitive performance and delirium. *J Am Geriatr Soc.* (2015) 63:977–82. doi: 10.1111/jgs.13383
7. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. *Ann Surg.* (2009) 249:173–8. doi: 10.1097/SLA.0b013e31818e4776

8. Raats JW, van Eijsden WA, Crolla RM, Steyerberg EW, van der Laan L. Risk factors and outcomes for postoperative delirium after major surgery in elderly patients. *PloS ONE.* (2015) 10:e0136071. doi: 10.1371/journal.pone.0136071
9. Hshieh TT, Inouye SK, Oh ES. Delirium in the elderly. *Clin Geriatr Med.* (2020) 36:183–99. doi: 10.1016/j.cger.2019.11.001
10. Naeije G, Pepersack T. Delirium in elderly people. *Lancet.* (2014) 383:2044–5. doi: 10.1016/S0140-6736(14)60993-4
11. Bienenstock J, Kunze W, Forsythe P. Microbiota and the gut-brain axis. *Nutr Rev.* (2015) 73:28–31. doi: 10.1093/nutrit/nuv019
12. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. *Cell Host Microbe.* (2015) 17:565–76. doi: 10.1016/j.chom.2015.04.011
13. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci.* (2012) 13:701–12. doi: 10.1038/nrn3346
14. Ridaura V, Belkaid Y. Gut microbiota: the link to your second brain. *Cell.* (2015) 161:193–4. doi: 10.1016/j.cell.2015.03.033
15. Ding H, Yi X, Zhang X, Wang H, Liu H, Mou WW. Imbalance in the gut microbiota of children with autism spectrum disorders. *Front Cell Infect Microbiol.* (2021) 11:572752. doi: 10.3389/fcimb.2021.572752
16. Guida F, Turco F, Iannotta M, De Gregorio D, Palumbo I, Sarnelli G, et al. Antibiotic-induced microbiota perturbation causes gut endocannabinoidome changes, hippocampal neuroglial reorganization and depression in mice. *Brain Behav Immun.* (2018) 67:230–45. doi: 10.1016/j.bbi.2017.09.001
17. van Kessel SP, Frye AK, El-Gendy AO, Castejon M, Keshavarzian A, van Dijk G, et al. Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. *Nat Commun.* (2019) 10:310. doi: 10.1038/s41467-019-08294-y
18. Evora PR, Bottura C, Arcencio L, Albuquerque AA, Evora PM, Rodrigues AJ. Key points for curbing cardiopulmonary bypass inflammation. *Acta Cir Bras.* (2016) 31:45–52. doi: 10.1590/S0102-86502016001300010
19. Mattison MLP. Delirium. *Ann Intern Med.* (2020) 173:ITC49–64. doi: 10.7326/AITC202010060
20. Clark IA, Vissel B. The inflammatory nature of post-surgical delirium predicts benefit of agents with anti-TNF effects such as dexmedetomidine. *Front Neurosci.* (2018) 12:257. doi: 10.3389/fnins.2018.00257
21. Zhang J, Bi JJ, Guo GJ, Yang L, Zhu B, Zhan GF, et al. Abnormal composition of gut microbiota contributes to delirium-like behaviors after abdominal surgery in mice. *CNS Neurosci Ther.* (2019) 25:685–96. doi: 10.1111/cns.13103
22. Maekawa M, Yoshitani K, Yahagi M, Asahara T, Shishido Y, Fukushima S, et al. Association between postoperative changes in the gut microbiota and pseudopsia after cardiac surgery: prospective observational study. *BMC Surg.* (2020) 20:247. doi: 10.1186/s12893-020-00907-4
23. Teng C, Frei CR. Delirium associations with antibiotics: a pharmacovigilance study of the FDA adverse event reporting system (FAERS). *Drugs Real World Outcomes.* (2021) 9:23–9. doi: 10.1007/s40801-021-00268-1
24. Pejcic AV. Delirium associated with the use of macrolide antibiotics: a review. *Int J Psychiatry Clin Pract.* (2020) 1–14. doi: 10.1080/13651501.2020.1828933
25. Logue JB, Stedmon CA, Kellerman AM, Nielsen NJ, Andersson AF, Laudon H, et al. Experimental insights into the importance of aquatic bacterial community composition to the degradation of dissolved organic matter. *ISME J.* (2016) 10:533–45. doi: 10.1038/ismej.2015.131
26. Tei M, Ikeda M, Haraguchi N, Takemasa I, Mizushima T, Ishii H, et al. Risk factors for postoperative delirium in elderly patients with colorectal cancer. *Surg Endosc.* (2010) 24:2135–9. doi: 10.1007/s00464-010-0911-7
27. Shin YH, Kim DK, Jeong HJ. Impact of surgical approach on postoperative delirium in elderly patients undergoing gastrectomy: laparoscopic versus open approaches. *Korean J Anesthesiol.* (2015) 68:379–85. doi: 10.4097/kjae.2015.68.4.379
28. Sun J, Xu J, Yang B, Chen K, Kong Y, Fang N, et al. Effect of Clostridium butyricum against microglia-mediated neuroinflammation in Alzheimer's Disease *via* regulating gut microbiota and metabolites butyrate. *Mol Nutr Food Res.* (2020) 64:e1900636. doi: 10.1002/mnfr.201900636
29. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of parkinson's disease. *Cell.* (2016) 167:1469–80.e12. doi: 10.1016/j.cell.2016.11.018
30. Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, et al. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. *Cell.* (2019) 177:1600–18.e17. doi: 10.1016/j.cell.2019.05.004
31. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nature microbiology.* (2019) 4:623–32. doi: 10.1038/s41564-018-0337-x
32. Al Bander Z, Nitert MD, Mousa A, Naderpoor N. The gut microbiota and inflammation: an overview. *Int J Environ Res Public Health.* (2020) 17:7618. doi: 10.3390/ijerph17207618
33. Megur A, Baltriukiene D, Bukelskiene V, Burokas A. The microbiota-gut-brain axis and alzheimer's disease: neuroinflammation is to blame? *Nutrients.* (2020) 13:37. doi: 10.3390/nu13010037
34. Kigerl KA, Hall JC, Wang L, Mo X, Yu Z, Popovich PG. Gut dysbiosis impairs recovery after spinal cord injury. *J Exp Med.* (2016) 213:2603–20. doi: 10.1084/jem.20151345
35. Morley WA, Seneff S. Diminished brain resilience syndrome: a modern day neurological pathology of increased susceptibility to mild brain trauma, concussion, downstream neurodegeneration. *Surg Neurol Int.* (2014) 5:97. doi: 10.4103/2152-7806.134731
36. Bickford PC, Flowers A, Grimmig B. Aging leads to altered microglial function that reduces brain resiliency increasing vulnerability to neurodegenerative diseases. *Exp Gerontol.* (2017) 94:4–8. doi: 10.1016/j.exger.2017.01.027
37. Kawano T, Yamanaka D, Aoyama B, Tateiwa H, Shigematsu-Locatelli M, Nishigaki A, et al. Involvement of acute neuroinflammation in postoperative delirium-like cognitive deficits in rats. *J Anesth.* (2018) 32:506–17. doi: 10.1007/s00540-018-2504-x
38. Seo CL, Park JY, Park J, Kim HE, Cho J, Seok JH, et al. Neutrophil-lymphocyte ratio as a potential biomarker for delirium in the intensive care unit. *Front Psychiatry.* (2021) 12:729421. doi: 10.3389/fpsyt.2021.729421
39. van der Eijk JAJ, Rodenburg TB, de Vries H, Kjaer JB, Smidt H, Naguib M, et al. Early-life microbiota transplantation affects behavioural responses, serotonin and immune characteristics in chicken lines divergently selected on feather pecking. *Sci Rep.* (2020) 10:2750. doi: 10.1038/s41598-020-59125-w
40. Rothhammer V, Mascanfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, et al. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation *via* the aryl hydrocarbon receptor. *Nat Med.* (2016) 22:586–97. doi: 10.1038/nm.4106
41. Yano JM Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell.* (2015) 161:264–76. doi: 10.1016/j.cell.2015.02.047
42. Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. *Med Hypotheses.* (2005) 64:471–5. doi: 10.1016/j.mehy.2004.08.007
43. Trzepacz PT. Anticholinergic model for delirium. *Semin Clin Neuropsychiatry.* (1996) 1:294–303.
44. Lederer AK, Pisarski P, Kousoulas L, Fichtner-Feigl S, Hess C, Huber R. Postoperative changes of the microbiome: are surgical complications related to the gut flora? a systematic review. *BMC surgery.* (2017) 17:125. doi: 10.1186/s12893-017-0325-8
45. Khan WA, Dhar U, Salam MA, Griffiths JK, Rand W, Bennish ML. Central nervous system manifestations of childhood shigellosis: prevalence, risk factors, and outcome. *Pediatrics.* (1999) 103:E18. doi: 10.1542/peds.103.2.e18
46. Liu RT, Rowan-Nash AD, Sheehan AE, Walsh RFL, Sanzari CM, Korry BJ, et al. Reductions in anti-inflammatory gut bacteria are associated with depression in a sample of young adults. *Brain Behav Immun.* (2020) 88:308–24. doi: 10.1016/j.bbi.2020.03.026
47. Plaza-Diaz J, Gomez-Fernandez A, Chueca N, Torre-Aguilar MJ, Gil A, Perez-Navero JL, et al. Autism spectrum disorder (ASD) with and without mental regression is associated with changes in the fecal microbiota. *Nutrients.* (2019) 11:337. doi: 10.3390/nu11020337
48. Qu Y, Yang C, Ren Q, Ma M, Dong C, Hashimoto K. Comparison of (R)-ketamine and lanicemine on depression-like phenotype and abnormal composition of gut microbiota in a social defeat stress model. *Sci Rep.* (2017) 7:15725. doi: 10.1038/s41598-017-16060-7
49. Karlidag R, Unal S, Sezer OH, Bay Karabulut A, Battaloglu B, But A, et al. The role of oxidative stress in postoperative delirium. *Gen Hosp Psychiatry.* (2006) 28:418–23. doi: 10.1016/j.genhosppsych.2006.06.002

50. Zhang J, Gao J, Guo G, Li S, Zhan G, Xie Z, et al. Anesthesia and surgery induce delirium-like behavior in susceptible mice: the role of oxidative stress. *Am J Transl Res.* (2018) 10:2435–44.

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EDITED BY
Jie Sun,
Southeast University, China

REVIEWED BY
Chun Yang,
Nanjing Medical University, China
Yimin Hu,
Second Affiliated Changzhou People's Hospital of Nanjing Medical University, China

*CORRESPONDENCE
Xue-sheng Liu
liuxuesheng@ahmu.edu.cn

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Response: Commentary: Preoperative status of gut microbiota predicts postoperative delirium in patients with gastric cancer

Hu Liu and Xue-sheng Liu*

Department of Anesthesiology, Key Laboratory of Anesthesiology and Perioperative Medicine of Anhui Higher Education Institutes, First Affiliated Hospital of Anhui Medical University, Anhui Medical University, Hefei, China

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A Commentary on

Preoperative status of gut microbiota predicts postoperative delirium in patients with gastric cancer

by Jiang, M., and Tan, W (2022). *Front. Psychiatry* 13:944236. doi: 10.3389/fpsyt.2022.944236

Introduction

We appreciate to receive an insightful comment by Tan et al. Our study preliminarily investigated the association between post-operative delirium (POD) and gut microbiota. We observed multiple differentially abundant bacteria between the patients with and without POD. The results indicated that there were significant associations between the pathogenesis of POD and composition of the gut microbiota. More details about bacterial types can be found in the context.

We admitted that the sample size was relatively small, so we noted the limitation in the discussion (1). Theoretically, the sample size should be set to meet the power value of statistics. We totally collected almost 100 samples during the study, but some samples were excluded from the final experiment of 16S rRNA sequencing because of restrictive conditions. These conditions helped the elimination of bias, such as surgical type, antibiotics application within the past 6 months before sampling, etc. Meanwhile, some samples were also excluded from quality control during the experiment. So the final sample size for experiment and analysis was 20 POD patients and 20 non-POD patients.

Tan et al. proposed another suggestive comment for the difference of delirium rate between anesthetic types. Previous studies have shown controversial results on the delirium rate between propofol anesthesia and sevoflurane anesthesia. For example, Isshii et al. (2) reported that the incidence of POD in sevoflurane anesthesia was significantly higher than that in propofol anesthesia; However, Mei et al. (3) and Nishikawa et al. (4) found no statistical differences in POD between the two anesthetics. It could reduce the bias to control the single variable for anesthetic. Therefore, we intend to perform a stratification analysis on POD with an augmented sample size. Second, in the β-diversity analysis, we performed Principal Component Analysis (PCA) and Principal Co-ordinates Analysis (PCoA) analyses to investigate the comparability of samples from the two cohorts. The results indicated that the *P*-values for PCA and PCoA were both >0.05. Given that fecal samples were derived from patients with gastric cancer, these results indicated comparability between the two cohorts. The analyses in our study were just performed according to an established analytical procedure (2). The quotiety of explanations on the X-axis in PCA and PCoA were missed, so we added the percentages in this letter: PCA1 (23%) in PCA analysis and PCoA1 (22.49%) in PCoA analysis.

Furthermore, we apologize for the mistake of the registration number, which should be changed from ChiCTR200030131 to ChiCTR2000030131. This study belongs to a sub-project of the clinical interventional trial.

Our study presented a preliminary investigation on the potential functions of "brain-gut" axis on POD. We are grateful for the reader's concern about the novelties and the limitations. We would like to make further studies on both clinical association and mechanism, and wish to develop a multi-center collaboration.

Author contributions

HL wrote the draft and X-sL rewrote it. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Liu H, Cheng G, Xu XL, Fang Q, Ye L, Wang CH, et al. Preoperative status of gut microbiota predicts postoperative delirium in patients with gastric cancer. *Front Psychiatry*. (2022) 13:852269. doi: 10.3389/fpsyt.2022.852269

2. Ishii K, Makita T, Yamashita H, Matsunaga S, Akiyama D, Toba K, et al. Total intravenous anesthesia with propofol is associated with a lower rate of postoperative delirium in comparison with sevoflurane anesthesia in elderly patients. *J Clin Anesth*. (2016) 33:428–31. doi: 10.1016/j.jclinane.2016.04.043

3. Mei X, Zheng HL, Li C, Ma X, Zheng H, Marcantonio E, et al. The effects of propofol and sevoflurane on postoperative delirium in older patients: a randomized clinical trial study. *J Alzheimers Dis*. (2020) 76:1627–36. doi: 10.3233/JAD-200322

4. Nishikawa K, Nakayama M, Omote K, Namiki A. Recovery characteristics and post-operative delirium after long-duration laparoscope-assisted surgery in elderly patients: propofol-based vs. sevoflurane-based anesthesia. *Acta Anaesthesiol Scand*. (2004) 48:162–8. doi: 10.1111/j.0001-5172.2004.00264.x

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Mechanical Bowel Preparation Is a Risk Factor for Postoperative Delirium as It Alters the Gut Microbiota Composition: A Prospective Randomized Single-Center Study

*Zhoujing Yang†, Chuandi Tong†, Xinye Qian, Hailian Wang and Yingwei Wang**

Department of Anesthesiology, Huashan Hospital, Fudan University, Shanghai, China

Edited by:
Kenji Hashimoto,
Chiba University, Japan

Reviewed by:
Chun Yang,
Nanjing Medical University, China
Hemraj B. Dodiya,
University of Chicago, United States

***Correspondence:**
Yingwei Wang
wangyw@fudan.edu.cn

†These authors have contributed equally to this work and share first authorship

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Background and Objective: Postoperative delirium (POD) is a frequent complication in patients undergoing gastrectomy. Increasing evidence suggests that abnormal gut microbiota composition may contribute to its morbidity. However, it is unclear whether mechanical bowel preparation would cause postoperative delirium by altering the gut microbiota of patients. This study aimed to investigate the association between mechanical bowel preparation and postoperative delirium in patients undergoing gastrectomy.

Methods: A prospective randomized single-center study was performed. A total of 81 patients with gastric cancer were enrolled and randomly assigned to two groups: preparation group and non-preparation group according to whether the patient received MBP before surgery. To diagnose postoperative delirium, we used the 3-Min Diagnostic Interview for Confusion Assessment Method-defined delirium for five successive days after surgery. 16s rRNA gene sequencing was used to investigate changes in the intestinal bacteria. The linear discriminant analysis and effect size (LefSe) analysis were also used to identify the different taxa of fecal microbiota between the postoperative delirium and non-postoperative delirium groups.

Results: We found that there was a significant difference in β-diversity of the gut microbiota between the preparation group and non-preparation group (P = 0.048). Furthermore, patients in the preparation group had a much higher rate of postoperative delirium (13/40, 32.5%) compared with that in non-preparation groups (4/41, 9.8%). Multivariate regression analysis adjusted by other risk factors indicated that mechanical bowel preparation was associated with the occurrence of delirium (odds ratio = 4.792; 95% confidence interval: 1.274–18.028; P = 0.020). When comparing the gut microbiota of patients with and without POD, *Bacteroides* and *Veillonella* (genus), which were higher in the preparation group, were also higher in delirium patients ($P < 0.05$). Genus *Olsenella* was both relatively higher in the non-preparation group and non-POD group ($P < 0.05$).

Conclusion: Mechanical bowel preparation not only altered the gut microbiota composition of patients with gastric cancer but also increased the incidence of postoperative delirium. Among all the gut microbiota altered by mechanical bowel preparation, *Bacteroides* and *Veillonella* genus might be a risk factor of POD. Genus *Olsenella* might be a beneficial bacteria to reduce the incidence of POD.

Keywords: mechanical bowel preparation (MBP), gut microbiota, postoperative delirium (POD), gastrectomy, perioperative interventions

INTRODUCTION

Postoperative delirium (POD) is a common complication after the operation, characterized by four features: an acute change in mental status with a fluctuating course, inattention, disorganized thinking, and an altered level of consciousness (Marcantonio, 2017; Oh et al., 2017). POD is associated with functional decline in normal activity, increased length of hospital days, higher costs, and other complications (Sprung et al., 2017). Its incidence ranges from 10 to 60% in patients receiving major abdominal surgery as reported (Brouquet et al., 2010). Various factors, namely, perioperative interventions and surgical procedures, are associated with POD.

Recent studies show that the gut microbiome can modulate brain function through the gut-brain axis, which is a complex bidirectional signaling system between the gut and the brain (Ridaura and Belkaid, 2015; Pascale et al., 2018). Moreover, studies are showing that abnormal gut microbiota composition after abdominal surgery may contribute to the pathogenesis of POD in mice (Zhang et al., 2019).

Mechanical bowel preparation (MBP) for elective gastrectomy is often used before abdominal surgeries. Previous studies focusing on the effects of mechanical bowel preparation on the intestinal microbiota are not consistent (Mai et al., 2006). Several studies have indicated that MBP did not have a significant impact on gut microbiota and it did not alter the microbial diversity even when the total bacterial load was halved (O'Brien et al., 2013). But other studies have found that bowel preparation had a substantial effect on the gut microbiota, and it might take 14 days for the majority of the intestinal microbiota to recover to the baseline composition (Nagata et al., 2019).

Thus, we conducted a single-center prospective randomized controlled study to verify our hypothesis that mechanical bowel preparations might be a risk factor of POD as MBP may change the state and composition of the gut microbiota in patients with gastric cancer.

MATERIALS AND METHODS

Patient Enrollment and Ethics

A prospective randomized single-center study was conducted between November 2018 and November 2019 at the Huashan Hospital, Fudan University. The clinical trial was approved by the ethical committee of Huashan Hospital (approval number: KY2018-354) under the declaration of Helsinki. Every patient enrolled should sign the informed consent. This study was registered at http://www.chictr.org.cn/index.aspx (registration number: ChiCTR1800019139). The initial date of registration was 26/10/2018.

Inclusion/Exclusion Criteria

Inclusion criteria: (1) patients were aged over 65 years old, no gender preference; (2) patient's ASA grade (American Society of Anesthesiologists physical status): I–III; (3) patients were diagnosed with gastric cancer (T1M0N0 and T2M0N0) and were scheduled to undergo elective radical gastrectomy; and (4) patients were able to communicate with researchers without difficulty and follow all the protocol of the trial.

Patients with the following conditions were excluded: (1) history of neurological disease, dementia, and other psychiatric illness; (2) history of using probiotics, antibiotics, prebiotics, or synbiotics within 3 months before fecal sample collection; (3) preoperative Mini-Mental State Examination (MMSE) score less than 24; (4) history of severe auditory, visual, or motor deficits; (5) history of digestive system diseases other than cancer; (6) history of other serious primary diseases; (7) illiteracy or communicative disorders; and (8) recent participation in other clinical trials.

Allocations

The patients were randomly assigned into two groups: the preparation group and the non-preparation group according to whether the patient received MBP before surgery. All participants enrolled in the study followed a recommended balanced diet during the study period (Drago et al., 2016).

Simple random treatment allocations were generated before starting the study and concealed in sequentially numbered and sealed opaque envelopes. After written informed consent was obtained, a patient was randomized by opening the next number envelope (Luangchosiri et al., 2015). An entire clinical trial of patients was performed by assigned anesthesiologists and surgeons who were not involved in the study and were blinded to the grouping.

Patients in the preparation group received a standard high-volume (2–4 L) polyethylene glycol electrolyte lavage solution (generic name: Polyethylene Glycol Electrolytes Powder, manufacturer: Shenzhen Wanhe Pharmaceutical Co., Ltd., SFDA approval number: H20030827) the day before surgery for

Abbreviations: MBP, mechanical bowel preparation; pre group, preparation group; non-pre group, non-preparation group; POD, postoperative delirium.

mechanical bowel preparation, while patients in the non-preparation group did not receive the lavage solution (Drago et al., 2016). The administration could be terminated when the stool was clear, and the total amount of the lavage solution was not more than 4 L. Fecal samples of both the groups were collected in fecal collection containers twice, respectively. The first fecal samples were collected 2 days before surgery, while the second fecal samples were collected on the morning of the operation day. The containers were immediately stored in −80°C refrigerator (Jiang et al., 2019).

Anesthesia Management

When entering the operation room, every patient received the same anesthesia protocol. Routine monitoring consisted of continuous electrocardiogram, pulse oximetry, non-invasive blood pressure, and end-tidal carbon dioxide monitoring. A Bispectral index monitoring (A-2000; Aspect Medical System, Newton, MA, United States) was applied to the forehead of the patient before the induction of anesthesia. The arterial catheter was also inserted before induction for continuous invasive arterial blood pressure measurements (Yi et al., 2020). Induction was performed using sufentanil 0.5–1 μg/kg, midazolam 1 mg, propofol 1.5–2 mg/kg, and cisatracurium 0.2 mg/kg. After tracheal intubation, mechanical ventilation with 60% oxygen was provided. Tidal volume was adjusted to maintain normal arterial carbon dioxide according to blood gas analysis. The depth of anesthesia was controlled by altering the inhaled sevoflurane concentration, based on the hemodynamic response and bispectral index (BIS) values (target values range from 40 to 60). The maintenance infusion rate of cisatracurium was 1–1.5 μg/kg/min. Sufentanil at a total dose of 2–3 μg/kg was administered during the surgery. If MABP < 70 mmHg, patients were treated with norepinephrine, or phenylephrine immediately to ensure their MABP was larger than 70 mmHg. Cardiovascular active drugs such as isoprotereno were used if HR < 50 bmp (anticholinergic drugs were avoided). Cefazolin was used 30–60 min before surgery to prevent infection (Maekawa et al., 2020). Cefazolin was added every 3 h or when the bleeding volume was greater than 1,000 ml. The temperature of patients was controlled and monitored at 36.3–36.9°C in our study. All patients were scheduled to undergo radical gastrectomy by the assigned four surgeons.

After surgery, short-acting analgesics, such as IV injection of morphine 5–10 mg, were required according to the numerical rating scale of the patient. The dose was adjusted according to individual conditions until sufficient analgesic effect is achieved.

Basic Information Analysis

Demographic, anesthetic, and surgical information of all patients were documented to detect any statistical difference between the preparation and non-preparation groups.

The baseline cognitive function of the patients was assessed using the MMSE (score range 0–30) (Cryan and Dinan, 2012) before surgery, which was conducted by a physician of neurology who was blinded to the group assignment.

Postoperative recovery profiles and postoperative complications were also documented (Shin et al., 2015).

Outcome Measures

Incidence of Postoperative Delirium

The primary outcome was the incidence of the POD. POD was diagnosed by the 3-Min Diagnostic Interview for Confusion Assessment Method-defined delirium (3D-CAM) (Inouye et al., 1990). It consisted of four criteria: (I) acute fluctuating mentation, inattention (II), disorganized thinking (III), and (IV) altered level of consciousness. Patients that met criteria I and II and either III or IV were diagnosed with postoperative delirium. Every patient was assessed twice a day (8:am–10:am and 4:00 pm–6:00 pm) for 5 days successively after surgery by 2 trained physicians blinded to the trial.

Severity of Postoperative Delirium

For patients diagnosed with POD, the severity of delirium was then assessed by the short form of the Confusion Assessment Method-Severity (CAM-S). The assessment lasted until the score of patients of 3D-CAM returned to normal (Mutch et al., 2018). We recorded each score of CAM-S short form of patients diagnosed with POD and the duration of POD. Also, patients were evaluated by 2 trained physicians blinded to the trial.

Difference of Gut Microbiota Composition Between the Preparation Group and the Non-preparation Group

The 16S rDNA high-throughput sequencing was performed on fecal samples by Realbio Genomics Institute (Shanghai, China) to evaluate differences in the gut microbiota composition between the two groups. Bacterial diversity was assessed by α-diversity (Chao 1) and β diversity (principal coordinates analysis, PCoA) (Cole et al., 2014). The linear discriminant analysis (LDA) and effect size (LefSe) analysis were used to search different taxa of fecal microbiota between the two groups (Ren et al., 2020).

Basic Information and Alteration in the Taxa Between the Postoperative Delirium Groups and Non-postoperative Delirium Groups

Patients were diagnosed with delirium according to the 3D-CAM and thus all of them were assigned to two groups—the POD group and the non-POD group.

We documented demographic data, anesthetic and surgical data, and postoperative data in the POD group and non-POD group, analyzed the *P*-value, and conducted univariable and multivariate logistic regression to explore the risk factors of POD.

Apart from these, we examined the different microbiota between the second fecal samples of patients of the POD group and the non-POD group. The LefSe analysis was used to identify the different taxa of fecal microbiota between the POD and non-POD groups.

Statistic Methods

The SPSS (ver. 21.0, SPSS Inc., Chicago, IL, United States) and R software (ver. 3.1.0, the R Project for Statistical Computing) were used for statistical analysis. In this study, all statistical tests were two-sided, and difference achieving values of $P<$ 0.05 were considered statistically significant (Minai et al., 2014). We summarized patient demographics along with the surgical and anesthetic characteristics in the two groups. Data were expressed as mean [interquartile range (IQR) (range)] or mean (SD) and number (proportion). Categorical variables were compared by Pearson's chi-squared test with a continuity correction, or Fisher's exact test, if applicable (Minai et al., 2014). The Kolmogorov–Smirnov test was used to examine the normality of quantitative variables (Brons et al., 2012). Non-normally distributed quantitative variables were analyzed by the Mann–Whitney *U*-test (Minai et al., 2014). Normally distributed variables were analyzed by the Student's *t*-test.

The incidence of POD between groups was analyzed by Fisher's precision probability test. The severity and duration of POD between groups were analyzed by Mann–Whitney *U*-test. Baseline patient characteristics and MBP that were significant in the univariable analysis at a threshold $P < 0.1$ were entered into a forward multivariable logistic regression model. A multivariate logistic regression analysis was performed to evaluate the effects of the MBP after adjustment for potential confounding factors. *P*-values < 0.05 were considered to indicate statistical significance (Velayati et al., 2020).

All reads of fecal samples were deposited and grouped into operational taxonomic units (OUTs) at a sequence identity of 97%, and the taxonomic affiliation of the OTUs was determined according to quantitative insights into microbial ecology (QIME, version 2.0). The following downstream data analyses were conducted in R software. Bacterial diversity was determined by α diversity (Chao 1) and β diversity (PCoA). LEfSe was used as a tool to identify the differences in bacteria taxa between groups based on $P < 0.05$ and LDA score > 2.0 (Li et al., 2020).

The sample size was calculated based on the incidence of POD. The pilot trial showed that the incidence of POD was 30% (3/10) in the preparation group and 10% (1/10) in the control group, respectively. Assuming a two-sided α = 0.05 and statistical power of 0.8, the sample size was calculated to be 40 in each group. Considering a 20% loss to follow-up, we determined to enroll 96 patients in this study.

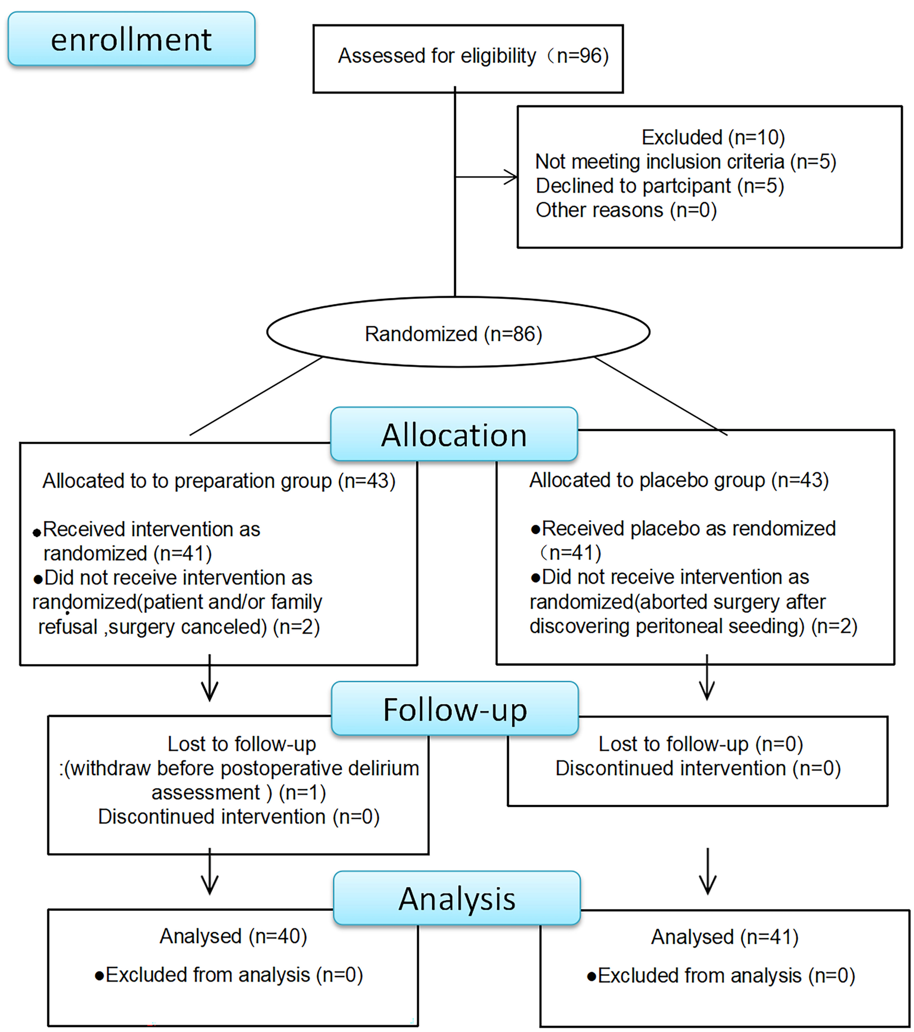

FIGURE 1 | Participants' recruitment and reasons for exclusions and treatment allocations.

RESULTS

Basic Information

A total of 96 patients were enrolled between November 2018 and November 2019. **Figure 1** illustrated participant recruitment, reasons for exclusions, and treatment allocations. Of all the patients, 10 were excluded before the trial. Of the remaining 86 patients, three in the preparation group and two in the non-preparation group dropped out. Finally, 40 subjects in the preparation group and 41 subjects in the non-preparation group were eligible for this trial.

TABLE 1 | Demographic data in the preparation group and non-preparation group.

	Pre group (n = 40)	Non-pre group (n = 41)
Male sex; *n*	25 (62.5%)	22 (53.7%)
Age;yr	73 (5)	74 (4)
BMI; kg/m^2	23.3 (3.0)	24.2 (3.1)
Education		
Primary school education	16 (40%)	21 (51%)
Secondary school education	21 (53%)	17 (42%)
University education	3 (7%)	3 (7%)
Heavy drinker*[1]		
Yes	10 (25%)	12 (29%)
No	30 (75%)	29 (71%)
Current smoker		
Yes	11 (28%)	9 (22%)
No	29 (72%)	32 (78%)
ASA physical status		
I	16 (40%)	15 (37%)
II	20 (50%)	21 (51%)
III	4 (10%)	5 (12%)
Preoperative baseline MMSE scores (0–30)	27.4 (1.6)	27.6(1.0)
Preoperative HAMD scores	2.6 (2.5)	3.0 (2.2)
Hemoglobin		
Normal	31 (78%)	33 (80%)
Abnormal	9 (22%)	8 (20%)
Tumor stage		
T1N0M0	12 (30%)	15 (37%)
T2N0M0	28 (70%)	26 (63%)
Diabetes		
Yes	13 (32.5%)	9 (22.0%)
No	27 (67.5%)	32 (78.0%)
Nutritional impairment*[2]		
Yes	2 (5%)	1 (2%)
No	38 (95%)	40 (98%)
Functional dependency*[3]		
Yes	0 (0%)	0 (0%)
No	40 (100%)	41 (100%)

Data were expressed as mean (SD), median [IQR (range)], or number (proportion). BMI, body mass index; MMSE, Mini-Mental State Examination; HAMD, Hamilton depression scale; pre group, preparation group; non-pre group, non-preparation group; *[1] Defined as current intake of alcohol, on average, 3–4 drinks per day at least four times per week; *[2] Defined as BMI < 18.5 kg/m^2; *[3] Defined as Functional Activities Questionnaire (FAQ) score ≥ 5.*

Table 1 illustrated the epidemiological information of all the patients recruited. There was no significant difference between the two groups in demographic information (**Table 1**). Detailed data of anesthesia and surgery were presented in **Table 2**. There was no significant between the two groups. As shown in **Table 3**, postoperative pain scores at 24, 48, and 72 h, and total morphine consumption were also similar between the two groups. There was also no significant difference in other clinical outcomes and postoperative complications between the two groups (**Table 3**).

Mechanical Bowel Preparation and Postoperative Delirium

Of all the 81 patients, 17 developed POD, making its morbidity 21.0%. The incidence of postoperative delirium was significantly higher in the preparation group than in the non-preparation group [32.5% (13 of 40) vs. 9.8% (4 of 41), P = 0.025]. **Figure 2** showed the number of patients with delirium on each of the 5 days after surgery from both groups. Most POD cases were observed on the first day after surgery [32.5% (13 of 40) in the preparation group vs. 9.8% (4 of 41) in the non-preparation group, P = 0.025]. The median [IQR (range)] severity of POD, expressed as the highest CAM-S scores, were similar between the preparation group and non-preparation group {4.0 [3.0–4.5 (3.0–5.0)] vs. 4.0 [3.3–4.8 (3.0–5.0)] points, P = 0.97}. Furthermore, there was no significant difference in POD duration between the preparation group and non-preparation group {2.0 [1.5–3.0 (1.0–4.0)] vs. 2.0 [1.0–3.0 (1.0–3.0)] days, P = 0.786}.

According to our result, the POD patients were 13 in the preparation group and 4 in the non-preparation group, so a total of 17 patients were classified into the POD group. The non-POD group patients were 27 in the preparation group and 37 in the non-preparation group, so a total of 64 patients in the non-POD group. Demographic data, anesthetic and surgical data, and postoperative data in the POD group and the non-POD group were documented and P-values were analyzed in **Supplementary Table 1**. The factors "age, duration of surgery, and mechanical bowel preparation" were significantly different in POD group and non-POD group (P = 0.025, P = 0.009, and P = 0.025, respectively). A similar result was acquired in the univariate analysis. We found that age [risk ratio, 1.16; 95% confidence interval (CI), 1.01–1.32; P = 0.032], duration of surgery (risk ratio, 1.01; 95% CI, 1.00–1.02; P = 0.019), and mechanical bowel preparation (risk ratio, 4.45; 95% CI, 1.31–15.17; P = 0.017) were significantly associated with delirium in univariate analysis. In multivariate analyses, when combining age and duration of surgery in multivariate analyses, we found that patients with MBP had a 4.792-fold higher odds of POD than those without MBP (CI: 1.274–18.028; P = 0.020) (**Table 4**).

Alternation of Gut Microbiota Between Preparation Group and Non-preparation Group

First, we explored the α-diversity and β-diversity of the gut microbiota in the preparation group and the non-preparation group before mechanical bowel preparation.

TABLE 2 | Anesthetic and surgical data in the preparation and non-preparation groups.

	Pre group (*n* = 25)	Non-pre group (*n* = 26)	*P*-value
Duration of surgery; min	190 [158–229 (95–436)]	210 [158–250 (120–407)]	0.431
Duration of anesthesia; min	250 [206–276 (130–480)]	255 [213–300 (155–466)]	0.422
EBL; ml	150 [100–200 (50–600)]	150 [100–275 (40–500)]	0.269

Data were expressed as mean (SD), median [IQR (range)], or number (proportion). EBL, estimated blood loss; pre group, preparation group; non-pre group, non-preparation group.

TABLE 3 | Postoperative data for the preparation group and non-preparation groups.

	Pre group (*n* = 40)	Non-pre group (*n* = 41)	*P*-value
Pain NRS score (0–10)			
24 h	3 [3–5 (0–9)]	3 [2–4 (0–7)]	0.346
48 h	3 [2–3 (0–5)]	3 [2–3 (0–5)]	0.335
72 h	2 [0–3 (0–3)]	1 [0–2 (0–3)]	0.274
Cumulative rescue morphine consumption; mg	4.3 (1.8)	4.7 (2.1)	0.225
Postoperative time out of bed; days	3 [2–4 (1–6)]	3 [2–4 (1–7)]	0.285
Length of hospital stay; days	8 [7–10 (3–21)]	9 [7–11 (5–24)]	0.337
Postoperative complications:			
Wound infection rate	2/40 (5.0%)	1/41 (2.4%)	0.616
Anastomotic leak rate	1/40 (2.5%)	0/41 (0.0%)	0.494
Postoperative bleeding rate	0/40 (0.0%)	1/41 (2.4%)	0.999
Gastroparesis rate	0/40 (0.0%)	0/41 (0.0%)	0.999
Dumping Syndrome rate	0/40 (0.0%)	0/41 (0.0%)	0.999
Duodenal stump rupture rate	0/40 (0.0%)	0/41 (0.0%)	0.999
Intestinal obstruction rate	1/40 (2.5%)	1/41 (2.4%)	0.999

Data were expressed as median (IQR[range]) or mean (SD) and number (proportion). NRS, numerical rating scale; pre group, preparation group; non-pre group, non-preparation group.

A-diversity refers to the diversity of bacteria or species within a community or habitat. It is mainly concerned with the number of bacteria or species (Bermon et al., 2015). B-diversity refers to the alternation rate of bacteria or species composition between different habitats along the environment gradient; it is also known as between-habitat diversity (Nakov et al., 2015).

We found that there was no difference in both α-diversity (**Figure 3A**) (P = 0.9) and β-diversity (**Figures 3C,E**) between the preparation group and non-preparation group before MBP (Adonis R^2 = 0.017, P = 0.618, based on the unweighted data; Adonis R^2 = 0.009, P = 0.855, based on the weighted). It indicated that the basic composition of gut microbiota between the preparation group and the non-preparation group was similar.

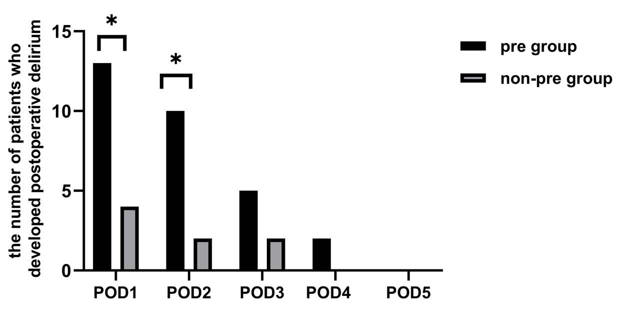

FIGURE 2 | The number of patients who developed postoperative delirium. There existed a difference between the two groups in the individual prevalence of delirium on POD 1 and 2 (P = 0.025 and P = 0.025). There was no significant difference between the two groups in the individual prevalence of delirium on POD 3, 4, and 5 (P = 0.409, P = 0.241, and P = 0.999, respectively). *pre-group*, *preparation group; non-pre group, non-preparation group.* *P < 0.05.

Then, we further investigated α-diversity and β-diversity of the gut microbiota in the preparation group and the non-preparation group after mechanical bowel preparation.

We found that there was no change in α-diversity between samples after MBP from 2 groups (P = 0.66) (**Figure 3B**). However, difference was found in β-diversity (**Figures 3D,F**) between the preparation group and the non-preparation group after MBP (Adonis R^2 = 0.038, P = 0.092, based on unweighted data; Adonis R^2 = 0.062, P = 0.048, based on the weighted). Taken together, we could infer that MBP did change the composition and state of gut microbiota.

Abundance of the Composition of Gut Microbiota in the Preparation Group and Non-preparation Group After Mechanical Bowel Preparation

We conducted a supervised comparison on the microbiota between the preparation group and the non-preparation group by utilizing the LEfSe analysis. We used a logarithmic LDA score with a cutoff value of 2.0 to identify important taxonomic differences between the preparation group and non-preparation group after MBP (**Figures 4A,B**). Our results

TABLE 4 | Univariable and multivariate logistic regression analysis of the factors associated with postoperative delirium.

Variables	Univariable			Multivariable		
	Unadjusted OR	95%CI	*P*-value	Adjusted OR	95%CI	*P*-value
Age	1.155	1.012, 1.317	0.032	1.200	1.030, 1.398	0.019
ASA physical status III	2.071	0.460, 9.319	0.343			
Preoperativebaseline MMSE scores	0.820	0.540, 1.245	0.351			
Duration of surgery	1.010	1.002, 1.018	0.019	1.010	1.001, 1.019	0.036
Duration of anesthesia	1.006	0.999, 1.014	0.107			
EBL	1.000	0.995, 1.005	0.953			
Mechanical bowel preparation	4.454	1.308, 15.169	0.017	4.792	1.274, 18.028	0.020

MMSE, Mini-Mental State Examination; EBL, estimated blood loss; OR, odds ratio.

suggested there was a remarkable difference in fecal microbiota between the two groups. We found that at the phylum level, the abundance of *Bacteroidetes* and *Fusobacteria* were obviously higher in the preparation group ($P < 0.05$), while *Actinobacteria* was more abundant in the non-preparation group. At the order level, *Pasteurellales* and *Bacillales* were obviously higher in the preparation group, while *Coriobacteriales* was higher in the non-preparation group. At the family level, *Pasteurellaceae* and *Neisseriaceae* were higher in the preparation group, while *Lactobacillaceae* and *Ruminococcaceae* were obviously higher in the non-preparation group. At the genus level*, Bacteroides, Enterobacter, Fusobacterium*, *Veillonella, Haemophilus*, *Aggreatibacter*, *Barnesiella,* and *Neisseria* were significantly higher in the preparation group ($P< 0.05$), while a relatively higher abundance of *Anaerotruncus, Coprobacillus, Lactobacillus, Blautia*, *Olsenella*, *Asaccharobacter*, *Gardnerella*, *Lachnospiracea_incertae_sedis,* and *Sporobacter* were in the non-preparation group (**Figures 4A,B**).

Alternations in the Taxa Between Postoperative Delirium and Non-postoperative Delirium Groups

To further investigate the correlation between gut microbiota and the incidence of POD, we examined the different microbiota between the second fecal samples of all POD patients (the total number is 17) and all the non-POD patients (the total number is 64) by the LEfSe analysis as we assumed it was this fecal status that caused POD in patients. We used a logarithmic LDA score cutoff of 2.0 to identify important taxonomic differences between the POD group and the non-POD group. Our results suggested a remarkable difference in fecal microbiota between the POD and non-POD groups. We found that the abundance of genus *Bacteroides*, *Mogibacterium, Campylobacter, Cloacibacillus*, *Clostridium XIVa*, *Peptostreptococcus*, and *Veillonella* were obviously higher in the POD group ($P < 0.05$), while the abundance of genus *Pseudomonas*, *Collinsella,* and *Olsenella* were significantly higher in the non-POD group (**Figure 5**).

Among them, *Bacteroides* genus and *Veillonella* genus significantly increased after MBP. Thus, we suspected that they might be the crime bacteria causing POD caused by MBP.

Olsenella genus was relatively higher in the non-preparation group which was also higher in the non-POD group. Thus we suspected that it might be a beneficial bacteria to reduce the incidence of POD.

DISCUSSION

According to our result, we found that mechanical bowel preparation could increase the incidence of POD in patients who underwent radical gastrectomy. Also, we found that the alternation of the gut microbiota caused by MBP, especially the abundance of *Bacteroides* and *Veillonella,* might be a risk factor of POD.

Mechanical bowel preparation (MBP) for elective gastric surgery has long been regarded as a clinical routine for many decades. Recently, it is reported that MBP introduces alterations to the intestinal microbiota. However, the results are not identical. In our study, we found that bowel preparation introduces significant alternations to the intestinal microbiota in terms of β-diversity (based on the weighted, Adonis $R^2 = 0.062$, $P = 0.048$). We found that the abundance of genus *Bacteroidetes*, *Enterobacter, Fusobacterium*, *Veillonella, Haemophilus*, *Aggreatibacter*, *Barnesiella,* and *Neisseria* were obviously higher in the preparation group, while genus *Anaerotruncus, Coprobacillus, Lactobacillus, Blautia*, *Olsenella*, *Asaccharobacter*, *Gardnerella*, *Lachnospiracea_incertae-sedis,* and *Sporobacter* were in the non-preparation group ($P < 0.05$).

It was easy to understand some taxa of microbiota were decreased after MBP. However, there are several taxa of microbiota elevated after MBP. We speculated these bacteria could replicate more freely when some other bacteria were decreased by MBP.

More importantly, we found that MBP is a risk factor of POD (32.5% vs. 9.8%, $P = 0.025$). The multivariate analysis revealed that patients with MBP had a 4.792-fold higher odds of POD than those without MBP (CI: 1.274–18.028; $P = 0.020$). Apart from MBP, delirium was also associated with patients' age and the duration of surgery according to our results, which were consistent with previous findings (Fukata et al., 2017). Our result showed that other factors such as ASA physical status III and intraoperative hypotension were not associated with POD, as other studies (Marcantonio et al., 1998). Wang et al. (2015) has found that intraoperative blood loss of less than 300 ml would not contribute to POD. As only five patients whose blood loss

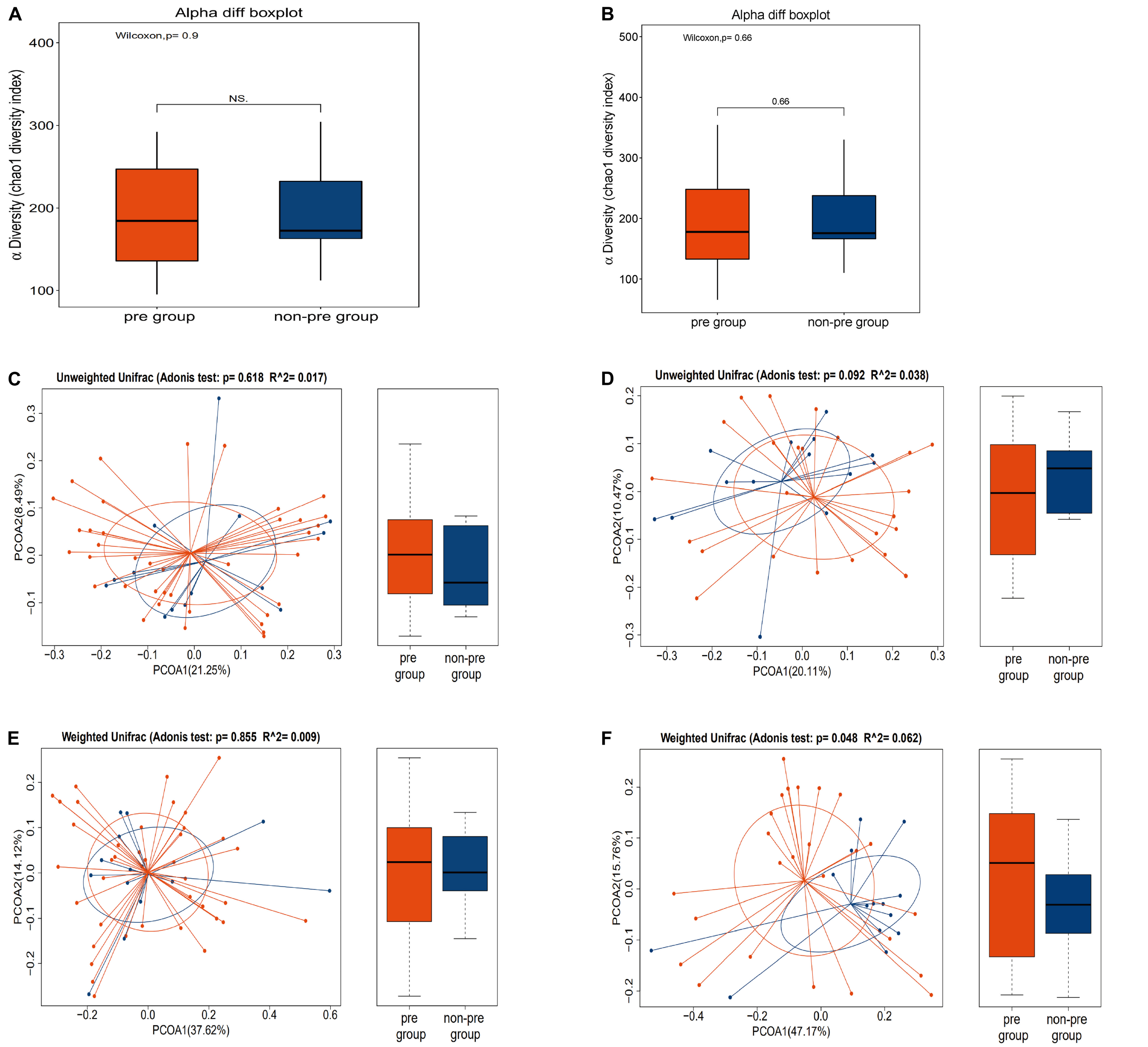

FIGURE 3 | (A,C,E) Different profiles of the gut microbiota before MBP between the preparation group and non-preparation group. **(A)** α-diversity: box plots showed differences in the fecal microbiome diversity indices between the two groups according to the Chao 1 index based on the OTU counts. **(C)** β-diversity: outcome of Adonis tests with Unweighted UniFracs distances for the two groups. **(E)** β-diversity: outcome of Adonis tests with Weighted UniFracs distances for the two groups. The yellow plot showed data of the preparation group, and the blue plot showed data of the non-preparation group. **(B,D,F)** Different profiles of the gut microbiota after MBP between the preparation group and non-preparation group. **(B)** α-diversity: box plots showed differences in the fecal microbiome diversity indices between the two groups according to the Chao 1 index based on the OTU counts. **(D)** β-diversity: outcome of Adonis tests with Unweighted UniFracs distances for the two groups. **(F)** β-diversity: outcome of Adonis tests with Weighted UniFracs distances for the two groups. The yellow plot showed data of the preparation group, and the blue plot showed data of the non-preparation group.

was greater than 300 ml. So we did not find it as a risk factor for POD. Other factors might cause POD, like cognitive impairment would interfere with the incidence of POD (Fukata et al., 2017). However, as a prospective study, we created inclusion criteria for patients, like that the preoperative baseline MMSE scores of all the patients selected in our study were higher than 24. So we did not find factors like preoperative baseline MMSE scores as a risk factor for POD. According to a previous study, anticholinergic drugs are commonly associated with cognitive changes, namely, hallucinations, and overt delirium (Molchan et al., 1992). So anticholinergic drugs were replaced by other cardiovascular active drugs such as isoprotereno in our study when the heart rate fell. Masatsugu Hiraki has found that maximum intraoperative temperature ≥ 37°C is an independent risk factor of early postoperative delirium after laparoscopic colorectal surgery in elderly patients (Hiraki et al., 2021). So we strictly controlled and monitored the patients' temperature at 36.3–36.9°C.

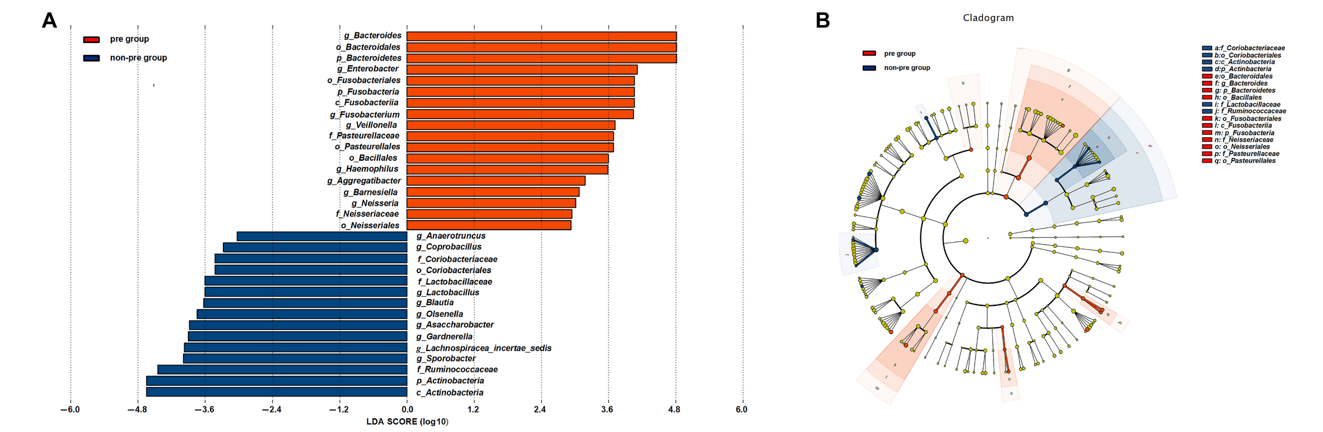

FIGURE 4 | (A) Changes in the gut microbiota after mechanical bowel preparation. The histogram of the LDA scores presented the relative abundance of the main bacterial in the two groups in the fecal samples. Blue boxes referred to the bacteria contributing a lot in the non-preparation groups, yellow boxes referred to the bacteria contributing a lot in the preparation group. **(B)** LEfSe results in a cladogram on fecal microbiomes between the two groups. Taxonomic representation of statistically and biologically consistent differences between the two groups. Each circle's diameter was proportional to the taxon's abundance. Blue nodes referred to the bacteria contributing a lot in the non-preparation groups, yellow nodes referred to the bacteria contributing a lot in the preparation group.

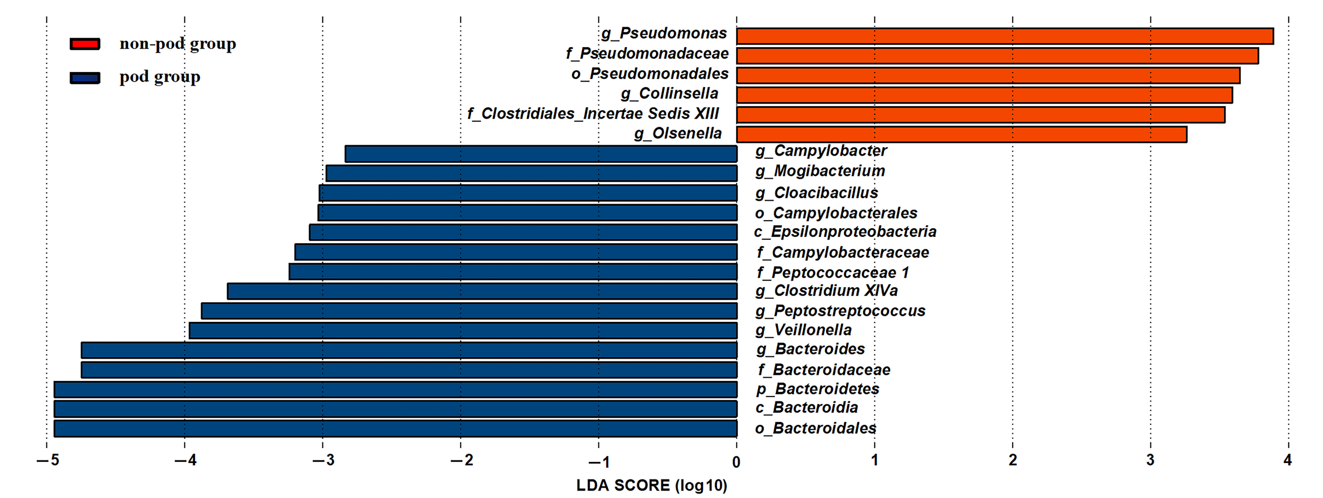

FIGURE 5 | Changes in the gut microbiota between the POD group and non-POD group. The histogram of the LDA scores presented the relative abundance of the main bacterial in the two groups in the fecal samples. Blue boxes referred to the bacteria contributing a lot in the POD groups, yellow boxes referred to the bacteria contributing a lot in the non-POD group.

Next, we analyzed the difference in gut microbiota between the POD groups and non-POD groups. Among them, the abundance of genus *Bacteroides* and *Veillonella* were higher in the MBP group than the non-MBP group when we compared the second fecal samples between the groups. Thus, we considered the increased abundance of *Bacteroides* and *Veillonella* after MBP might be a factor causing POD in patients scheduled for radical gastrectomy in this study.

A previous study has found that *Bacteroides* could impair cognitive function (Cattaneo et al., 2017). Saji et al. (2019) have found that an increased prevalence of *Bacteroides* is independently associated with the presence of mild cognitive impairment. Apart from these, some other studies revealed that patients with Alzheimer's disease have a larger population of *Bacterodietes* in their gut (Guo et al., 2021). These results could support our study that *Bacteroides* might be a risk factor for POD.

Moreover, a previous study has also revealed that the genus *Veillonella* (Liu et al., 2021) which belongs to the phylum Firmicutes, contributed to cognitive dysfunction. Liu et al. (2021) have found that *Veillonellacea* was negatively correlated with orientation and delayed in patients with mild cognitive impairment. V*eillonellaceae* was also associated with the severity of schizophrenia (Zheng et al., 2019). According to our result, the genus *Veillonella* might also play a role in causing POD.

We also found that the genus *Pseudomonas*, *Collinsella*, and *Olsenella* were relatively higher in the non-POD group. So, these genera could be assumed to have protective effects on cognitive function.

The relative abundance of *Olsenella* was also higher in the non-preparation group, further indicating its role in preventing POD. It has been reported that most of *Olsenella* could produce acetic acid, one part of SCFAs (Zhang et al., 2020). The SCFAs (mainly acetate, propionate, and butyrate) exert crucial physiological effects against several cognitive dysfunction, namely, depression, Alzheimer's disease (AD), and Parkinson's disease (PD), and autism spectrum disorder (ASD) (Dalile et al., 2019). Furthermore, SCFA administration has been proposed as a treatment target for such cognitive dysfunction (Dalile et al., 2019). So, we speculated that *Olsenella* might help reduce the incidence of POD by producing SCFAs.

Pseudomonas genus has been found to do good to the nervous system. It was reported that halophilic crude (extracts from *Pseudomonas zhaodongensis*) exerted protective effects against memory deficits and anxiety- and depression-like behaviors in methionine-induced schizophrenia in mice (Massaoudi et al., 2020), which was consistent with our results.

However, the role of *Collinsella* on the nervous system was not consistent. *Collinsella* was found to be increased in patients with AD but decreased in relapsing-remitting multiple sclerosis which is a disease also presenting cognitive dysfunction (Ling et al., 2020). Another study found that diet introduced *Collinsella* increasing did not interfere with cognition (van Soest et al., 2020). Further study is needed to validate its function in cognition as many factors such as different disease patterns, sequencing techniques, and geographical location might be responsible for the different roles of *Collinsella*.

As for other bacteria altered after MBP, although we did not find a correlation between them and POD, they are still worth studying. Among them, the genus *Lactobacillus*, family *Ruminococcaceae* were significantly decreased after MBP. Many studies have shown that they are beneficial to the central nervous system. Wen et al. (2020) showed that *Lactobacillus* protected the postoperative cognitive functions of the aged mice with gut dysbiosis. It could also prevent the learning and memory deficits induced by anesthesia/surgery (Jiang et al., 2019). Another study has found that probiotic consumption (containing *Lactobacillus*) for 12 weeks improved cognitive function in patients with AD (Akbari et al., 2016).

Furthermore, Zhang et al. (2019) have found that POD mice had fewer *Ruminococcaceae* compared with the non-POD ones in their digestive tract. Ren et al. (2020) have found that patients with PD who present cognitive impairment had a lower abundance of genus *Ruminococcus* in their fecal samples. With more patients enrolled, we might identify more exact taxa of gut microbiota contribute to POD or cognitive dysfunction.

Our study does have limitations. One limitation of this study was the relatively small number of patients enrolled. Further studies are needed to detect the effect of MBP on a greater number of individuals; another limitation was that our study mainly focused on the instant effect of changes in the microbiota composition on patients' cognitive function. We will continue to monitor a relatively long time of patients' cognitive status to detect the long-term impact of MBP on patients' cognitive function and gut microbiota.

CONCLUSION

In conclusion, we found that, compared with the non-preparation group, mechanical bowel preparation increased the incidence of postoperative delirium in the patient with gastric cancer. Among all the genera altered by the MBP, genus *Bacteroides* and genus *Veillonella*, which were increased in the POD group, might participate in the pathogenesis of POD. Meanwhile, genus *Olsenella* which was relatively higher in both the non-preparation and non-POD groups might reduce the incidence of POD.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: doi: 10.6084/m9.figshare.18095891.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethical committee of Huashan Hospital (approval number: KY2018-354). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YW designed the study, revised the manuscript, and participated in the final approval of the version to be submitted. ZY was involved in writing the manuscript and interpreting the data. CT collected the data and analyzed the data. XQ collected the data and completed figures and tables. HW revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

Akbari, E., Asemi, Z., Daneshvar Kakhaki, R., Bahmani, F., Kouchaki, E., Tamtaji, O. R., et al. (2016). Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. *Front. Aging Neurosci.* 8:256. doi: 10.3389/fnagi.2016.00256

Bermon, S., Petriz, B., Kajeniene, A., Prestes, J., Castell, L., and Franco, O. L. (2015). The microbiota: an exercise immunology perspective. *Exerc. Immunol. Rev.* 21, 70–79.

Brons, C., Jacobsen, S., Hiscock, N., White, A., Nilsson, E., Dunger, D., et al. (2012). Effects of high-fat overfeeding on mitochondrial function, glucose and fat metabolism, and adipokine levels in low-birth-weight subjects. *Am. J. Physiol. Endocrinol. Metab.* 302, E43–E51. doi: 10.1152/ajpendo.00095.2011

Brouquet, A., Cudennec, T., Benoist, S., Moulias, S., Beauchet, A., Penna, C., et al. (2010). Impaired mobility, ASA status and administration of tramadol are risk factors for postoperative delirium in patients aged 75 years or more after major abdominal surgery. *Ann. Surg.* 251, 759–765. doi: 10.1097/SLA.0b013e3181c1cfc9

Cattaneo, A., Cattane, N., Galluzzi, S., Provasi, S., Lopizzo, N., Festari, C., et al. (2017). Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol. Aging* 49, 60–68. doi: 10.1016/j.neurobiolaging.2016.08.019

Cole, J. R., Wang, Q., Fish, J. A., Chai, B., Mcgarrell, D. M., Sun, Y., et al. (2014). Ribosomal Database Project: data and tools for high throughput rRNA analysis. *Nucleic Acids Res.* 42, D633–D642. doi: 10.1093/nar/gkt1244

Cryan, J. F., and Dinan, T. G. (2012). Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci.* 13, 701–712. doi: 10.1038/nrn3346

Dalile, B., Van Oudenhove, L., Vervliet, B., and Verbeke, K. (2019). The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat. Rev. Gastroenterol. Hepatol.* 16, 461–478. doi: 10.1038/s41575-019-0157-3

Drago, L., Toscano, M., De Grandi, R., Casini, V., and Pace, F. (2016). Persisting changes of intestinal microbiota after bowel lavage and colonoscopy. *Eur. J. Gastroenterol. Hepatol.* 28, 532–537. doi: 10.1097/Meg.0000000000000581

Fukata, S., Kawabata, Y., Fujishiro, K., Kitagawa, Y., Kuroiwa, K., Akiyama, H., et al. (2017). Haloperidol prophylaxis for preventing aggravation of postoperative delirium in elderly patients: a randomized, open-label prospective trial. *Surg. Today* 47, 815–826. doi: 10.1007/s00595-016-1441-2

Guo, M., Peng, J., Huang, X., Xiao, L., Huang, F., and Zuo, Z. (2021). Gut microbiome features of Chinese patients newly diagnosed with Alzheimer's disease or mild cognitive impairment. *J. Alzheimers Dis.* 80, 299–310. doi: 10.3233/jad-201040

Hiraki, M., Tanaka, T., Ishii, H., Sadashima, E., Miura, D., Sunami, T., et al. (2021). A clinical risk analysis of early post-operative delirium after laparoscopic colorectal cancer surgery in elderly patients: a retrospective study. *Int. J. Colorectal Dis.* 36, 1461–1468. doi: 10.1007/s00384-021-03919-5

Inouye, S. K., Van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P., and Horwitz, R. I. (1990). Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann. Intern. Med.* 113, 941–948. doi: 10.7326/0003-4819-113-12-941

Jiang, X. L., Gu, X. Y., Zhou, X. X., Chen, X. M., Zhang, X., Yang, Y. T., et al. (2019). Intestinal dysbacteriosis mediates the reference memory deficit induced by Anaesthesia/surgery in aged mice. *Brain Behav. Immun.* 80, 605–615. doi: 10.1016/j.bbi.2019.05.006

Li, G. Q., Zhang, T., Yang, W. G., Zhong, H. L., Xiao, P., Liu, L. W., et al. (2020). Gut microbiota patterns associated with somatostatin in patients undergoing pancreaticoduodenectomy: a prospective study. *Cell Death Discov.* 6:94. doi: 10.1038/s41420-020-00329-4

Ling, Z., Zhu, M., Yan, X., Cheng, Y., Shao, L., Liu, X., et al. (2020). Structural and functional dysbiosis of fecal microbiota in Chinese patients with Alzheimer's disease. *Front. Cell Dev. Biol.* 8:634069. doi: 10.3389/fcell.2020.634069

Liu, P., Jia, X. Z., Chen, Y., Yu, Y., Zhang, K., Lin, Y. J., et al. (2021). Gut microbiota interacts with intrinsic brain activity of patients with amnestic mild cognitive impairment. *CNS Neurosci. Ther.* 27, 163–173. doi: 10.1111/cns.13451

Luangchosiri, C., Thakkinstian, A., Chitphuk, S., Stitchantrakul, W., Petraksa, S., and Sobhonslidsuk, A. (2015). A double-blinded randomized controlled trial of silymarin for the prevention of antituberculosis drug-induced liver injury. *BMC Complement. Altern. Med.* 15:334. doi: 10.1186/s12906-015-0861-7

Maekawa, M., Yoshitani, K., Yahagi, M., Asahara, T., Shishido, Y., Fukushima, S., et al. (2020). Association between postoperative changes in the gut microbiota and Pseudopsia after cardiac surgery: prospective observational study. *BMC Surg.* 20:247. doi: 10.1186/s12893-020-00907-4

Mai, V., Greenwald, B., Morris, J. G. Jr., Raufman, J. P., and Stine, O. C. (2006). Effect of bowel preparation and colonoscopy on post-procedure intestinal microbiota composition. *Gut* 55, 1822–1823. doi: 10.1136/gut.2006.108266

Marcantonio, E. R. (2017). Delirium in hospitalized older adults. *N. Engl. J. Med.* 377, 1456–1466. doi: 10.1056/NEJMcp1605501

Marcantonio, E. R., Goldman, L., Orav, E. J., Cook, E. F., and Lee, T. H. (1998). The association of intraoperative factors with the development of postoperative delirium. *Am. J. Med.* 105, 380–384. doi: 10.1016/s0002-9343(98)00292-7

Massaoudi, Y., Anissi, J., Lefter, R., Lobiuc, A., Sendide, K., Ciobica, A., et al. (2020). Protective effects of two halophilic crude extracts from *Pseudomonas* zhaodongensis and *Bacillus stratosphericus* against memory deficits and anxiety- and depression-like behaviors in methionine-induced schizophrenia in mice focusing on oxidative stress status. *Evid. Based Complement. Alternat. Med.* 2020:8852418. doi: 10.1155/2020/8852418

Minai, K., Ogawa, T., Kawai, M., Komukai, K., Tanaka, T., Ogawa, K., et al. (2014). The plasma B-type natriuretic peptide levels are low in males with stable ischemic heart disease (IHD) compared to those observed in patients with non-IHD: a retrospective study. *PLoS One* 9:e108983. doi: 10.1371/journal.pone.0108983

Molchan, S. E., Martinez, R. A., Hill, J. L., Weingartner, H. J., Thompson, K., Vitiello, B., et al. (1992). Increased cognitive sensitivity to scopolamine with age and a perspective on the scopolamine model. *Brain Res. Brain Res. Rev.* 17, 215–226. doi: 10.1016/0165-0173(92)90017-g

Mutch, W. a. C., El-Gabalawy, R., Girling, L., Kilborn, K., and Jacobsohn, E. (2018). End-tidal hypocapnia under anesthesia predicts postoperative delirium. *Front. Neurol.* 9:678. doi: 10.3389/fneur.2018.00678

Nagata, N., Tohya, M., Fukuda, S., Suda, W., Nishijima, S., Takeuchi, F., et al. (2019). Effects of bowel preparation on the human gut microbiome and metabolome. *Sci. Rep.* 9:4042. doi: 10.1038/s41598-019-40182-9

Nakov, T., Ashworth, M., and Theriot, E. C. (2015). Comparative analysis of the interaction between habitat and growth form in diatoms. *ISME J.* 9, 246–255. doi: 10.1038/ismej.2014.108

O'Brien, C. L., Allison, G. E., Grimpen, F., and Pavli, P. (2013). Impact of colonoscopy bowel preparation on intestinal microbiota. *PLoS One* 8:e62815. doi: 10.1371/journal.pone.0062815

Oh, E. S., Fong, T. G., Hshieh, T. T., and Inouye, S. K. (2017). Delirium in older persons: advances in diagnosis and treatment. *JAMA* 318, 1161–1174. doi: 10.1001/jama.2017.12067

Pascale, A., Marchesi, N., Marelli, C., Coppola, A., Luzi, L., Govoni, S., et al. (2018). Microbiota and metabolic diseases. *Endocrine* 61, 357–371. doi: 10.1007/s12020-018-1605-5

Ren, T., Gao, Y., Qiu, Y., Jiang, S., Zhang, Q., Zhang, J., et al. (2020). Gut microbiota altered in mild cognitive impairment compared with normal cognition in sporadic Parkinson's disease. *Front. Neurol.* 11:137. doi: 10.3389/fneur.2020.00137

Ridaura, V., and Belkaid, Y. (2015). Gut microbiota: the link to your second brain. *Cell* 161, 193–194. doi: 10.1016/j.cell.2015.03.033

Saji, N., Murotani, K., Hisada, T., Tsuduki, T., Sugimoto, T., Kimura, A., et al. (2019). The relationship between the gut microbiome and mild cognitive impairment in patients without dementia: a cross-sectional study conducted in Japan. *Sci. Rep.* 9:19227. doi: 10.1038/s41598-019-55851-y

Shin, Y. H., Kim, D. K., and Jeong, H. J. (2015). Impact of surgical approach on postoperative delirium in elderly patients undergoing gastrectomy: laparoscopic versus open approaches. *Korean J. Anesthesiol.* 68, 379–385. doi: 10.4097/kjae.2015.68.4.379

Sprung, J., Roberts, R. O., Weingarten, T. N., Nunes Cavalcante, A., Knopman, D. S., Petersen, R. C., et al. (2017). Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. *Br. J. Anaesth.* 119, 316–323. doi: 10.1093/bja/aex130

van Soest, A. P. M., Hermes, G. D. A., Berendsen, A. a. M., Van De Rest, O., Zoetendal, E. G., Fuentes, S., et al. (2020). Associations between pro- and anti-inflammatory gastro-intestinal microbiota, diet, and cognitive functioning in Dutch healthy older adults: the NU-AGE study. *Nutrients* 12:3471. doi: 10.3390/nu12113471

Velayati, A., Vahdat Shariatpanahi, M., Dehghan, S., Zayeri, F., and Vahdat Shariatpanahi, Z. (2020). Vitamin D and postoperative delirium after coronary artery bypass grafting: a prospective cohort study. *J. Cardiothorac. Vasc. Anesth.* 34, 1774–1779. doi: 10.1053/j.jvca.2020.02.008

Wang, J., Li, Z., Yu, Y., Li, B., Shao, G., and Wang, Q. (2015). Risk factors contributing to postoperative delirium in geriatric patients postorthopedic surgery. *Asia Pac. Psychiatry* 7, 375–382. doi: 10.1111/appy.12193

Wen, J., Ding, Y., Wang, L., and Xiao, Y. (2020). Gut microbiome improves postoperative cognitive function by decreasing permeability of the blood-brain barrier in aged mice. *Brain Res. Bull.* 164, 249–256. doi: 10.1016/j.brainresbull.2020.08.017

Yi, P., Li, Q., Yang, Z., Cao, L., Hu, X., and Gu, H. (2020). High-flow nasal cannula improves clinical efficacy of airway management in patients undergoing awake craniotomy. *BMC Anesthesiol.* 20:156. doi: 10.1186/s12871-020-01073-z

Zhang, J., Bi, J. J., Guo, G. J., Yang, L., Zhu, B., Zhan, G. F., et al. (2019). Abnormal composition of gut microbiota contributes to delirium-like behaviors after abdominal surgery in mice. *CNS Neurosci. Ther.* 25, 685–696. doi: 10.1111/cns.13103

Zhang, W., Zou, G., Li, B., Du, X., Sun, Z., Sun, Y., et al. (2020). Fecal microbiota transplantation (FMT) alleviates experimental colitis in mice by gut microbiota regulation. *J. Microbiol. Biotechnol.* 30, 1132–1141. doi: 10.4014/jmb.2002.02044

Zheng, P., Zeng, B., Liu, M., Chen, J., Pan, J., Han, Y., et al. (2019). The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. *Sci. Adv.* 5:eaau8317. doi: 10.1126/sciadv.aau8317

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Potential Value of Serum Lipid in the Identication of Postoperative Delirium Undergoing Knee/Hip Arthroplasty: The Perioperative Neurocognitive Disorder and Biomarker Lifestyle Study

Yanan Lin[1], Xiaoyan Peng[1], Xu Lin[1], Xiyuan Deng[2], Fanghao Liu[1], He Tao[2], Rui Dong[3], Bin Wang[1]* and Yanlin Bi[1]**

[1] Department of Anesthesiology, Qingdao Municipal Hospital Affiliated to Qingdao University, Qingdao, China, [2] Department of Anesthesiology, Dalian Medical University, Dalian, China, [3] Department of Anesthesiology, Drum Tower Hospital Affiliated to Nanjing University Medical School, Nanjing, China

Objective: We aimed to investigate the relationship between preoperative lipid level and postoperative delirium (POD) and explore whether lipid's effect on POD is mediated by POD core protein.

Methods: A total of 635 patients who were planned to undergo knee/hip arthroplasty under combined spinal-epidural anesthesia, regardless of gender, were selected. The patients were aged 40–90 years with American Society of Anesthesiologists physical status I II. The Mini-Mental State Examination (MMSE) was completed 1 day before the operation. Five milliliter elbow venous blood was taken from the patients before anesthesia, and serum levels of total cholesterol (TG), triglyceride (TC), low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) were detected. Cerebrospinal fluid (CSF) was extracted after successful spinal-epidural combined puncture, and amyloid beta$_{40}$ (Aβ_{40}), amyloid beta$_{42}$ (Aβ_{42}), total Tau (t-Tau), and phosphorylated Tau (p-Tau) in the CSF were measured by enzyme-linked immunosorbent assays (ELISA). After the operation, the occurrence and severity of POD were assessed using the Confusion Assessment Method and the Memorial Delirium Assessment Scale (MDAS), respectively. Patients were categorized into POD group and NPOD group. Logistic regression was used to analyze the relationship between POD and TC, TG, LDL-C, and HDL-C, and the mediating effect was used to analyze the role of POD core proteins in the relationship between lipid and MDAS. We used the receiver operating characteristic (ROC) and the precision-recall curve (PRC) analysis to assess the ability of TC, TG, LDL-C, and HDL-C ability to predict POD. Finally, we performed a sensitivity analysis to assess the stability of the results.

Results: A total of 562 patients were finally enrolled in this study, and 66 patients developed POD, with an incidence of 11.7%. Logistic regression analysis showed that high concentration of TC (OR = 3.148, 95%CI 1.858~5.333, $P < 0.001$), TG

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Edited by:
*Yiying Zhang,
Massachusetts General Hospital and Harvard Medical School, United States*

Reviewed by:
*Wenyu Song,
Brigham and Women's Hospital and Harvard Medical School, United States
Biyue Zhu,
Massachusetts General Hospital and Harvard Medical School, United States
Xiaoyu Yang,
University of California, San Francisco, United States*

***Correspondence:**
*Xu Lin
linxu_green@126.com
Bin Wang
wangbin328@sina.com
Yanlin Bi
pndable2021@sina.com*

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(OR = 2.483, 95%CI 1.573∼3.918, $P < 0.001$), and LDL-C (OR = 2.469, 95%CI 1.310∼4.656, $P = 0.005$) in serum were risk factors for POD. A high concentration of HDL-C (OR = 0.258, 95%CI 0.112∼0.594, $P = 0.001$) was a protective factor for POD after adjusted for age, sex, education, and MMSE score. ROC curves showed that HDL-C have the highest sensitivity and specificity in predicting POD. For these four lipid markers, the PRC range from 0.602 to 0.731, respectively. The mediating analysis showed that POD core proteins could partially mediate the relationship between lipid and POD (effect value: 16.19∼91.04%). The results were barely changed in the sensitivity analysis, and the sensitivity analysis has shown that the results were stable.

Conclusion: The increase of serum TG, TC, and LDL-C concentration is a risk factor for POD development, while high HDL-C concentration is a protective factor for POD, and the occurrence of POD is caused by hyperlipidemia may be caused by POD core proteins.

Clinical Trial Registration: [www.ClinicalTrials.gov], identifier [Chictr200033439].

Keywords: delirium, triglycerides (TG), cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), mediation effect

INTRODUCTION

Postoperative delirium (POD) is one of the most common complications in patients after surgery. POD may bring about a decline in cognitive ability, impair environmental interpretation, attention-deficit disorder, and dyssomnia (1). Moreover, it can ultimately lead to adverse outcomes such as an increased incidence of postoperative complications, more extended hospital stays, increased medical costs, and increased postoperative mortality (2). In consequence, it is of great importance to explore the effective forecasting methods for POD occurrence.

Metabolic disorder of blood lipids is also familiar in senior citizens. Some researchers found that hemorheology was associated with cognitive decline (3). Hyperlipidemia can lead to abnormal deposition of lipids in vascular endothelium and formation of atherosclerosis, damage the blood-brain barrier, resulting in abnormal accumulation of lipids in the brain, finally leading to the occurrence of neurodegenerative diseases. Changes in lipid-related metabolism and transport levels played a role in the prediction of Alzheimer's disease (AD) (4), and plasma lipid metabolism levels in patients with cognitive impairment were also apparent differences from those in the normal subjects (5). Furthermore, elevated plasma triglyceride levels precede Amyloid-beta (Aβ) protein deposition (6), the value of triglyceride in predicting the occurrence of AD is not negligible. Hypercholesterolemia can exacerbate Aβ protein deposition in animal models (7), while in humans, lowering cholesterol levels can reduce the Aβ burden and reduce AD occurrence (8). A Retrospective cohort study shows that high cholesterol increases the risk of dementia (9). Aβ abnormal deposition is proportional to neurotoxicity (10, 11), abnormally phosphorylated tau protein deposited in cells to can form neurofibrillary tangles, which all can cause neurodegeneration finally (12). It is a neurodegenerative disease with AD, and delirium pathophysiology is similar to AD (13, 14). For the time being, however, there is still a lack of studies concerning whether Aβ and tau could modulate the relationships of hemorheology with POD.

Thus, we aimed to investigate the relevance between lipid levels and POD, test whether the influences of lipids on delirium were mediated by POD core pathology. All these analyses were conducted based on the Perioperative Neurocognitive Disorder and Biomarker Lifestyle (PNDABLE) study.

MATERIALS AND METHODS

Participants

A total of 635 Han Chinese patients who were planned to undergo knee or hip arthroplasty under combined spinal-epidural anesthesia were selected from the PNDABLE study. The trial was carried out at Qingdao Municipal Hospital in Shandong Province, China. The PNDABLE study is an ongoing, large-sample cohort study that began in 2018 to explore the pathogenesis, risk factors, and biomarkers of perioperative neurocognitive dysfunction (PND) in the Han Chinese population in northern China for early detection, diagnosis, and intervention of PND. Cerebrospinal fluid (CSF) and blood samples were collected from all enrolled patients after they signed informed consent. The Ethics Committee (Ethical Committee N 2020 *PRO FORMA* Y number 005) approved this study of Qingdao Municipal Hospital.

We included the following patients: (1) The patients were aged 40 90 years old; (2) American Society of Anesthesiologists physical status(ASA)I∼II; (3) The patients had intact preoperative cognitive function without communication disorders; (4) The patients had sufficient education to complete the preoperative neuropsychological tests. Exclusion criteria included: (1) Mini-Mental State Examination (MMSE) scores of

23 or less; (2) ASA III or higher level; (3) Serious psychological disorders; (4) Severe systemic diseases that may affect related biomarkers in CSF or blood, including but not limited to malignant tumors; (5) Familial genetic diseases; (6) Coagulation dysfunction (possibly due to the long-term use of anticoagulants);

Cognitive Measurements

The MMSE was used to evaluate the basic cognitive level of the patients the day before surgery. The Confusion Assessment Method (CAM) (15) was used to evaluate the postoperative cognitive level at 9:00–10:00 a.m. and at 2:00–3:00 p.m. twice a day on 1–7 days (or before discharge) by an anesthesiologist post-operatively. The diagnostic criteria for POD were as follows: ① acute changes and repeated fluctuations in the state of consciousness; ② lack of attention; ③ disorganized thinking; ④ alterations in the level of consciousness. CAM was determined to be positive if both ① and ② were present on any day, and at the same time either ③ or ④ was met. According to the assessment results, they were divided into the POD group and the NPOD group. Moreover, the POD severity was assessed using the MDAS (16).

Anesthesia and Surgery

All the patients did not need any medication preoperatively. After the patients entered the operating room, peripheral veins were opened, and the same team of surgeons performed knee or hip arthroplasty. ECG, pulse blood oxygen saturation monitoring, and non-invasive arterial pressure measurement were routinely conducted. After the preparation was completed, the spinal and epidural anesthesia was performed in the lateral decubitus under $L_{3\sim4}$ space. After a successful puncture, 0.67% ropivacaine 2.0 ∼ 2.5 ml was injected into the subarachnoid space, and then 3–5 ml 2% lidocaine was added into the epidural catheter according to actual needs to maintain the level of anesthesia at $T_8 \sim S_5$. If the intraoperative systolic blood pressure of the patient was < 90 mmHg, intravenous ephedrine 6 mg was given; If the patient's heart rate was < 50 bpm, an intravenous injection of atropine 0.5 mg was given. Every patient was treated with a patient-controlled intravenous analgesia pump (Tropisetron 5 mg + Butorphanol Tartrate Injection 10 mg, diluted to 100 ml with normal saline at a rate of 2 ml/h) for 48 h postoperatively. After the operation, the patient was sent to the recovery room, observed for 30 min, and sent back to the ward if there was no abnormality. The duration of surgery, duration of anesthesia, intraoperative blood loss, and fluid input were recorded.

Measurements of Cerebrospinal Fluid Sampling and Blood Sampling

After successful spinal-epidural anesthesia puncture, 2 ml of CSF was taken in 10 mL polypropylene tubes and sent to the laboratory within 2 h. The CSF samples were immediately centrifuged at 2,000 g at room temperature for 10 min and then stored at -80°C for further analysis. The levels of $A\beta_{40}$, $A\beta_{42}$, t-Tau and p-Tau in CSF were determined by enzyme-linked immunosorbent assays (ELISAs) on the microplate reader. CSF biomarkers of POD measurements were done with ELISA kits [$A\beta_{42}$ (BioVendor, Ghent, Belgium Lot: No. 296-64401), P-tau (BioVendor, Ghent, Belgium Lot: QY-PF9092) and T-tau (BioVendor, Ghent, Belgium Lot: No. EK-H12242)]. All CSF samples were randomly distributed on the same batch of plates. All experimental procedures were performed by researchers who were blinded to patient information. All the antibodies and plates were from a single lot to exclude variability between batches. Moreover, the within-batch CV was < 5% and the inter-batch CV was < 15%.

After fasting for at least 8 h, the patient entered the operating room, and 5 ml of medial cubital vein blood was drawn. Venous blood was collected into vacuum tube, which was then measured by the hospital's laboratory staff. Serum concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) were measured under standardized research protocols using an automatic biochemical analyzer (DURUI CS-600B, China).

Statistical Analysis

SPSS statistical software, version 25.0 (SPSS, Inc., Chicago, IL, United States), and Medcalc software (version 20.0.1, Ostend, Belgium) were used for data analysis. Continuous variables were expressed as median and interquartile range (M, IQR), and compared using Mann-Whitney *U*-test. Categorical variables will be tested for baseline comparability with the chi-square test or Fisher's exact test, expressed in frequency and percentage. To evaluate potential risk factors for POD, we used logistic regression analysis without and with adjustment for age, sex, education, and MMSE score. We also used the receiver operating characteristic (ROC) and the precision-recall curve (PRC) analysis to assess the ability of TG, TC, HDL-C, and LDL-C for predicting POD.

The mediation effect was also evaluated by PROCESS macro Version2.16.3. Statistical significance of the mediating effect was set at zero, which was not encompassed in the 95% CI. where each path of the model was controlled for age, sex, education, and MMSE score.

In addition, a sensitivity analysis was performed to assess the results stability. Sensitivity analysis was carried out as follows: First, we analyzed whether the association would change if only individuals who were aged over 65 at the baseline were selected; Secondly, we added more covariates, including self-reported history of type 2 diabetes (yes or no) and hypertension (yes or no).

The expected sensitivity was 80%, the expected specificity was 50%, and the allowable errors were all 0.05. Bilateral test was required, α was 0.05, and the missed visit ratio was calculated as 20%. The minimum sample size calculated by PASS software was 503.

RESULTS

Participant Characteristics

Among the 635 eligible patients, a total of 562 patients were finally included in this study. In the 562 patients, there were 66 POD cases, with an incidence of 11.7%, as shown in **Figure 1**. The

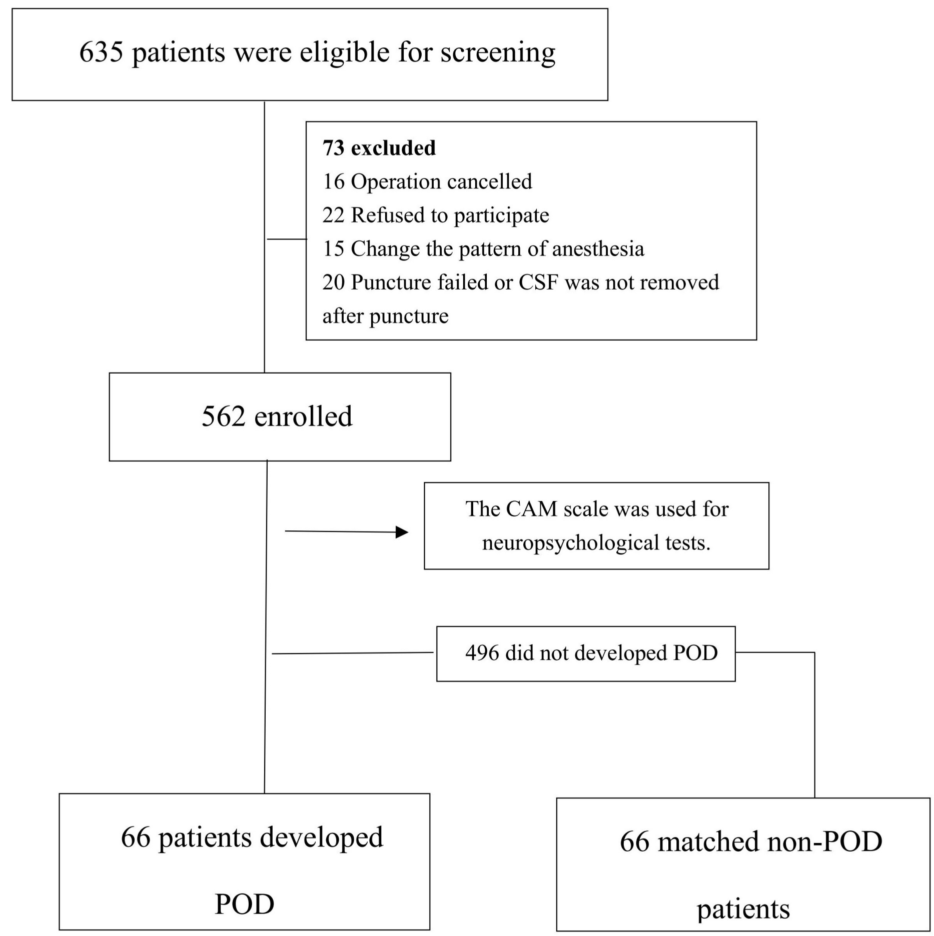

FIGURE 1 | Flow diagram.

incidence density sampling was used for the comparison between the POD group and the non-POD group, and 1:1 matching was performed on 5 variables, including ASA physical status, duration of surgery, duration of anesthesia, intraoperative blood loss, and fluid input.

The general conditions of the POD group and the NPOD group were compared (**Table 1**). There was no statistical significance in years of education, preoperative MMSE score, history of diabetes, or history of hypertension ($P > 0.05$), while the differences in sex, age, Serum TC, TG, LDL-C, HDL-C, CSF $A\beta_{40}$, $A\beta_{42}$, t-Tau, p-Tau, $A\beta_{42}/A\beta_{40}$, $A\beta_{42}$/t-Tau, $A\beta_{42}$/p-Tau, $A\beta_{40}$/t-Tau, $A\beta_{40}$/p-Tau, t-Tau/p-Tau, and Postoperative MDAS score were statistically significant ($P < 0.05$).

Logistic Regression Analysis

Logistic regression analysis showed that high concentration of TC (OR = 3.148, 95%CI 1.858∼5.333, $P < 0.001$), TG (OR = 2.483, 95%CI 1.573∼3.918, $P < 0.001$), and LDL-C (OR = 2.469, 95%CI 1.310∼4.656, $P = 0.005$) in serum were risk factors for POD. A high concentration of HDL-C (OR = 0.258, 95%CI 0.112∼0.594, $P = 0.001$) was a protective factor for POD after adjusted for age, sex, education, and MMSE score (**Table 2**).

We performed two sensitivity analyses. In our first sensitivity analysis, we added more covariates, including self-reported history of type 2 diabetes and hypertension, and the results showed that high concentration of TC (OR = 3.394, 95%CI 1.953∼5.898, $P < 0.001$), TG (OR = 2.456, 95%CI 1.557∼3.872, $P < 0.001$) and LDL-C (OR = 2.650, 95%CI 1.376∼5.101, $P = 0.004$) in serum were remain risk factors for POD. After adjusted for age, sex, education, MMSE score, self-reported history of type 2 diabetes, and hypertension, high concentration of HDL-C (OR = 0.263, 95%CI 0.115∼0.601, $P = 0.002$) was a protective factor for POD (**Supplementary Table 1**). In the second sensitivity analysis, we selected patients older than 65 years old. The implication of these results is that high concentration of TC (OR = 3.880, 95%CI 1.653∼9.108, $P = 0.002$), TG (OR = 2.421, 95%CI 1.218∼4.809, $P = 0.012$) and LDL-C (OR = 2.639, 95%CI 1.032∼6.743, $P = 0.043$) in serum were remain risk factors for POD. After adjusted for age, sex, education and MMSE score, high concentration of HDL-C (OR = 0.163, 95%CI 0.040∼0.659, $P = 0.011$) was a protective factor for POD (**Supplementary Table 2**). The results were barely changed in the sensitivity analysis, and the sensitivity analysis have showed that the results were stable.

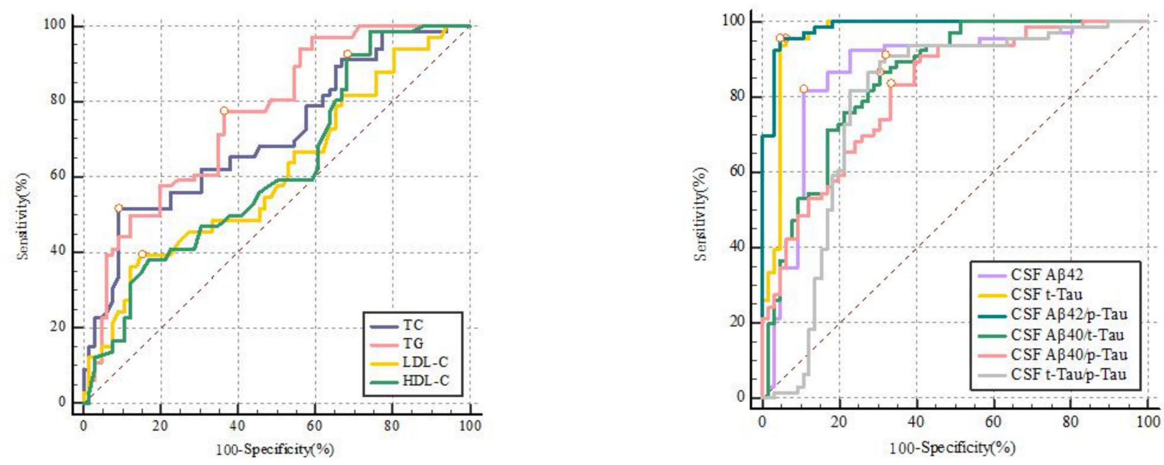

FIGURE 2 | The receiver-operator characteristic analyses for TC [0.708 (0.623–0.784)], TG [0.761 (0.679–0.831)], LDL-C [0.607 (0.519–0.691)], HDL-C [0.620 (0.531–0.703)] and CSF biomarkers in predicting delirium.

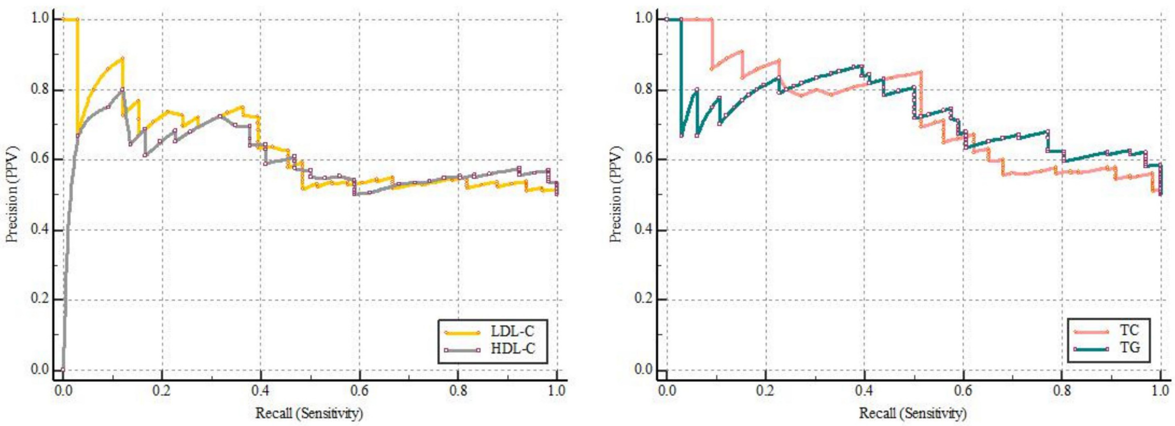

FIGURE 3 | The precision-recall curve of predicting postoperative delirium.

Receiver Operating Characteristic Analysis and Precision-Recall Curve Analysis

ROC curves showed that LDL-C [0.607 (0.519–0.691)], HDL-C [0.620 (0.531–0.703)], TG [0.761 (0.679–0.831)], and TC [0.708 (0.623–0.784)] can all predict POD (**Figure 2** and **Supplementary Table 3**). Among which, HDL-C had the highest sensitivity and specificity in predicting POD, although AUC was not the largest. We calculated the area under curve and F1 score of TG, TC, LDL-C, and HDL-C in PRC analysis. The results showed that these four lipid markers, the PRC range from 0.602 to 0.731, respectively. The F1 score of TG, TC, LDL-C, and HDL-C were 0.757, 0.714, 0.685, and 0.722, respectively (**Figure 3** and **Supplementary Table 4**).

Mediation Analyses

In the mediation modeling analysis, we assessed the mediation effects of CSF proteins on the associations of lipid levels with MDAS, after controlling for age, sex, education, and MMSE score. The relationship between TC and POD severity was mediated by amyloid and tau pathology indicated by $A\beta_{42}$, t-Tau, $A\beta_{42}$/t-Tau ratios, $A\beta_{42}$/p-Tau ratios, and $A\beta_{40}$/p-Tau ratios. While, the relationship between TG and MDAS was mediated by t-Tau, $A\beta_{42}$/t-Tau ratios, $A\beta_{40}$/t-Tau ratios, and $A\beta_{40}$/p-Tau ratios. $A\beta_{42}$ and t-Tau act as full mediators between LDL-C and MDAS. The result of this study shows that t-Tau, $A\beta_{40}$/t-Tau ratios, and $A\beta_{40}$/p-Tau have different performance on HDL-C and MDAS (**Figure 4**).

DISCUSSION

As far as we are aware, the study is the first that reported the relationship including mediator effects between serum lipid and POD. We mainly screened out several POD core proteins as mediators. Of course, they played different mediating effects in the relationship between different serum lipoprotein and POD.

TABLE 1 | Demographic and clinical characteristics.

Participant features	NPOD (*n* = 66)	POD (*n* = 66)	*P*
Male, *n* (%)	46 (69.7%)	33 (50%)	0.021
Age (year)	61 (53.75 – 69.25)	68 (57.00 – 71.00)	0.043
ASA physical status I, *n* (%)	58 (87.9%)	51 (77.3%)	0.108
History of hypertension, *n* (%)	21 (31.8%)	30 (45.5%)	0.108
History of diabetes, *n* (%)	11 (16.7%)	16 (24.2%)	0.281
Years of education (year)	12 (9 – 14)	9 (6 – 15)	0.392
Preoperative MMSE score	28 (26.75 – 30)	28 (25.75 – 29)	0.129
Serum TC (mmol/L)	4.59 (3.89 – 5.00)	5.28 (4.46 – 5.69)	<0.001
Serum TG (mmol/L)	1.26 (0.97 – 1.77)	2.09 (1.39 – 2.92)	<0.001
Serum HDL-C (mmol/L)	1.22 (1.18 – 2.29)	1.18 (1.01 – 1.39)	0.018
Serum LDL-C (mmol/L)	2.71 (2.34 – 3.04)	2.76 (2.51 – 3.34)	0.033
CSF Aβ_{40} (100 pg/mL)	37.35 (26.86 – 49.74)	48.58 (29.32 – 61.12)	0.032
CSF Aβ_{42} (pg/mL)	277.54 (215.75 – 308.03)	142.57 (114.29 – 184.02)	<0.001
CSF t-Tau (pg/mL)	167.02 (141.30 – 252.79)	601.64 (512.25 – 671.19)	<0.001
CSF p-Tau (pg/mL)	31.54 (29.12 – 41.99)	82.03 (75.84 – 90.05)	<0.001
CSF Aβ_{42}/Aβ_{40}	0.07 (0.05 – 0.13)	0.03 (0.02 – 0.05)	<0.001
CSF Aβ_{42}/t-Tau	1.52 (1.01 – 2.09)	0.24 (0.19 – 0.34)	<0.001
CSF Aβ_{42}/p-Tau	8.56 (6.01 – 10.58)	1.81 (1.42 – 2.26)	<0.001
CSF Aβ_{40}/t-Tau	20.91 (12.39 – 31.79)	7.94 (4.73 – 11.79)	<0.001
CSF Aβ_{40}/p-Tau	109.24 (75.10 – 146.84)	58.51 (35.32 – 82.11)	<0.001
CSF t-Tau/p-Tau	4.93 (4.38 – 5.75)	7.22 (6.29 – 8.26)	<0.001
Postoperative MDAS score	4.50 (3.00 – 7.00)	18.00 (17.00 – 20.00)	<0.001
Duration of surgery (min)	110 (90 – 151.25)	110 (90 – 138.75)	0.507
Duration of anesthesia (min)	170 (135 – 200)	172.5 (145 – 200)	0.417
Intraoperative blood loss (ml)	200 (100 – 200)	200 (130 – 200)	0.241
Intraoperative fluid input (ml)	1, 100 (712.5 – 1, 100)	1, 100 (1, 075 – 1, 200)	0.290

ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; TC, triglyceride; TG, total cholesterol; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; MDAS, Memorial Delirium Assessment Scale.

TABLE 2 | Logistic regression analysis.

	Unadjusted			Adjusted*		
	P	OR	95% CI	*P*	OR	95% CI
Serum TC (mmol/L)	<0.001	2.584	1.633–4.089	<0.001	3.148	1.858–5.333
Serum TG (mmol/L)	<0.001	2.433	1.554–3.809	<0.001	2.483	1.573–3.918
Serum HDL-C (mmol/L)	0.001	0.271	0.124–0.590	0.001	0.258	0.112–0.594
Serum LDL-C (mmol/L)	0.012	2.111	1.177–3.787	0.005	2.469	1.310–4.656
CSF Aβ_{40} (100 pg/mL)	0.022	1.000	1.000–1.000	–	–	–
CSF Aβ_{42} (pg/mL)	<0.001	0.979	0.972–0.986	<0.001	0.979	0.971–0.986
CSF t-Tau (pg/mL)	<0.001	1.016	1.011–1.022	<0.001	1.021	1.012–1.031
CSF p-Tau (pg/mL)	<0.001	1.281	1.137–1.443	0.070	1.759	0.954–3.244
CSF Aβ_{42}/Aβ_{40}	<0.001	0.000	0.000–0.000	–	–	–
CSF Aβ_{42}/t-Tau	<0.001	0.000	0.000–0.001	–	–	–
CSF Aβ_{42}/p-Tau	<0.001	0.157	0.074–0.333	<0.001	0.142	0.061–0.332
CSF Aβ_{40}/t-Tau	<0.001	0.825	0.769–0.884	<0.001	0.795	0.729–0.866
CSF Aβ_{40}/p-Tau	<0.001	0.969	0.957–0.980	<0.001	0.966	0.953–0.978
CSF t-Tau/p-Tau	0.019	1.208	1.031–1.414	0.012	1.224	1.046–1.434

**The adjustment factors include age, sex, education, and MMSE score.*

Cholesterol is an essential component of membranes and plasma lipoprotein, and it also plays an essential part in the accommodation of synaptic function and cell plasticity (17). An independent study (18) found that hypercholesterolemia caused memory impairment, inflammation response, and cholinergic dysfunction. Conversely, taking cholesterol-reducing

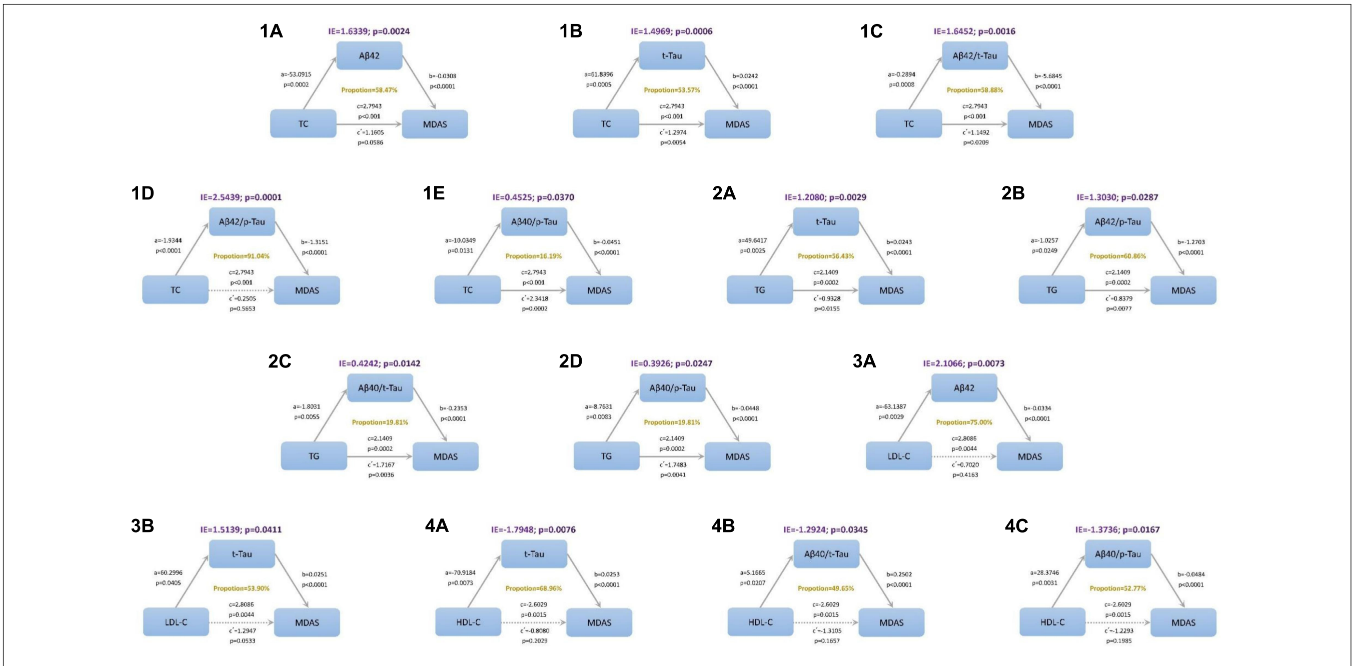

FIGURE 4 | Mediation analyses with Memorial Delirium Assessment Scale (MDAS) as outcome. The relationship between triglyceride (TC) and postoperative delirium severity was mediated by amyloid and tau pathology indicated by (1A) amyloid beta$_{42}$ (Aβ_{42}), (1B) total Tau (t-Tau), (1C) amyloid beta$_{42}$/t-Tau (Aβ_{42}/t-Tau) ratios, (1D) Aβ_{42}/p-Tau ratios, (1E) Aβ_{40}/p-Tau ratios. The relationship between total cholesterol (TG) and postoperative delirium severity was mediated by amyloid and tau pathology indicated by (2A) t-Tau, (2B) Aβ_{42}/t-Tau ratios, (2C) Aβ_{40}/t-Tau ratios, (2D) Aβ_{40}/p-Tau ratios. The relationship between low-density lipoprotein (LDL-C) and postoperative delirium severity was mediated by amyloid and tau pathology indicated by (3A) Aβ_{42} and (3B) t-Tau. The relationship between high-density lipoprotein (HDL-C) and postoperative delirium severity was mediated by amyloid and tau pathology indicated by (4A) t-Tau, (4B) Aβ_{40}/t-Tau ratios and (4C) Aβ_{40}/p-Tau ratios. IE, indirect effect.

medications can bring down the risk of neurocognitive-related diseases (19). Our findings indicate that cholesterol amounts altered was concerned with POD, and serum cholesterol was proportional to the severity of POD; that is, it is positively correlated with MDAS scores. Hypercholesterolemia leading to POD partly by Aβ_{42}, t-Tau, Aβ_{42}/t-Tau ratios, Aβ_{42}/p-Tau ratios, and Aβ_{40}/p-Tau ratios, explanation by mediation effects. Likewise, Umeda et al. found that hypercholesterolemia accelerates the accumulation of Aβ oligomers and resulting in memory impairment (20). It is universally recognized that reduced CSF Aβ_{42} concentration reflects the accumulation of aggregated Aβ_{42} in amyloid plaques in the brain (21). In patients with hip fracture, this group found lower CSF Aβ_{42} levels and increased CSF t-Tau levels who developed delirium compared to the control group, the biomarkers remained significant after adjusting for age, gender, and Informant Questionnaire on Cognitive Decline in the Elderly score. This result is consistent with our findings. Some research has found that cholesterol amounts modification altered amyloid precursor protein (APP) and Aβ expression (22, 23). Cholesterol transcellular transportation was altered by Aβ, while inhibition of intracellular transport of cholesterol reduced cleavage of Aβ from APP in neurons (24, 25). Intracellular cholesterol plays a significant role in modulating tau phosphorylation and maintaining microtubule stability, the researchers found (26). Van der et al. (27) found that the effects of cholesterol on tau proteostasis are correlated with APP and Aβ. We also find this relationship by calculating the mediating effect. The interesting thing is that exercise can lower the tau pathology and its pathophysiological consequences (28). Exercise decreased the levels of soluble Aβ_{40} and Aβ_{42} (29), also reducing the lipid level in serum. It is tempting to think there is at least a case to be made for exercise to lower cholesterol levels and thus reduce the risk of POD.

Moreover, our results showed that triglyceride levels were higher than the NPOD group in POD patients, and the difference between the two groups has statistical significance. t-Tau, Aβ_{42}/t-Tau ratios, Aβ_{40}/t-Tau ratios, and Aβ_{40}/p-Tau ratios may mediate the effect of triglyceride on POD. Triglyceride components were found to be significantly associated with CSF Aβ_{42} values (30). A longitudinal cohort study in cognitively healthy individuals concluded that increased levels of triglycerides could even predict CSF Aβ and tau pathology 20 years later (31). Higher serum triglyceride levels are associated with Parkinson's disease mild cognitive impairment (32) and are one of the risk factors for AD (33). It was proved that triglycerides could cross the blood-brain barrier (BBB), consisting of human CSF, resulting in cognitive impairment (34). Some scholars have argued that the relation between triglycerides and cognition may be mediated by triglyceride regulation of the BBB transport of cognitively active gastrointestinal hormones (35). In animal models, an influential study showed that plasma triglyceride levels increased precede Aβ deposition (6), but total cholesterol levels were not significantly different in this research. In another model of hyperlipidemia-induced age-related neurodegeneration (36), chronic hypertriglyceridemia may lead to impaired neuronal function and neurodegeneration, possibly via hyperphosphorylation of tau protein, and this is similar to our findings.

More importantly, our analysis found that serum HDL level is associated with POD development, and high serum HDL level before surgery is one of the protective factors of POD. HDL-C is known as the "good cholesterol" because of its ability to reverse cholesterol transport. It protects against elevated lipid levels and protects against endothelial dysfunction, oxidative stress, inflammation, thrombosis, and more. Therefore, it is well known that serum HDL-C level is associated with a lower risk of cardiovascular disease. In addition, several studies have shown that individuals with higher levels of serum HDL-C is related to better cognitive function status (37–39), One possible reason is that HDL-C is capable of binding Aβ (40) and prevent Aβ aggregation into amyloid (41), and then improve clearance of Aβ from the brain, which in turn decreases the neurotoxicity of Aβ peptides (42). Another factor may be that serum HDL-C levels are inversely correlated with brain Aβ deposits (43). Our study did not support a significant mediation effect of Aβ deposits in the associations between serum HDL-C and MDAS, while the t-Tau, $A\beta_{40}$/t-Tau ratios, and $A\beta_{40}$/p-Tau ratios play full mediators on the relationship between HDL-C and MDAS. A study of older adults in China's rural area showed that low HDL-C is associated with structural brain aging and cognitive dysfunction, but the association of low HDL-C with cognitive aging is not mediated by brain structure (44). Our data agree with previous research that low HDL-C is associated with cognitive impairment and dementia and is a risk factor for memory deficit and decline (45).

Our data insinuate that preoperative LDL-C levels were positively correlated with POD occurrence. $A\beta_{42}$ and t-Tau may mediate the effect of LDL-C on POD. In addition, $A\beta_{42}$ is a complete mediation. Our data support the view that a higher LDL-C level was associated with higher Aβ deposition and lower cognitive function (46, 47). In an Australian study, researchers discovered that higher levels of cholesterol and LDL-C were related to impaired processing speed, recognition memory, and working memory (48). However, in a prospective cohort study in Japan, higher LDL-C levels were associated with higher scores in memory performance after controlling for confounders (49), The Japanese study is broadly similar to the results of a cross-sectional study from China (50). According to the Chinese study, higher LDL-C was significantly negatively related to higher MMSE scores among the oldest old (aged 80 + years). Another Chinese study showed that a high level of LDL-C may be considered a potentially protective factor against cognition decline (51). Still, some research showed that LDL-C level did not influence the incidence of cognitive disorder or global cognitive performance (52, 53). All of the above studies come from different countries and regions, with different living standards and educational levels, so many factors influence the results. Therefore, future large-sample multicenter studies are needed to support the relationship between LDL-C and POD.

There are limitations to this study. As this is an observational cross-sectional design, we only tried to infer the causal relationship, but the specific relationship needs further study. In addition, our study only measured lipid levels at a one-time point before surgery, and more comprehensive monitoring of lipid levels is needed in the future. The research population we included come from the same hospital, which is also the deficiency of our experimental study. If possible, we hope to conduct verification of our experimental model in other independent and comparable hospitals in future studies.

To sum up, the present study indicated that the increase of serum TG, TC, and LDL-C concentration are risk factors for the development of POD, while high HDL-C concentration is a protective factor for POD, and the occurrence of POD caused by hyperlipidemia may be caused by POD core protein. Therefore, we advocate maintaining a healthy lifestyle to reduce lipid levels and thus reduce the incidence of POD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Clinical Trial Ethics Committee of Qingdao Municipal Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL contributed to the statistical analysis, and manuscript preparation. XD, FL, and HT involved in the data collection and ELISA performance. XP, XL, and RD revised the manuscript. YB and BW conceived the current study. All authors have contributed to the manuscript revising and editing critically for important intellectual content and given final approval of the version and agreed to be accountable for all aspects of the work presented here, reviewed, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.870317/full#supplementary-material

REFERENCES

1. Lin X, Tang J, Liu C, Li X, Cao X, Wang B, et al. Cerebrospinal fluid cholinergic biomarkers are associated with postoperative delirium in elderly patients undergoing Total hip/knee replacement: a prospective cohort study. *BMC Anesthesiol.* (2020) 20:246. doi: 10.1186/s12871-020-01166-9
2. Bai J, Liang Y, Zhang P, Liang X, He J, Wang J, et al. Association between postoperative delirium and mortality in elderly patients undergoing hip fractures surgery: a meta-analysis. *Osteoporos Int.* (2020) 31:317–26. doi: 10.1007/s00198-019-05172-7
3. Ma YH, Shen XN, Xu W, Huang YY, Li HQ, Tan L, et al. A panel of blood lipids associated with cognitive performance, brain atrophy, and Alzheimer's diagnosis: a longitudinal study of elders without dementia. *Alzheimers Dement (Amst).* (2020) 12:e12041. doi: 10.1002/dad2.12041
4. Buckley RF, Mormino EC, Amariglio RE, Properzi MJ, Rabin JS, Lim YY, et al. Sex, amyloid, and APOE epsilon4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. *Alzheimers Dement.* (2018) 14:1193–203. doi: 10.1016/j.jalz.2018.04.010
5. Perez-Galvez A, Jaren-Galan M, Garrido-Fernandez J, Calvo MV, Visioli F, Fontecha J. Activities, bioavailability, and metabolism of lipids from structural membranes and oils: promising research on mild cognitive impairment. *Pharmacol Res.* (2018) 134:299–304. doi: 10.1016/j.phrs.2018.07.013
6. Burgess BL, McIsaac SA, Naus KE, Chan JY, Tansley GHK, Yang J, et al. Elevated plasma triglyceride levels precede amyloid deposition in Alzheimer's disease mouse models with abundant Aβ in plasma. *Neurobiol Dis.* (2006) 24:114–27. doi: 10.1016/j.nbd.2006.06.007
7. Shie FS, Jin LW, Cook DG, Leverenz JB, Le Boeuf RC. Diet-induced hypercholesterolemia enhances brain Ab accumulation in transgenic mice. *Neuroreport.* (2002) 13:455–9.
8. Fassbender K, Bergmann Simons M, Stroick M. Simvastatin strongly reduces levels of Alzheimer's disease ␤-amyloid peptides A␤ 42 and A␤ 40 *in vitro* and *in vivo*. *Proc Natl Acad Sci USA*. (2001) 98:5856–61.
9. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology.* (2005) 64:277–81. doi: 10.1212/01.WNL.0000149519.47454.F2
10. Ji MH, Yuan HM, Zhang GF, Li XM, Dong L, Li WY, et al. Changes in plasma and cerebrospinal fluid biomarkers in aged patients with early postoperative cognitive dysfunction following total hip-replacement surgery. *J Anesth.* (2013) 27:236–42. doi: 10.1007/s00540-012-1506-3
11. Rolandi E, Cavedo E, Pievani M, Galluzzi S, Ribaldi F, Buckley C, et al. Association of postoperative delirium with markers of neurodegeneration and brain amyloidosis: a pilot study. *Neurobiol Aging.* (2018) 61:93–101. doi: 10.1016/j.neurobiolaging.2017.09.020
12. Wu Z, Zhang M, Zhang Z, Dong W, Wang Q, Ren J. Ratio of beta-amyloid protein (Abeta) and Tau predicts the postoperative cognitive dysfunction on patients undergoing total hip/knee replacement surgery. *Exp Ther Med.* (2018) 15:878–84. doi: 10.3892/etm.2017.5480
13. Racine AM, Fong TG, Travison TG, Jones RN, Gou Y, Vasunilashorn SM, et al. Alzheimer's-related cortical atrophy is associated with postoperative delirium severity in persons without dementia. *Neurobiol Aging.* (2017) 59:55–63. doi: 10.1016/j.neurobiolaging.2017.07.010
14. Fong TG, Vasunilashorn SM, Gou Y, Libermann TA, Dillon S, Schmitt E, et al. Association of CSF Alzheimer's disease biomarkers with postoperative delirium in older adults. *Alzheimers Dement.* (2021) 7:e12125. doi: 10.1002/trc2.12125
15. Inouye S, van Dyck C, Alessi C, Balkin S, Siegal A, Horwitz R. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* (1990) 113:941–8. doi: 10.7326/0003-4819-113-12-941
16. Schuurmans MJ, Deschamps PI, Markham SW, Shortridge-Baggett LM, Duursma SA. The measurement of delirium: review of scales. *Res Theory Nurs Pract.* (2003) 17:207–24. doi: 10.1891/rtnp.17.3.207.53186
17. Eckert G, Kirsch C, Leutz S, Wood W, Müller W. Cholesterol modulates amyloid beta-peptide's membrane interactions. *Pharmacopsychiatry.* (2003) 36(Suppl. 2):S136–43.
18. Ullrich C, Pirchl M, Humpel C. Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits. *Mol Cell Neurosci.* (2010) 45:408–17. doi: 10.1016/j.mcn.2010.08.001
19. Gibson Wood W, Eckert GP, Igbavboa U, Müller WE. Amyloid beta-protein interactions with membranes and cholesterol: causes or casualties of Alzheimer's disease. *Biochim Biophys Acta.* (2003) 1610:281–90. doi: 10.1016/s0005-2736(03)00025-7
20. Umeda T, Tomiyama T, Kitajima E, Idomoto T, Nomura S, Lambert MP, et al. Hypercholesterolemia accelerates intraneuronal accumulation of Abeta oligomers resulting in memory impairment in Alzheimer's disease model mice. *Life Sci.* (2012) 91:1169–76. doi: 10.1016/j.lfs.2011.12.022
21. Idland AV, Wyller TB, Stoen R, Eri LM, Frihagen F, Raeder J, et al. Preclinical Amyloid-beta and axonal degeneration pathology in delirium. *J Alzheimers Dis.* (2017) 55:371–9. doi: 10.3233/JAD-160461
22. Cho YY, Kwon OH, Park MK, Kim TW, Chung S. Elevated cellular cholesterol in Familial Alzheimer's presenilin 1 mutation is associated with lipid raft localization of beta-amyloid precursor protein. *PLoS One.* (2019) 14:e0210535. doi: 10.1371/journal.pone.0210535
23. Pantelopulos GA, Panahi A, Straub JE. Impact of cholesterol concentration and lipid phase on structure and fluctuation of amyloid precursor protein. *J Phys Chem.* (2020) 124:10173–85. doi: 10.1021/acs.jpcb.0c07615
24. Avila-Munoz E, Arias C. Cholesterol-induced astrocyte activation is associated with increased amyloid precursor protein expression and processing. *Glia.* (2015) 63:2010–22. doi: 10.1002/glia.22874
25. Chung J, Phukan G, Vergote D, Mohamed A, Maulik M, Stahn M, et al. Endosomal-lysosomal cholesterol sequestration by U18666A differentially regulates amyloid precursor protein (APP) metabolism in normal and APP-overexpressing cells. *Mol Cell Biol.* (2018) 38:e529–517. doi: 10.1128/MCB.00529-17
26. Fan QW, Yu W, Senda T, Yanagisawa K, Michikawa M. Cholesterol-dependent modulation of tau phosphorylation in cultured neurons. *J Neurochem.* (2001) 76:391–400.
27. van der Kant R, Langness VF, Herrera CM, Williams DA, Fong LK, Leestemaker Y, et al. cholesterol metabolism is a druggable axis that independently regulates tau and amyloid-beta in iPSC-derived Alzheimer's disease neurons. *Cell Stem Cell.* (2019) 24:363–375e9. doi: 10.1016/j.stem.2018.12.013
28. Belarbi K, Burnouf S, Fernandez-Gomez FJ, Laurent C, Lestavel S, Figeac M, et al. Beneficial effects of exercise in a transgenic mouse model of Alzheimer's disease-like Tau pathology. *Neurobiol Dis.* (2011) 43:486–94. doi: 10.1016/j.nbd.2011.04.022
29. Zeng B, Zhao G, Liu HL. The differential effect of treadmill exercise intensity on hippocampal soluble abeta and lipid metabolism in APP/PS1 Mice. *Neuroscience.* (2020) 430:73–81. doi: 10.1016/j.neuroscience.2020.01.005
30. Bernath MM, Bhattacharyya S, Nho K, Barupal DK, Fiehn O, Baillie R, et al. Serum triglycerides in Alzheimer disease: relation to neuroimaging and CSF biomarkers. *Neurology.* (2020) 94:e2088–98. doi: 10.1212/WNL.0000000000009436
31. Nagga K, Gustavsson AM, Stomrud E, Lindqvist D, van Westen D, Blennow K, et al. Increased midlife triglycerides predict brain beta-amyloid and tau pathology 20 years later. *Neurology.* (2018) 90:e73–81. doi: 10.1212/WNL.0000000000004749
32. Huang X, Ng SY, Chia NS, Acharyya S, Setiawan F, Lu Z, et al. Higher serum triglyceride levels are associated with Parkinson's disease mild cognitive impairment. *Mov Disord.* (2018) 33:1970–1. doi: 10.1002/mds.27521
33. Proitsi P, Lupton MK, Velayudhan L, Newhouse S, Fogh I, Tsolaki M, et al. Genetic predisposition to increased blood cholesterol and triglyceride lipid levels and risk of Alzheimer disease: a Mendelian randomization analysis. *PLoS Med.* (2014) 11:e1001713. doi: 10.1371/journal.pmed.1001713
34. Banks WA, Farr SA, Salameh TS, Niehoff ML, Rhea EM, Morley JE, et al. Triglycerides cross the blood-brain barrier and induce central leptin and insulin receptor resistance. *Int J Obes (Lond).* (2018) 42:391–7. doi: 10.1038/ijo.2017.231
35. Banks WA. Role of the blood-brain barrier in the evolution of feeding and cognition. *Ann N Y Acad Sci.* (2012) 1264:13–9. doi: 10.1111/j.1749-6632.2012.06568.x
36. Lenart N, Szegedi V, Juhasz G, Kasztner A, Horvath J, Bereczki E, et al. Increased tau phosphorylation and impaired presynaptic function in

hypertriglyceridemic ApoB-100 transgenic mice. *PLoS One.* (2012) 7:e46007. doi: 10.1371/journal.pone.0046007
37. Formiga F, Ferrer A, Chivite D, Pinto X, Cuerpo S, Pujol R. Serum high-density lipoprotein cholesterol levels, their relationship with baseline functional and cognitive status, and their utility in predicting mortality in nonagenarians. *Geriatr Gerontol Int.* (2011) 11:358–64. doi: 10.1111/j.1447-0594.2010.00681.x
38. Formiga F, Ferrer A, Chivite D, Pinto X, Badia T, Padros G, et al. Serum high-density lipoprotein cholesterol levels correlate well with functional but not with cognitive status in 85-year-old subjects. *J Nutr Health Aging.* (2012) 16:449–53.
39. Bates KA, Sohrabi HR, Rainey-Smith SR, Weinborn M, Bucks RS, Rodrigues M, et al. Serum high-density lipoprotein is associated with better cognitive function in a cross-sectional study of aging women. *Int J Neurosci.* (2017) 127:243–52. doi: 10.1080/00207454.2016.1182527
40. Cole G, Beech W, Frautschy S, Sigel J, Glasgow C, Ard M. Lipoprotein effects on Abeta accumulation and degradation by microglia *in vitro*. *J Neurosci Res.* (1999) 57:504–20.
41. Olesen OF, Dago L. High density lipoprotein inhibits assembly of amyloid beta-peptides into fibrils. *Biochem Biophys Res Commun.* (2000) 270:62–6. doi: 10.1006/bbrc.2000.2372
42. Farhangrazi Z, Ying H, Bu G, Dugan L, Fagan A, Choi D, et al. High density lipoprotein decreases beta-amyloid toxicity in cortical cell culture. *Neuroreport.* (1997) 8:1127–30. doi: 10.1097/00001756-199703240-00013
43. Bates KA, Sohrabi HR, Rodrigues M, Beilby J, Dhaliwal SS, Taddei K, et al. Association of cardiovascular factors and Alzheimer's disease plasma amyloid-beta protein in subjective memory complainers. *J Alzheimers Dis.* (2009) 17:305–18. doi: 10.3233/JAD-2009-1050
44. Wang M, Li Y, Cong L, Hou T, Luo Y, Shi L, et al. High-density lipoprotein cholesterol and brain aging amongst rural-dwelling older adults: a population-based magnetic resonance imaging study. *Eur J Neurol.* (2021) 28:2882–92. doi: 10.1111/ene.14939
45. Singh-Manoux A, Gimeno D, Kivimaki M, Brunner E, Marmot M. Low HDL cholesterol is a risk factor for deficit and decline in memory in midlife: the whitehall II study. *Arterioscler Thromb Vasc Biol.* (2008) 28:1556–62. doi: 10.1161/atvbaha.108.163998
46. Reed B, Villeneuve S, Mack W, DeCarli C, Chui HC, Jagust W. Associations between serum cholesterol levels and cerebral amyloidosis. *JAMA Neurol.* (2014) 71:195–200. doi: 10.1001/jamaneurol.2013.5390
47. Smit RA, Trompet S, Sabayan B, le Cessie S, van der Grond J, van Buchem MA, et al. Higher visit-to-visit low-density lipoprotein cholesterol variability is associated with lower cognitive performance, lower cerebral blood flow, and greater white matter hyperintensity load in older subjects. *Circulation.* (2016) 134:212–21. doi: 10.1161/CIRCULATIONAHA.115.020627
48. Stough C, Pipingas A, Camfield D, Nolidin K, Savage K, Deleuil S, et al. Increases in total cholesterol and low density lipoprotein associated with decreased cognitive performance in healthy elderly adults. *Metab Brain Dis.* (2019) 34:477–84. doi: 10.1007/s11011-018-0373-5
49. Katsumata Y, Todoriki H, Higashiuesato Y, Yasura S, Ohya Y, Willcox DC, et al. Very old adults with better memory function have higher low-density lipoprotein cholesterol levels and lower triglyceride to high-density lipoprotein cholesterol ratios: KOCOA Project. *J Alzheimers Dis.* (2013) 34:273–9. doi: 10.3233/JAD-121138
50. Lv YB, Yin ZX, Chei CL, Brasher MS, Zhang J, Kraus VB, et al. Serum cholesterol levels within the high normal range are associated with better cognitive performance among Chinese elderly. *J Nutr Health Aging.* (2016) 20:280–7.
51. Zhou F, Deng W, Ding D, Zhao Q, Liang X, Wang F, et al. High low-density lipoprotein cholesterol inversely relates to dementia in community-dwelling older adults: the Shanghai aging study. *Front Neurol.* (2018) 9:952. doi: 10.3389/fneur.2018.00952
52. Rej S, Saleem M, Herrmann N, Stefatos A, Rau A, Lanctot KL. Serum low-density lipoprotein levels, statin use, and cognition in patients with coronary artery disease. *Neuropsychiatr Dis Treat.* (2016) 12:2913–20. doi: 10.2147/NDT.S115505
53. Ying H, Wang J, Shen Z, Wang M, Zhou B. Impact of lowering low-density lipoprotein cholesterol with contemporary lipid-lowering medicines on cognitive function: a systematic review and meta-analysis. *Cardiovasc Drugs Ther.* (2021) 35:153–66. doi: 10.1007/s10557-020-07045-2

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Correlation Analysis of Serum Vitamin D Levels and Postoperative Cognitive Disorder in Elderly Patients With Gastrointestinal Tumor

*Jialei Zhang [1,2], Xiaoling Zhang [3], Yongyan Yang [1], Jun Zhao [3] and Yonghao Yu [1]**

[1] Department of Anesthesiology, Tianjin Medical University General Hospital, Tianjin, China, [2] Department of Anesthesiology, Changzhi People's Hospital Affiliated to Shanxi Medical University, Changzhi, China, [3] Department of Oncology, Changzhi People's Hospital Affiliated to Shanxi Medical University, Changzhi, China

Purpose: Vitamin D prevents hypocalcaemia, osteoporosis, and infections, among other problems, and is involved in the prevention and treatment of cardiovascular and neurological diseases. Recently, vitamin D was shown to improve cognitive dysfunction caused by Alzheimer's disease and vascular dementia. This study aims to explore the correlation between preoperative serum vitamin D and postoperative cognitive disorder (POCD) occurrence in elderly patients with gastrointestinal tumors to guide perioperative medication use and promote early patient recovery.

Methods: This study recruited 238 elderly patients ($65 \leq$ age ≤ 85) who underwent gastrointestinal tumor surgery; 117 cases were enrolled, and 55 controls of the same age and education level as the cases were included. Blood samples were taken preoperatively and at 7, 15, 30, and 90 days postoperatively, and plasma vitamin D (25OH-D3) and glutathione (GSH) was measured. Different from the previous diagnosis of POCD was obtained by telephone interview through Cognitive Status Modified Telephone Interview (TICS-m), mainly for memory impairment, a series of neuropsychological tests was used to evaluate cognitive function, Picture Recollect Test, Stroop Color-word Test, and Digit Symbol Substitution Test were used to comprehensively evaluate the three domains of cognitive function of patients, namely memory, attention and information processing ability. All neuropsychiatric assessments were performed at the bedside and completed face-to-face by the assessment staff and the patient.

Results: A total of 65.8% (77/117) of elderly patients undergoing gastrointestinal tumor surgery had preoperative vitamin D deficiency (serum 25OH-D concentration < 12 ng/ml), of whom 46.7% (36/77, 7 days after surgery), 31.2% (24/77, 15 days after surgery), 15.6% (12/77, 30 days after surgery), and 9% (7/77, 90 days after surgery) of patients developed POCD; 7.5% (3/40) of patients without vitamin D deficiency developed PNDs, which was detected only on the 7th day after surgery.

Conclusions: Vitamin D deficiency can increase neurocognitive disorder risk in elderly patients during the perioperative period, possibly because low vitamin D levels cannot effectively inhibit the postoperative oxidative stress increase.

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Guanghong Xu,
First Affiliated Hospital of Anhui Medical University, China
Jianhui Liu,
Tongji Hospital Affiliated to Tongji University, China

***Correspondence:**
Yonghao Yu
yuyonghao@126.com;
yyu@tmu.edu.cn
orcid.org/0000-0003-2556-3814

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Keywords: elderly population, perioperative, vitamin D, GSH, POCD

KEY SUMMARY POINTS

- **Aim:** To explore the correlation between vitamin D levels in elderly patients and the occurrence of postoperative cognitive disorder.
- **Findings:** The elderly are prone to vitamin D deficiency, and preoperative vitamin D deficiency is prone to postoperative cognitive disorder.
- **Message:** Low levels of vitamin D in elderly patients are associated with the occurrence of postoperative cognitive disorder.

INTRODUCTION

The aging population has become a focus of society as a whole, and because of the continuous development of medical technology and continuous progress of science, the number of elderly patients undergoing surgery with anesthesia also increases every year. Although great progress has been made in surgical and anesthesia methods, the incidence of postoperative cognitive dysfunction in patients has indisputably increased. Studies have shown (1) that surgical factors (such as a long duration, a complex surgery, and the occurrence of postoperative complications) and anesthesia factors (such as the use of anesthetic drugs, occurrence of hypoxia and hypoperfusion caused by controlled hypotension, and occurrence of postoperative anesthesia-related complications) are the main factors that lead to postoperative cognitive dysfunction. However, regardless of the type of surgery and anesthesia, advanced age can be regarded as an independent risk factor for cognitive dysfunction after surgical anesthesia (2, 3), which merits close attention by medical workers.

Vitamin D deficiency has become a public health problem affecting the world, especially the elderly, and this problem is becoming more and more serious (4). China has conducted two general surveys on the vitamin D content of the elderly (5, 6), and the results show that up to 90% of the elderly lack vitamin D. Studies have shown that (7–9), as a neuroprotective hormone, vitamin D can pass through the blood-brain barrier, regulate the expression of key enzymes in neurotransmitter synthesis and metabolism in the brain, and participate in a variety of brains activity including neurotrophic, neuroimmunological regulation, and neurotransmission, thereby playing a certain protective effect on the central nervous system. The lack of vitamin D may be closely related to the occurrence of neuropsychiatric diseases such as Parkinson's disease, schizophrenia, and depression (10, 11).

Postoperative Cognitive Disorder (POCD) (12) refers to the disturbance of brain function activity after surgical anesthesia in patients without mental disorders before surgery, resulting in different degrees of disorder activity in consciousness, cognition, orientation, thinking, memory, and sleep. It is a reversible and fluctuating acute mental disorder syndrome, commonly known as postoperative mental disorder, postoperative delirium, etc., and is one of the important postoperative complications. With ongoing developments in medicine and improvements in quality of life, the average life expectancy of human beings has been extended, and an increasing number of elderly patients undergo surgical procedures each year. Although the techniques of surgery and anesthesia management are constantly improving, the incidence of POCD is increasing, and this is a problem that cannot be ignored. Once a patient develops POCD, not only are the effect of surgical treatment and recovery after anesthesia surgery affected but so are the workload and mental stress of the surgical and anesthesia medical staff. This study used long-term dynamic monitoring of perioperative serum vitamin D levels in patients with gastrointestinal tumors and long-term observation of patients' cognitive function to determine the correlation between vitamin D level and POCD and to present a comparative discussion.

EXPERIMENTAL PROCEDURES

Study Design

This study is a single-center prospective cohort study. By comparing the effects of preoperative serum vitamin D levels on the occurrence of POCD in olderly patients undergoing gastrointestinal tumor surgery under intravenous inhalation combined with general anesthesia, we explored the correlation between serum vitamin D level and the occurrence of POCD in elderly patients. All subjects signed an informed consent form. This experiment was approved and registered by the China Clinical Trial Registration Center, registration number ChiCTR2100046900.

Patients

The inclusion criteria were as follows: men and women aged 65-85 years old; American Society of Anesthesiologists (ASA) classification I-III; years of education $\geq$ 8 years; and no abnormal liver or kidney function.

The exclusion criteria were as follows: patients with severe respiratory and circulatory diseases, cognitive dysfunction, history of brain trauma and craniocerebral surgery or history of cerebral infarction; patients who have taken medical drugs containing vitamin D and folic acid in the past 2 months; and patients with a history of severe drug allergy.

The subjects in the control group were all patient spouses or siblings, and the inclusion and exclusion criteria were the same as those of the patients. No relevant surgery was performed on the control subjects. The controls and patients underwent neuropsychological testing at the same time. The purpose of the control group was to provide the standard deviation of the two cognitive tests of normal people and to eliminate the learning effect produced by the calculation test patients when they performed multiple repeated cognitive tests.

Data Collection

The researchers responsible for patient data collection underwent thorough training before the start of the study. Data collection was only carried out after obtaining written informed consent. Basic data included demographic parameters (age, sex, height, weight, year of education), preoperative diagnosis, preoperative ASA classification, and coexisting diseases (hypertension, coronary heart disease, diabetes, chronic obstructive pulmonary disease, stroke, etc.), smoking history, drinking history, surgical history, preoperative neuropsychological test scores, preoperative serum vitamin D level and glutathione (GSH) content. Blood samples were collected at the bedside and sent to the Experimental Center of Changzhi People's Hospital for serum 25-hydroxyvitamin D and reduced glutathione concentration determination.

Intraoperative data included operation type, anesthesia time, operation time, type and dosage of anesthetic drugs, and bleeding volume. The depth of anesthesia was monitored, and the bispectral index (BIS) of all patients was maintained at 50∼60.Intraoperative data were recorded by the anaesthesiologist following the operation. Basic data and postoperative data were the responsibility of the anaesthesiologist who was not involved in the operation and perioperative care. The two did not communicate on the patient's intraoperative and postoperative conditions. The patients and data collectors were not aware of the grouping of patients.

Postoperative data included the occurrence of complications within 30 days after surgery, the length of postoperative hospital stay, the 30-day mortality rate after surgery, the scores for various neuropsychological tests for patients at 7, 15, 30, and 90 days after surgery, serum vitamin D level and reduced GSH content.

All neuropsychiatric assessments were performed at the bedside and completed face-to-face by the assessment staff and the patient.

The researchers conducting the neuropsychological evaluations received specialized training in neuropsychological test management prior to the study. The neuropsychological tests included the following: the Mini Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST), Stroop color-word test, and picture recollect test. Before surgery, all patients who met the inclusion criteria were tested by MMSE to identify whether cognitive dysfunction already existed. Studies have shown that (13), MMSE evaluates the cognitive function of elderly patients with a sensitivity of 87% and a specificity of 82%, so the reliability and reliability are high, and it is one of the most influential screening tools for cognitive function changes. Since the MMSE score is closely related to the level of education, the preoperative screening should be adjusted according to the level of education: 17 points for the illiterate group (no education); 20 points for the primary group (education years $\leq$ 6 years); the middle school group (education years 7∼9 years) had 22 points, and the University group (education years $\geq$ 1 year) had 24 points. Patients with scores lower than the above criteria were excluded. After passing the MMSE test, they were included in the study. The DSST, Stroop color-word test and picture recollect test were performed preoperatively and 7, 15, 30, and 90 days postoperatively.

The diagnosis of POCD was based on the International Postoperative Cognitive Dysfunction Research Group (ISPOCD) (3). The diagnostic criterion was calculated as follows:

$$Z = \frac{\Delta X - \Delta Xc}{SD(\Delta Xc)}$$

ΔX is the difference between the change in one test scale before and after the experiment. The ΔXc of the control group was also calculated, and the two values were subtracted and then divided by the standard deviation of ΔXc to obtain the Z-value. If there were multiple scales, the Zcombined value was calculated by determining the sum of the Z-values of each scale and dividing by the standard deviation of the Z-value of the control group. The calculation formula is:

$$\text{Zcombined} = \frac{\sum Za, b, c, d}{SD(\sum \Delta Xca, b, c, d)}$$

When there are two or more Z-values $\geq$ 1.96 on all scales, or one scale Z-value $\geq$ 1.96 on all scales and a Zcombined $\geq$1.96 at the same time, POCD is diagnosed. This diagnostic method excludes the learning effect of repeated measurements and errors caused by measurements at different times and has good sensitivity and specificity.

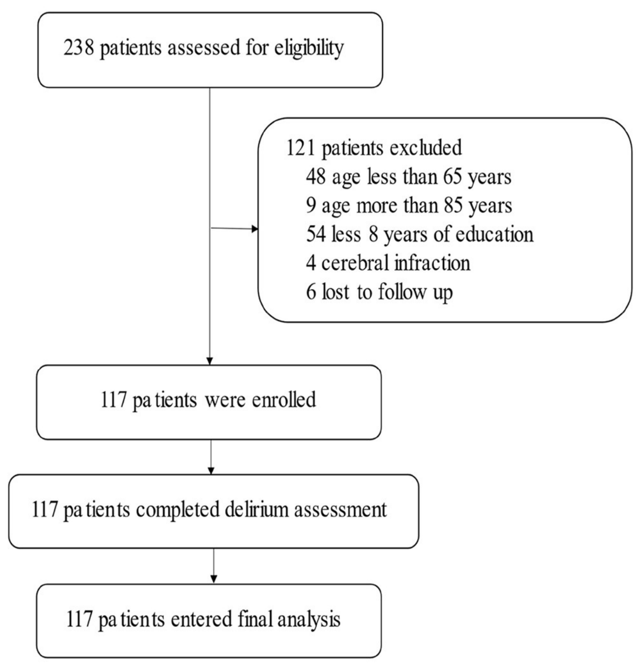

FIGURE 1 | Flow chart of the study.

TABLE 1 | Demographic and baseline characteristics.

	All patients *n* = 117	VD deficiency *n* = 77	No VD deficiency *n* = 40	*P*-value
Age, year	71.08 ± 3.62	71.36 ± 3.63	70.57 ± 3.65	0.27
Male, *n*(%)	83(70.9)	50(64.9)	33(82.5)	0.055
BMI, kg/m^2	23.57 ± 2.97	23.83 ± 3.19	23.07 ± 2.42	0.19
ASA classification, *n*(%)				
I	24(20.5)	15(19.5)	9(22.5)	
II	81(69.2)	56(72.7)	25(62.5)	
III	12(10.3)	6(7.8)	6(15)	
Educational level, year	9.17 ± 1.74	9.23 ± 1.73	9.09 ± 1.77	0.59
Chronic smoking, *n* (%)	24(20.5)	13(16.9)	11(27.5)	0.228
Alcoholism, *n* (%)	9(7.7)	6(7.8)	3(7.5)	0.955
Comorbidity, *n* (%)				
Hypertension	70(59.8)	46(59.7)	24(60)	0.978
Diabetes mellitus	36(30.8)	25(32.5)	11(27.5)	0.675
Coronary heart disease	12(10.3)	6(7.8)	6(15)	0.335
Chronic lung diseases	7(6.0)	5(6.5)	2(5)	0.747
History of surgery, *n* (%)	14(11.9)	9(11.7)	5(8)	0.898
preoperative MMSE, score	27.05 ± 1.17	27.15 ± 1.27	27.05 ± 1.12	0.67
Vitamin D concentration, ng/ml	11.91 ± 3.67	9.59 ± 1.64	16.04 ± 3.27	<0.001
Vitamin D level, *n*(%)				
Adequate	6(5.1)	–	6(15)	
Insufficient	34(29.1)	–	34(85)	
Deficient	77(65.8)	77(100)	–	
Serum GSH concentration, ug/ml	330.25 ± 16.49	336.46 ± 14.15	340.69 ± 19.18	0.179

Enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of vitamin D and GSH in the blood. According to the literature (14), vitamin D levels are defined as follows: adequate: >20 ng/ml; sufficient: 12-20 ng/ml; deficient: <12 ng/ml.

Statistical Analysis

Sample Size Estimation

We used a cross-sectional study on the correlation coefficient to calculate the sample size. Previous studies have shown that older age is moderately related to POCD (15–17). We assumed that low serum levels of vitamin D and POCD are at least correlated, setting significance (two-sided) at 0.05, power set at 0.8, and the effect size (r) = 0.3, dropouts = 0.20, the required sample size is 107 cases.

Outcome Analyses

Patients were grouped according to whether the vitamin D deficiency was present before surgery and whether they developed POCD after surgery. IBM SPSS Statistics 26.0, which is produced by SPSS, Inc., was used for data analysis. Measurement data are expressed as the mean ± standard deviation (x ± s), count data are expressed as the median and interquartile range, and classification data are expressed as quantity and percentage. One-way analysis of variance (one-way ANOVA) was used for comparisons between the two groups. The Shapiro-Wilk normality test was used to detect whether each group of data was normally distributed, and comparisons between the two groups was performed by t-test (normally distributed data) and Welch's correction test (nonpositive distribution data); categorical variables were analyzed by the chi-square test, continuity-adjusted chi-square test, or Fisher's exact test; and multiple comparisons were analyzed by the least significant difference (LSD) method. P <0.05 was considered statistically significant.

RESULTS

Patient Recruitment

From October 1, 2020, to March 30, 2021, 238 cases of gastrointestinal tumor surgery occurred in our hospital; 121 cases were excluded, and 117 cases were included (**Figure 1**; **Table 1**). At the same time, 55 close relatives of patients were included in the control group and completed the same tests. There was no significant difference between the experimental group and the control group in terms of age ($P = 0.085$), body mass index (BMI) ($P = 0.982$), or education level ($P = 0.414$) (**Table 2**).

Perioperative Outcome

Comparing patients with VD deficiency and patients without VD deficiency, there was no significant difference between the two in the use of anesthetic drugs, anesthesia time, operation time, blood loss and complications within 30 days after surgery ($P > 0.05$). Compared with non-POCD patients, POCD patients had more postoperative complications ($P = 0.009$) and longer hospital stay ($P = 0.030$) (**Table 3**).

PND Statistics

This study showed that the number of patients who developed POCD after surgical anesthesia was 39 at 7 days, 24 at 15 days, 12 at 30 days, and 7 at 90 days. Among them, the incidence of POCD in patients with vitamin D deficiency (77/117) was 46.7% (36/77) 7 days after surgery, 31.2% (24/77, four new cases) 15 days after surgery, 15.6% (12/77) 30 days after surgery, and 9% (7/77) 90 days after surgery, which was much higher than that in patients without vitamin D deficiency (40/117), the incidence of POCD in non-deficient patients was 7.5% (3/40, present only 7 days after surgery) ($P < 0.000$), showing that there was a correlation between preoperative vitamin D deficiency and POCD, and that higher preoperative levels of serum vitamin D (25OH-D) effectively reduced the occurrence of POCD (**Figure 2**; **Table 4**).

Changes in Serum Vitamin D and GSH

This study also found that 65.8% (77/117) of patients had vitamin D deficiency before surgery, which is consistent with the findings of previous related studies (5, 18). Moreover, after surgical anesthesia, the serum levels of 25OH-D (vitamin D) of all patients decreased significantly compared with those before surgery ($P < 0.001$) (**Figure 3**), reaching the lowest value 15 days after surgery then rising gradually. Patients with vitamin D deficiency had a greater rate of increase than those without vitamin D deficiency.

TABLE 2 | Baseline and follow-up data of control subjects and patients.

	Control subjects ($n = 55$)	All patients ($n = 117$)	P-value
Age, year	71.91 ± 3.61	71.08 ± 3.62	0.165
BMI, kg/m^2	24.08 ± 2.12	23.57 ± 2.97	0.252
Male gender	42(76.4)	83(70.9)	0.457
Educational level, year	9.07 ± 1.69	9.17 ± 1.74	0.728
MMSE, score	27.41 ± 1.27	27.05 ± 1.17	0.064

This study also analyzed the trend of changes in serum GSH, found that there was no significant difference between patients with vitamin D deficiency and those without deficiency before surgery ($P = 0.179$). After surgical anesthesia, GSH and vitamin D decreased significantly, and the decrease in vitamin D deficient patients was greater than that in patients who were not vitamin D deficient ($P < 0.000$) (**Figure 4**).

Analysis of the Correlation Between Vitamin D Level and POCD

We use rank correlation, also called rank correlation, to analyze the correlation between preoperative vitamin D levels and POCD to describe the degree and direction of the correlation between the two. The results showed that the Spearman correlation coefficient was −0.417 and $P < 0.001$ when the two variables were at a two-sided confidence level of 0.01, indicating that the two variables are correlated and negatively correlated, that is, the higher the vitamin D level, the lower the probability of POCD.

Confounding Factor Analysis

This study used single factor logistic regression analysis to analyse count data [sex, smoking, drinking, hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease (COPD), history of surgery, ASA classification] and measurement data (vitamin D content, age, operation time, anesthesia). Time, education time, BMI, intraoperative blood loss, and anesthetic dosage were analyzed separately. The analysis showed that preoperative vitamin D content (deficiency, <12 ng/ml) was related to the occurrence of POCD ($P < 0.000$), and two potential confounding factors were identified: sex ($P = 0.034$) and age ($P = 0.048$). Further analysis concluded that non-vitamin D deficient patients had a reduced occurrence of POCD (OR: 0.075, 95% CI: 0.021-0.264, $P < 0.000$), and vitamin D deficient patients had an increased risk of POCD (OR: 13.333, 95% CI: 3.787-46.942, $P < 0.000$).

DISCUSSION

Due to the advancement of medical technology, the improvement of public health and the implementation of social welfare policies,

TABLE 3 | Perioperative variables.

	All patients $n = 117$	VD deficiency $n = 77$	No VD deficiency $n = 40$	P-value	POCD $n = 43$	No POCD $n = 74$	P-value
Duration of anesthesia, min	251.12 ± 20.63	250.44 ± 20.03	252.42 ± 21.93	0.624	250.91 ± 19.20	250.44 ± 21.54	0.933
Duration of surgery, min	205.55 ± 19.39	206.28 ± 19.80	204.12 ± 18.73	0.573	209.44 ± 20.03	200.14 ± 19.03	0.802
Anaesthetic drugs							
Propofol	500.89 ± 57.18	501.48 ± 57.02	499.75 ± 58.19	0.882	495.42 ± 58.37	504.07 ± 56.63	0.433
Remifentanil	1.20 ± 0.12	1.21 ± 0.12	1.19 ± 0.11	0.519	1.19 ± 0.13	1.21 ± 0.11	0.626
Sevoflurane	43.92 ± 8.61	44.23 ± 8.44	43.32 ± 9.00	0.587	45.30 ± 9.24	42.53 ± 8.84	0.681
Estimated blood loss	109.32 ± 12.92	108.45 ± 13.33	111.03 ± 12.08	0.313	109.27.44 ±10.91	101.44 ± 14.03	0.614
Complications within 30 days	19(16.2)	16(20.8)	3(7.5)	0.111	12(27.9)	7(9.4)	0.009
Mortality within 30 daysLength of stay in hospital	0(0.0) 15.01 ± 1.65	0(0.0) 15.25 ± 1.75	0(0.0) 14.88 ± 1.59	0.257	0(0.0) 15.44 ± 1.50	0(0.0) 14.76 ± 1.69	0.030

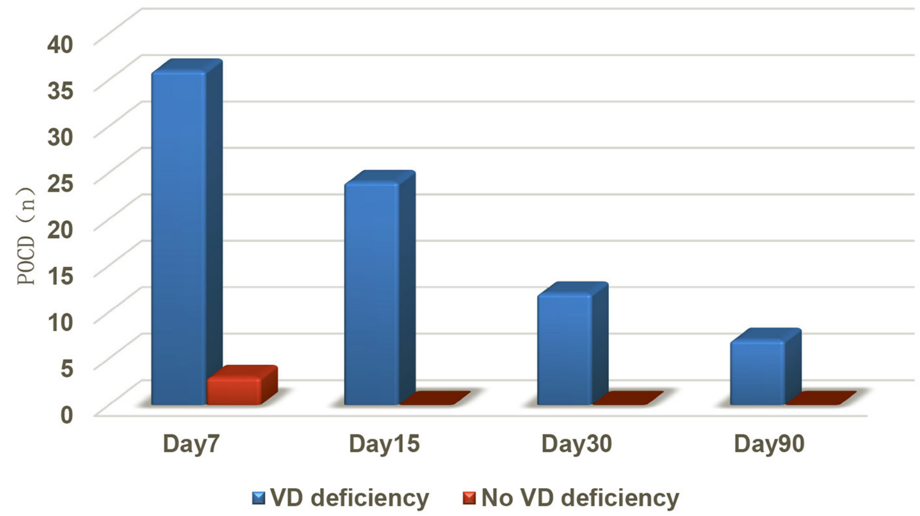

FIGURE 2 | Comparison of the number of patients with POCD between the two groups.

TABLE 4 | PND analysis.

	POCD $n = 43$	No POCD $n = 74$	*P*-value
VD deficiency	40(93.02)	37(50.00)	$P < 0.001$
No VD deficiency	3(6.98)	37(50.00)	
Vitamin D concentration, ng/ml	9.90 ± 1.71	13.03 ± 4.04	$P < 0.001$
Z-score, score			
day 7	2.94(2.81,3.07)	0.98(0.94,1.02)	$P < 0.001$
day 15	2.54(2.55,2.82)	1.11(1.10,1.18)	$P < 0.001$
day 30	2.46(2.15,2.54)	0.76(0.84,0.91)	$P < 0.001$
day 90	2.44(1.98,2.37)	0.71(0.62,0.67)	$P < 0.001$

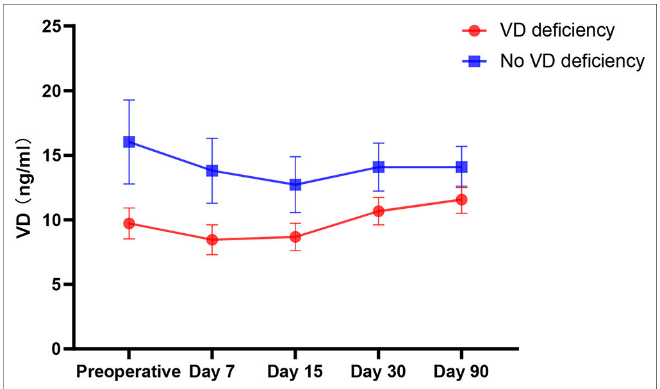

FIGURE 3 | Trends in Vitamin D.

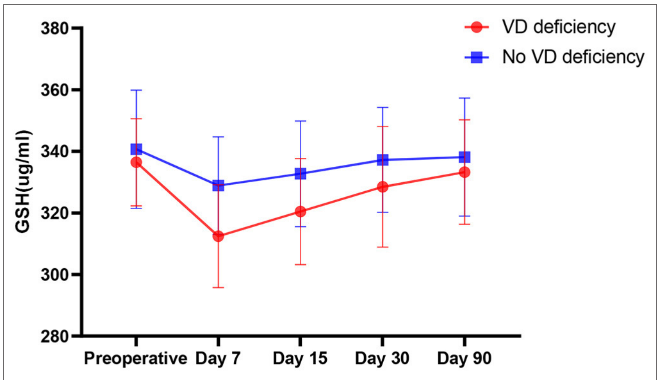

FIGURE 4 | Comparison of the change trend of serum GSH in patients with VD deficiency and non-VD deficiency before operation.

the proportion of the elderly in the global population has accelerated, and the problem of population aging has become the focus of attention of the whole society (19). At the 14th Vitamin D Nutrition Guidelines Symposium, some researchers proposed that half of the elderly in North America have vitamin D deficiency, and in other countries around the world, 2/3 of the elderly have the same problem (20). In recent years, researchers have begun to study the relationship between vitamin D deficiency and cognitive dysfunction in the elderly. Although a large number of studies have shown that vitamin D has a positive effect on brain function (21–23), but some studies have raised objections to this (24–26), they believe that the incidence of vitamin D on cerebrovascular adverse events is no different from the placebo group.

This study aims to better discover and explore the relationship between low levels of vitamin D and POCD in elderly patients through long-term clinical trials, so as to guide the direction of clinical perioperative medication and animal experiments. As far as we know, this is the first time that such a long period of perioperative vitamin D level monitoring has been carried out, and study the effect of surgical anesthesia on the vitamin

D concentration in the body, as well as the analysis of the relationship between preoperative vitamin D level and POCD.

Current investigations on the correlation of cognitive decline lack clinical case diagnosis and can only rely on functional scales. For patients after surgery, the diagnosis of POCD was obtained through telephone interviews via the Telephone Interview for Cognitive Status-modified (TICS-m), which is mainly used for the evaluation of cognitive impairment, namely, memory impairment, but has poorer mental flexibility and function evaluation. Compared with the method adopted in this experiment, it is more sensitive to diagnosis, and the specificity is poor. In this study, we used color-word separation experiments, digital symbol conversion experiments, and picture memory experiments on all patients, including those in the control group, to evaluate cognitive status. These experiments included the possible influence of surgery and anesthesia on areas such as memory, concentration, graphic and visual memory, writing flexibility, judgment, and brain speed. The diagnosis is based on the International Study of POCD1 (ISPOCD1). This diagnostic method excludes the learning effect of repeated measurement and the error caused by measurement at different times and has good sensitivity and specificity.

Our research results show that among 117 elderly patients who underwent gastrointestinal tumor surgery, 65.8% (77/117) were vitamin D deficient, and of these, 46.7% (36/77, 7 days after surgery) and 31.2% (24/77, 15 days after surgery), 15.6% (12/77, 30 days after surgery), and 9% (7/77, 90 days after surgery) of patients developed PND, which is much higher than the percentage of patients without vitamin D deficiency (3/40, 7.5%, and only exists 7 days after surgery) ($P < 0.000$). This suggests that low levels of serum 25(OH)D may be related to POCD, and higher concentrations of serum 25(OH)D can reduce the incidence of POCD.

After statistical analysis of other confounding factors that may cause POCD, we found that sex ($P = 0.034$) and age ($P = 0.048$) were also related to the occurrence of POCD. However, after correcting for these confounding factors (logistic regression), sex ($P = 0.080$, 95% CI: 0.906-5.664) and age ($P = 0.219$, 95% CI: 0.953-1.232) were excluded. Vitamin D level was still the key factor affecting the occurrence of POCD (P<0.000, 95% CI: 0.565-0.847).

The study also found that 65.8% (77/117) of patients were vitamin D deficient before surgery and that after surgery anesthesia, the serum 25OH-D (vitamin D) content of all patients decreased significantly compared with that before surgery ($P < 0.001$); the lowest value was reached 15 days after surgery. It is speculated that oxidative stress occurs in the human body after surgery, which depletes the body of vitamin D. At the same time, gastrointestinal function was not restored after the operation, and vitamin D in food could not be well absorbed. Moreover, long-term bed rest after surgery and insufficient sun exposure may reduce the synthesis of vitamin D in the body. After 15 days after surgery, vitamin D levels began to rise gradually, and patients with vitamin D deficiency had a greater rate of increase than non-deficient patients. It is speculated that on the one hand, the patient's gastrointestinal function recovers after the operation and can absorb nutrients in the diet well; on the other hand, whether there is a "ceiling" effect in the vitamin D absorption process in elderly patients—that is, if the patient is presently vitamin D deficiency, the rate of increase will increase rapidly after supplementation, and if the patient is in a non-deficient state, the rate of increase will be slower as the patient cannot fully absorb and synthesize vitamin D in food. This requires further research.

Studies have shown that the antioxidant effect of vitamin D is achieved, on the one hand, by inhibiting the production of nitric oxide synthase (27) and, on the other hand, by activating the inherent antioxidant pathway to enhance the content of γ-glutamyl transpeptidase, thus increasing the level of glutathione (28). As a natural antioxidant, glutathione can protect the integrity of oligodendrocytes and nerve conduction pathways and play a vital role in the transmission of nerve information. Therefore, we also carried out simultaneous detection of GSH in the body. According to the experimental results, compared with preoperative levels, serum GSH after surgical anesthesia also decreased to varying degrees, and the levels of preoperative vitamin D deficient patients decreased more significantly than those of patients without a vitamin D deficiency ($P < 0.000$). This also indirectly proves that surgical anesthesia causes oxidative stress in patients, and preoperative vitamin D deficient patients have more severe oxidative stress. At the same time, studies have confirmed (29) that the decline in serum GSH may cause cognitive dysfunction in elderly patients. It is speculated that this may also be one of the reasons for the occurrence of POCD due to vitamin D deficiency.

Although this study found differences in the effects of serum vitamin D concentrations on POCD, there are still some shortcomings. First, studies have shown that there is a correlation between the patient education levels and the occurrence of postoperative cognitive dysfunction (13). In order to eliminate this interfering factor, this study set a higher level of education time (≥8 years). The setting excluded many elderly patients from the scope of this experiment, which is the biggest regret of the experiment. Second, the experimental cases were mainly collected in winter, and the vitamin D levels of elderly patients are generally low in this season, and the patients all underwent gastrointestinal tumor surgery, so they spent a long time in bed, which decreased sun exposure and affected the postoperative vitamin D concentration. Third, the patients all received radiotherapy and chemotherapy after the operation, and the radiotherapy and chemotherapy drugs used may have had some influence on the experimental results. Fourth, there was a large difference in the number of males and females in the included cases, which makes it impossible to fully analyse the sex differences.

CONCLUSION

Our results show that 65.8% of elderly patients undergoing gastrointestinal tumor surgery have vitamin D deficiencies and that 46.7% of them have neurocognitive disorders after surgery, the incidence of POCD is much higher than that of patients without vitamin D deficiency; moreover, a small number of patients still have cognitive dysfunction even 90 days after surgery. Thus, a correlation between low levels of serum vitamin D and the occurrence of POCD in elderly patients is thought to exist, this may be related to the decrease in antioxidant stress in the body caused by vitamin D deficiency. The underlying mechanism and whether vitamin D supplementation can reduce the occurrence of POCD requires further study.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of People's Hospital of Changzhi City. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZhan and YYu designed the study and wrote the manuscript. JZhan, XZ, YYa, and JZhao performed the experiments. JZhan and XZ analyzed the data. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Rundshagen I. Postoperative cognitive dysfunction. *Dtsch Arztebl Int.* (2014) 111:119-25. doi: 10.3238/arztebl.2014.0119
2. Scott DA, Evered LA, Silbert BS. Cardiac surgery, the brain, and inflammation. *J Extra Corpor Technol.* (2014) 46:15–22. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4557505/
3. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, et al. Long term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD Investigators. International study of post-operative cognitive dysfunction. *Lancet.* (1998) 351:857–61. doi: 10.1016/S0140-6736(97)07382-0
4. Kweder H, Eidi H. Vitamin D deficiency in elderly: risk factors and drugs impact on vitamin D status. *Avicenna J Med.* (2018) 8:139-46. doi: 10.4103/ajm.AJM_20_18
5. Lu L, Yu Z, Pan A, Hu FB, Franco OH, et al. Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. *Diabetes Care.* (2009) 32:1278-83. doi: 10.2337/dc09-0209
6. Zhao J, Xia W, Nie M, Zheng X, Wang Q, et al. The levels of bone turnover markers in Chinese postmenopausal women:Peking vertebral fracture study. *Menopause.* (2011) 18:1237-43. doi: 10.1097/gme.0b013e31821d7ff7
7. Groves NJ, McGrath JJ, Burne TH. Vitamin D as a neurosteroid affecting the developing and adult brain. *Annu Rev Nutr.* (2014) 34:117-41. doi: 10.1146/annurev-nutr-071813-105557
8. Shin YC, Jung CH, Kim HJ, Kim EJ, Lim SW. The associations among vitamin D deficiency, C-reactive protein, and depressive symptoms. *J Psychosom Res.* (2016) 90:98-104. doi: 10.1016/j.jpsychores.2016.10.001
9. Jiang P, Zhang LH, Cai HL, Li HD, Liu YP, Tang MM, et al. Neurochemical effects of chronic administration of calcitriol in rats. *Nutrients.* (2014) 6:6048-59. doi: 10.3390/nu6126048
10. Stewart A, Wong K, Cachat J, Elegante M, Gilder T, et al. Neurosteroid vitamin D system as a nontraditional drug target in neuropsychopharmacology. *Behav Pharmacol.* (2010) 21:420-6. doi: 10.1097/FBP.0b013e32833c850f
11. DeLuca GC, Kimball SM, Kolasinski J. Review: the role of vitamin d in nervous system health and disease. *Neuropathol Appl Neurobiol.* (2013) 39:458-84. doi: 10.1111/nan.12020
12. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Anesthesiology.* (2018) 129:872–9. doi: 10.1097/ALN.0000000000002334
13. Li X, Wen DX, Chen J, Li LZ, Wan YJ, Diao S, et al. Multi-center clinical study on morbidity and related factors of postoperative mental and cognitive disorder in the elderly. *J Clin Anesthesiol.* (2009) 25:652–4. Available online at: https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjIwMzIyEhBsY216eHp6MjAwOTA4MDAyGgg0azFqeHlkMw%3D%3D
14. Institute of Medicine, Food and Nutrition Board; Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D.* Washington, DC: National Academies Press (2011).
15. Monk TG, Weldon BC, Garvan CW, Dede DE, Aa MT, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology.* (2008) 108:18–30. doi: 10.1097/01.anes.0000296071.19434.1e
16. Canet J, Raeder J, Rasmussen LS, Enlund M, Kuipers HM, et al. Cognitive dysfunction after minor surgery in the elderly. *Acta Anaesthesiol Scand.* (2003) 47:1204–10. doi: 10.1046/j.1399-6576.2003.00238.x
17. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med.* (2001) 344:395–402. doi: 10.1056/NEJM200102083440601
18. Zhang Y, Shan GJ, Zhang YX, Cao SJ, Zhu SN, Li HJ, et al. Preoperative vitamin D deficiency increases the risk of postoperative cognitive dysfunction: a predefined exploratory sub-analysis. *Acta Anaesthesiol Scand.* (2018) 62:924–35. doi: 10.1111/aas.13116
19. Kirkwood TB. Global aging and brain. *Nutr Rev.* (2010) 68:65-9. doi: 10.1111/j.1753-4887.2010.00343.x
20. Anthony WN, Roger B, Susan JW, Reinhold V, Paul L. 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol.* (2007) 103:204-5. doi: 10.1016/j.jsbmb.2006.12.071
21. Skalaka A, Galas A, Grodzicki T. 25-hydroxy vitamin D and physical and cognitive performance in older people with chronic conditions. *Pol Arch Med Wewn.* (2012) 122:162-9. doi: 10.20452/pamw.1186
22. Slinin Y, Paudel M, Taylor BC, Ishani A, Rossom R, et al. Association between serum25(OH) vitamin D and the risk of cognitive decline in older women. *J Gerontol A Biol Sci Med Sci.* (2012) 67:1092-8. doi: 10.1093/gerona/gls075
23. Llewellyn DJ, Lang IA, Langa KM, Melzer D. Vitamin D and cognitive impairment in the elderly U.S. population. *J Gerontol A Biol Sci Med Sci.* (2011) 66:59-65. doi: 10.1093/gerona/glq185
24. Mahmoud B, Babikir K, Yazan Z, Owais B, Harsukh D, et al. Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. *JAMA Cardiol.* (2019) 4:765-76. doi: 10.1001/jamacardio.2019.1870
25. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* (2019) 380:33-44. doi: 10.1056/NEJMoa1809944
26. Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, et al. Effect of monthly high-dose vitamin d supplementation on cardiovascular disease in the vitamin D assessment study : a randomized clinical trial. *JAMA Cardiol.* (2017) 2:608–16. doi: 10.1001/jamacardio.2017.0175
27. Chang JM, Kuo MC, Kuo HT, Hwang SJ, Tsai JC, Chen HC, et al. 1-alpha, 25-Dihydroxyvitamin D3 regulates inducible nitric oxide synthase messenger RNA expression and nitric oxide release in macrophage-like RAW 264.7 cells. *J Lab Clin Med.* (2004) 143:14–22. doi: 10.1016/j.lab.2003.08.002
28. Garcion E, Sindji L, Leblondel G, Brachet P, Darcy F. 1,25-dihydroxyvitamin D3 regulates the synthesis of gamma-glutamyl transpeptidase and glutathione levels in rat primary astrocytes. *J Neurochem.* (1999) 73:859–66. doi: 10.1046/j.1471-4159.1999.0730859.x

29. Charisis S, Ntanasi E, Yannakoulia M, Anastasiou CA, Kosmidis MH, Dardiotis E, et al. Plasma GSH levels and Alzheimer's disease. A prospective approach: results from the Heliad study. *Free Radic Biol Med.* (2021) 162:274–82. doi: 10.1016/j.freeradbiomed.2020.10.027

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Attila Szabo,
University of Oslo, Norway

REVIEWED BY
Manu Suresh Sharma,
Yale University, United States

*CORRESPONDENCE
Nikhil Ravindranath Tondehal
drnik.tondehal@gmail.com

†These authors have contributed equally to this work and share last authorship

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Commentary: Correlation analysis of serum vitamin D levels and post-operative cognitive disorder in elderly patients with gastrointestinal tumor

Nikhil Ravindranath Tondehal[1]*, Saadiya Hawa[2], Anem Sajid Malik[3], Kazi Nadia Hamid[4], Ashley Malekunnel[5], Mahwish Adnan[6†], Chintan Trivedi[6†], Zeeshan Mansuri[7†] and Shailesh Jain[6†]

[1]Department of Psychiatry, Mount Sinai Beth Israel, New York, NY, United States, [2]Department of Epidemiology and Population Health, Stanford University, Palo Alto, CA, United States, [3]King Edward Medical University, Lahore, Pakistan, [4]Sylhet MAG Osmani Medical College, Sylhet, Bangladesh, [5]Amala Institute of Medical Sciences, Thrissur, Kerala, India, [6]Department of Psychiatry, Texas Tech University of Health Sciences, Midland, TX, United States, [7]Department of Psychiatry, Boston Children's Hospital, Boston, MA, United States

KEYWORDS

POCD, gastrointestinal surgery, abdominal surgery, vitamin D level deficiency, cognitive change

A Commentary on

Correlation analysis of serum vitamin D levels and postoperative cognitive disorder in elderly patients with gastrointestinal tumor

Zhang, J., Zhang, X., Yang, Y., Zhao. J., and Yu, Y. *Front Psychiatry.* (2022) 13:893309. doi: 10.3389/fpsyt.2022.893309

Dear Editor,

We read with great interest the article, 'Correlation Analysis of Serum Vitamin D Levels and Post-operative Cognitive Disorder (POCD) in Elderly Patients With Gastrointestinal Tumor' (1). This relevant article has explored the ongoing discussion regarding Vitamin D's multiple roles in maintaining health.

We have the following additional thoughts. The study missed addressing the complications faced during recovery from the surgery. Examples that can influence cognition are anesthesia recovery and electrolyte imbalance because of fluid loss during or after the surgery. Also, body weight plays a role in anesthesia recovery, i.e., lipid-soluble anesthetics with redistribution may affect a smooth recovery and result in continued confusion (2). The study failed to consider the association between the different anesthesia depths and POCD (3). The study misses considering the role of post-operative pain management in altering cognition (4). Elderly patients with gastrointestinal tumors may have fat depletion, influencing the absorption of fat-soluble vitamins such as Vitamins A, D, E, and K (5). Nutrient absorption is affected in most gastrointestinal tumors, especially fat absorption (6). Vitamins D, A, and K have antioxidant properties that influence post-surgery recovery (7, 8). Therefore, one way to identify absorption abnormalities could be to check the levels of other fat-soluble vitamins (A, E, and K). These findings suggest that low Vitamin D levels could be an expected and coincidental finding (9).

As Major Depressive Disorder affects cognition, screening patients for pre-existing depression could have been informative (10). The study discusses different confounders and mentions age and sex as significant confounders. However, the article does not clarify whether the odds ratios presented are crude or adjusted using multivariate logistic regression. In addition, women are more prone to osteoporosis and low vitamin D levels after menopause (11). It would be helpful to know the extent of confounding by reviewing the crude and adjusted odds ratios. Controlling for factors mentioned above (depression, anesthesia recovery, and pain management) would help provide a robust result that would assist the clinicians.

We believe that addressing the above issues will further improve the impact of this study.

Author contributions

NT, SH, and ASM wrote the initial manuscript. AM and KH searched relevant literature and added references. NT, MA, CT, ZM, and SJ further proofread and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Zhang J, Zhang X, Yang Y, Zhao J, Yu Y. Correlation analysis of serum vitamin D levels and postoperative cognitive disorder in elderly patients with gastrointestinal tumor. *Front Psychiatry.* (2022) 13:893309. doi: 10.3389/fpsyt.2022.893309

2. Xie S, Xie M. Effect of dexmedetomidine on postoperative delirium in elderly patients undergoing hip fracture surgery. *Pak J Pharm Sci.* (2018) 31:2277–81.

3. Shu AH, Wang Q, Chen XB. Effect of different depths of anesthesia on postoperative cognitive function in laparoscopic patients: a randomized clinical trial. *Curr Med Res Opin.* (2015) 31:1883–7. doi: 10.1185/03007995.2015.1075968

4. Wang Y, Sands LP, Vaurio L, Mullen EA, Leung JM. The effects of postoperative pain and its management on postoperative cognitive dysfunction. *Am J Geriatr Psychiatry.* (2007) 15:50–9. doi: 10.1097/01.JGP.0000229792.31009.da

5. Rino Y, Oshima T, Yoshikawa T. Changes in fat-soluble vitamin levels after gastrectomy for gastric cancer. *Surg Today.* (2017) 47:145–50. doi: 10.1007/s00595-016-1341-5

6. Montoro-Huguet MA, Belloc B, Domínguez-Cajal M. Small and large intestine (I): malabsorption of nutrients. *Nutrients.* (2021) 13:1254. doi: 10.3390/nu13041254

7. National Research Council (US) Committee on Diet and *Health. Diet and Health: Implications for Reducing Chronic Disease Risk. Fat-Soluble Vitamins.* Washington, DC: National Academies Press (US) (1989). p. 11. Available online at: https://www.ncbi.nlm.nih.gov/books/NBK218749/ (accessed June 17, 2022).

8. Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res.* (2010) 89:219–29. doi: 10.1177/0022034509359125

9. Javorsky BR, Maybee N, Padia SH, Dalkin AC. Vitamin D deficiency in gastrointestinal disease. *Pract Gastroenterol.* (2006) 30:52–72.

10. Morimoto SS, Kanellopoulos D, Alexopoulos GS. Cognitive impairment in depressed older adults: implications for prognosis and treatment. *Psychiatr Ann.* (2014) 44:138–42. doi: 10.3928/00485713-20140306-05

11. Narula R, Tauseef M, Ahmad IA, Agarwal K, Ashok A, Anjana A. Vitamin d deficiency among postmenopausal women with osteoporosis. *J Clin Diagn Res.* (2013) 7:336–8. doi: 10.7860/JCDR/2013/5022.2761

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ORIGINAL RESEARCH
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Effect of Different Vitamin D Levels on Cognitive Function in Aged Mice After Sevoflurane Anesthesia

Jialei Zhang[1,2†], Xiaoling Zhang[3], Yongyan Yang[1], Jun Zhao[3], Wenqing Hu[4] and Yonghao Yu[1†]*

[1] Department of Anesthesiology, Tianjin Medical University General Hospital, Tianjin, China, [2] Department of Anesthesiology, Changzhi People's Hospital Affiliated to Changzhi Medical College, Changzhi, China, [3] Department of Oncology, Changzhi People's Hospital Affiliated to Changzhi Medical College, Changzhi, China, [4] Department of Gastrointestinal Surgery, Changzhi People's Hospital Affiliated to Changzhi Medical College, Changzhi, China

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Edited by:
Diansan Su,
Shanghai Jiao Tong University, China

Reviewed by:
Lei Zhang,
Shanghai Jiao Tong University, China
Fuhai Ji,
The First Affiliated Hospital of Soochow University, China

***Correspondence:**
Yonghao Yu
yuyonghao@126.com;
yyu@tmu.edu.cn

†ORCID:
Jialei Zhang
orcid.org/0000-0001-7251-0075
Yonghao Yu
orcid.org/0000-0003-2556-3814

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Although the biological relationship between vitamin D (VD) deficiency and cognitive function has been recognized by many scholars, the theoretical mechanisms involved are still not well-understood. In this study, we demonstrated the role of VD in alleviating the cognitive dysfunction in aged mice caused by sevoflurane anesthesia. Forty female C57BL/6 mice aged 12 months were selected for the experiment. VD (-) and VD (+) mouse models and sevoflurane anesthesia models were established. Mice were randomly divided into normal elderly group (NC group), normal aged mice + sevoflurane anesthesia treatment group (NS group), aged VD (-) mice + sevoflurane anesthesia treatment group [VD (-) group], and aged VD (+) + sevoflurane anesthesia treatment group [VD (+) group]. To compare the emergence time after sevoflurane anesthesia in aged mice with different levels of VD and to test the cognitive function of four groups through the water maze. Inflammatory factor expression and cholinergic activity in hippocampus tissue of all mice were measured at the end of behavioral tests. These data show that, low levels of VD aggravated the delayed emergence and cognitive dysfunction in aged mice caused by sevoflurane anesthesia, while higher levels of VD mitigated this impairment by enhancing cholinergic activity and reducing inflammatory factor expression in the hippocampus.

Keywords: vitamin D, sevoflurane, aged, POCD, inflammatory, cholinergic system

INTRODUCTION

The aging population has become a focus of society as a whole, and with the advent of an aging society and advances in surgical techniques and anesthesia management, more elderly patients are being treated surgically and the incidence of post-operative cognitive dysfunction (POCD) is increasing and gaining more attention. POCD is one of the common complications after surgery, which is mainly manifested by the degeneration of cognitive functions such as memory, attention and information processing speed after anesthesia and surgery (Vutskits and Xie, 2016). The occurrence of POCD may prolong a patient's hospital stay, increase the risk of death, consume a large amount of medical resources, and impose a heavy economic and social burden on patients and their families. Studies have shown that (Monk et al., 2008), advanced age is an independent risk factor for the development of POCD, regardless of the type of surgery. Delayed emergence is also a common complication after general anesthesia in elderly patients, and anesthesia and surgery are currently considered to be the main causes of its occurrence, while advanced age is a clear risk factor, with the degree of this risk increasing with age (Dringenberg and Olmstead, 2003).

Vitamin D (VD) deficiency has become a public health problem that affects the whole world, especially in the elderly population, and it is becoming more and more serious (Kweder and Eidi, 2018). It has been shown that (Groves et al., 2014; Jiang et al., 2014; Shin et al., 2016), VD as a neuroprotective hormone, is able to cross the blood-brain barrier to exert central protective effects by regulating the expression of key enzymes of neurotransmitter anabolism in the brain and is involved in a variety of brain activities including neurotrophy, neuroimmune regulation, and neurotransmission, and its deficiency is associated with a variety of neuropsychiatric disorders such as Parkinson's disease, schizophrenia, and depression (Stewart et al., 2010; DeLuca et al., 2013).

In recent years, many studies have investigated the correlation between VD deficiency and POCD in elderly patients, but the results have not been very clear. Previous clinical studies by our team have shown that (Zhang et al., 2022), low levels of serum VD correlate with POCD in elderly patients. To further investigate the relationship between VD levels and perioperative cognitive function, we constructed an animal model of VD deficiency and supplementation in aged mice, compared the emergence time and cognitive function of aged mice with different levels of VD after sevoflurane anesthesia treatment, and measured and analyzed the levels of ChAT, IL-1β and TNF-α in hippocampus to determine whether VD deficiency could cause delayed awakening and cognitive function impairment in aged mice after anesthesia and its possible mechanism, and whether VD supplementation could reverse this impairment.

MATERIALS AND METHODS

Experimental Animals

Forty female C57BL/6 mice aged 12 to 14 months [SCXK (Beijing) Biotechnology Co., Ltd., License No. SCXK (Beijing) 2019-0010] were selected for the experiment. All animals were numbered and grouped using the random number method with SPSS statistical software. Mice were randomly divided into normal elderly group (NC group), normal aged mice + sevoflurane anesthesia treatment group (NS group), aged VD (-) mice + sevoflurane anesthesia treatment group [VD (-) group], and aged VD (+) + sevoflurane anesthesia treatment group [VD (+) group], with 10 mice in each group. VD (-) and VD (+) mouse models and sevoflurane anesthesia models were established.

Vitamin D (-) mouse model was established: the outside of the cage of aged mice was covered with a shading curtain, without ultraviolet light, and the ratio of day to night was 12:12, keep the environment dry and ventilated, and feed them with special feeds that do not contain VD. After two months (during the pre-experiment, blood was collected once a month, and compared with normal aged mice, it was finally found that there was a difference in the dark for two months, in the formal experiment, the mice were directly kept in the dark for two months), blood was collected from the inner canthal vein. The content of VD [25 (OH) D3] was measured, and the difference was statistically significant compared with the normal elderly group, which was regarded as successful modeling.

Establishment of VD (+) mouse model: According to the literature (Jiang et al., 2014), 100 ng/kg calcitriol (Roche, Germany) was administered to aged mice in the VD (+) group by gavage every morning. One month later (during the pre-experiment, blood was collected once a month, and compared with normal aged mice, it was finally found that there was a difference in gavage for 1 month, and in the formal test, the gavage was chosen for 1 month), blood was collected from the inner canthal vein. The content of VD [25 (OH) D3] was measured, and the difference was statistically significant compared with the normal elderly group, which was regarded as successful modeling.

The normal elderly group was fed with normal feed, tap water and clean-grade feeding.

Feeding is carried out according to the results of the pre-experiment. Model feeding was performed on the aged mice in the aged VD (-) group first, and after one month, the aged mice in the aged VD (+) group were modeled and fed to ensure that all experimental mice were kept in the same age group.

After the model of VD (+) and VD (-) was successfully established, treated with sevoflurane anesthesia with the NS group together. Three groups were exposed to 3% sevoflurane and 60% O_2 daily for 2 h in a closed environment for 3 consecutive days, while mice in the NC group were exposed to the same closed environment and inhaled only 60% O2 daily for 2 h for 3 consecutive days.

After the anesthesia time was over, the mice were removed from the confined environment and the recovery time of the flip reflex was recorded. According to the literature (Rebuelto et al., 2004), the recovery time of the flip reflex was defined as the ability to flip the mice to the prone position twice in a row within 2 s after flipping them to the dorsal recumbent position, and this time was taken as the emergence time.

After the pre-paration of the anesthesia model, the water maze directional navigation experiment was performed at a fixed time every morning on the 3th to the 7th day, and the water maze space exploration experiment was performed on the morning of the 8th day. All feeding programs were performed normally during the behavioral testing.

The experimental scheme was approved by the Ethics Committee of the Animal Experiment Center of Tianjin Medical University.

Water Maze Experiment

The water maze experiment consisted of two parts: a navigation experiment and a spatial exploration experiment. This experiment is mainly used to test the long-term spatial memory of mice. The water maze consisted of a cylindrical tank with a diameter of 120 cm and a depth of 50 cm containing a platform with a diameter of 10 cm. Four signs with different colors and shapes were placed in symmetrical positions on the wall of the cylinder to facilitate learning and memory in the mice. An infrared monitoring device was installed at a central

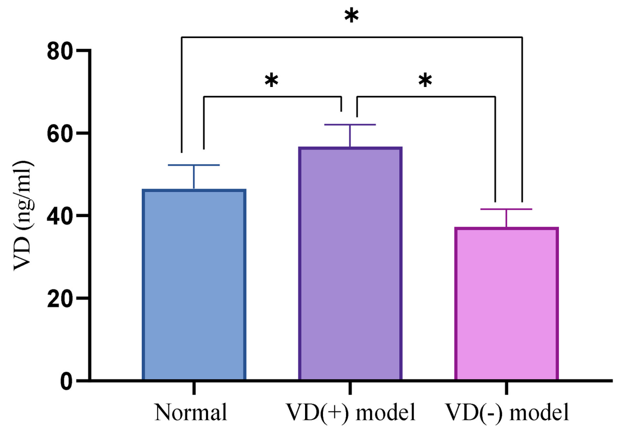

FIGURE 1 | Comparison of VD content after successful modeling, *$P < 0.05$.

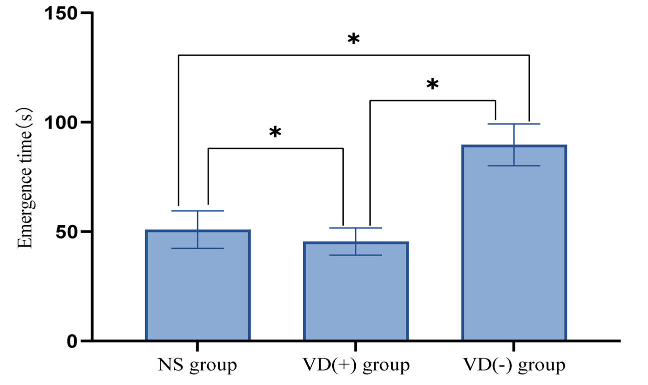

FIGURE 2 | Comparison of emergence time among the anesthesia treatment group, *$P < 0.05$.

location over the water maze and was connected to external devices. System software (Xinxin, Shanghai) was used to track the movements of the mice. Before the experiment, the tank was filled with water to 1 cm above the platform, and titanium dioxide water color pigment was added to the water and mixed well such that the platform was not visible. At the same time, heating equipment was used to maintain the water temperature at 21°C. Under the monitoring equipment, the tank was divided into four quadrants I, II, III, and IV—and the platform was placed in the first quadrant (target quadrant). The experiment consisted of two parts: a positioning navigation experiment and a spatial exploration experiment. From the first to the fourth day of the experiment, the mice were placed into the water from the midpoints of the four quadrants, facing the wall of the cylinder. The time to find the platform was recorded, while swimming (latency time) followed by staying on the platform for 5 s. If the mouse could not find the platform within 120 s, it was artificially induced to find the platform and allowed to stay on it for 20 to 30 s; in this case, the latency time was recorded as 120 s. Each mouse was placed into the water at an interval of 20 min. On the fifth day of the experiment, the platform was removed, and the mice were placed in the water facing the wall at the center point of the quadrant opposite to the target quadrant (quadrant III). The proportion of time spent swimming in the target quadrant and the number of platform crossings were counted and recorded.

Specimen Collection and Testing

The contents of VD in blood, ChAT,IL-1β and TNF-α in hippocampus were detected by ELISA.

After the model was successfully established, 0.1 ml of blood was collected from the medial canthal vein. After standing for 30 min, the supernatant serum was collected to detect the content of VD, which centrifuge at 4°C at 3000 r/min for 20 min. After all behavioral tests were completed, 0.5 ml of blood was collected by removing the eyeballs, and after standing for 30 min, centrifuged at 3,000 r/min at 4°C for 20 min, and the supernatant serum was collected to detect the content of VD. Mice were killed by dislocation method, hippocampal tissue was separated on ice, residual blood was washed with prefabricated PBS (0.01 mmol/L, pH = 7.40), weighed, cut into pieces, mixed with PBS solution, and ground on ice to a homogenized state, stand for 30 min, centrifuge at 5,000 r/min at 4°C for 10 min, take the supernatant. The contents of ChAT,IL-1β and TNF-α in hippocampus were determined by Elx800 microplate reader (Bio-Tek, United States).

Statistical Analysis

IBM SPSS Statistics 26.0, which is produced by SPSS, Inc., was used for data analysis. To compare data within groups, the *t*-test was utilized. To compare data between groups, one-way ANOVA and two-way ANOVA were utilized. The water maze test data were analyzed using repeated measures ANOVA. At the same time, Pearson correlation analysis was performed on the VD value and inflammatory factors in mice to determine the relationship between VD content and the expression of inflammatory factors. $P < 0.05$ means the difference is statistically significant.

RESULTS

Model Establishment

After aged mice in the VD (-) group were kept away from light and fed a VD-deficient diet for 2 months and those in the VD (+) group were administered calcitriol *via* gavage for 1 month, blood from the inner canthus vein was collected from NC group, NS group, and mice in the VD (+) and VD (-) groups. ELISA method was used to test the VD level of normal aged mice compared with VD (+) and VD (-) groups, and if the difference was statistically significant, the model was considered successful.

The results show that, VD (+) group (58.21 ± 5.62) has a VD concentration is higher than the NC group (45.30 ± 5.02) ($P < 0.001$), and the concentration of VD in VD (-) group (33.69 ± 5.33) is lower than NC group ($P < 0.001$). The data indicated that VD (+) and VD (-) models were established successfully (**Figure 1**).

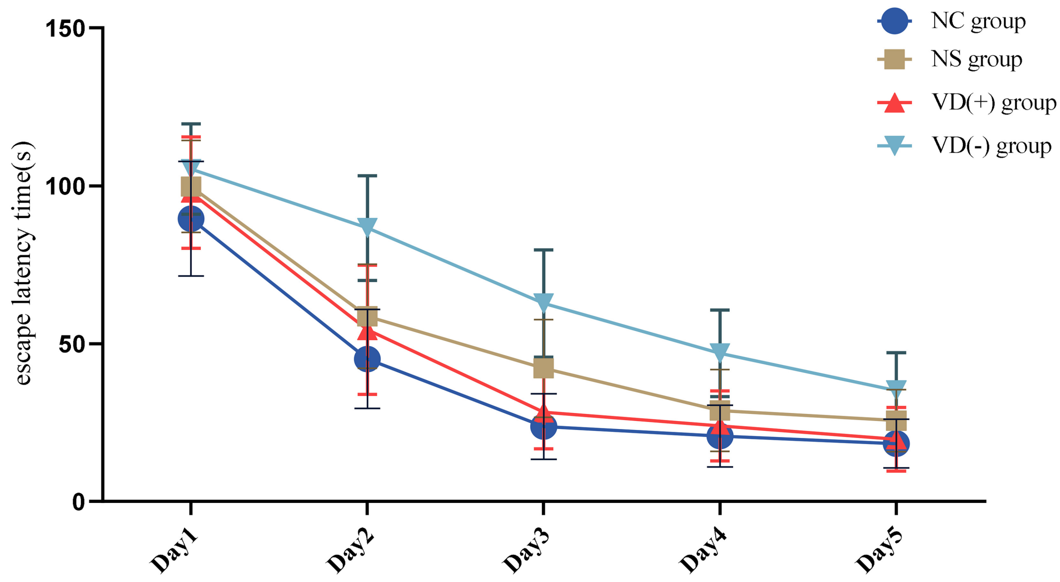

FIGURE 3 | Comparison of the results of the positioning navigation experiment between groups.

TABLE 1 | One-way ANOVA for NS group, VD (+) group and VD (-) group.

	Day 1	Day 2	Day 3	Day 4	Day 5
NS group	99.79 ± 14.57	58.72 ± 16.47	42.17 ± 15.52	28.88 ± 12.95	25.64 ± 9.81
VD (+) group	97.87 ± 17.59	54.38 ± 20.43	28.23 ± 11.52	23.97 ± 11.11	19.75 ± 10.06
VD (-) group	105.35 + 14.26	86.63 ± 16.61	62.78 ± 16.98	46.93 ± 13.67	35.17 ± 11.98
F	2.496	38.096	54.757	36.655	21.277
P	0.087	<0.001	<0.001	<0.001	<0.001

Comparison of Emergence Time Among the Anesthesia Treatment Group

The experimental results showed that the emergence time of VD (-) aged mice was significantly longer than that of NS group ($P < 0.001$) and VD (+) group ($P < 0.001$), while the emergence time of aged VD (+) mice was significantly lower than that of NS group ($P = 0.001$) (**Figure 2**).

Water Maze Test Results

In the water maze experiment, we conducted statistical analysis of each swimming escape latency time (positioning navigation experiment), the number of platform crossings (spatial exploration experiment) and the proportion of time spent in the target quadrant (spatial exploration experiment).

Comparison of Positioning Navigation Experiment (Escape Latency Time)

Statistical results showed that the duration of escape latency time was significantly longer in the NS and VD (-) groups compared with the NC group ($P < 0.05$), while the VD (+) group was longer than the NC group on days 1 and 2 ($P < 0.05$), and no significant difference was seen between days 3 and 5 and the NC group ($P > 0.05$) (**Figure 3**).

Meanwhile, we conducted a one-way ANOVA on the anesthesia-treated NS, VD (+), and VD (-) groups (**Table 1**).

Comparison of Spatial Exploration Experiment (the Number of Platform Crossings and Target Quadrant Time Percentage)

When comparing the number of platform crossings between groups, there was an overall decrease in the data for the NS, VD (+) and VD (-) groups after sevoflurane anesthesia treatment compared to the NC group. There was no statistical difference between the NC group and the VD (+) group ($P = 0.482$), but both groups were higher and statistically significant than the NS group ($P = 0.003$, $= 0.019$) and the VD (-) group ($P < 0.001$, < 0.001), while there was also a significant difference between the NS group and the VD (-) group ($P = 0.008$).

Compared with the NC group, the target quadrant activity time of aged mice in the NS, VD (+) and VD (-) groups were significantly decreased. Similar to the results of the crossing platform, there was no statistical difference between the NC group and the VD (+) group ($P = 0.456$), also, no significant difference was seen between the NS and the VD (+) group ($P = 0.129$), but there was a significant difference between the NC and NS groups ($P = 0.025$). The target quadrant dwell time was shortest in the aged mice of VD (-) group, much lower than that in the NC group (P = 0.003) and the VD (+) group (P = 0.020), but there was no statistical difference than the NS group (P = 0.262) (**Figure 4**).

Choline Acetyltransferase Vitality Results

Results of Choline Acetyltransferase Vitality Changes in the Hippocampus

In this study, ChAT vitality was chosen to represent the altered cholinergic system in hippocampal tissue. The ELISA results showed that ChAT viability tended to decrease in NS, VD (+) and VD (-) group compared with NC group, and no significant abnormalities were seen between the NC and VD (+) groups (P = 0.470), but both were higher than the NS (P = 0.010, = 0.029) and VD (-) groups ($P < 0.001$, < 0.001), while the NS group was higher than the VD (-) group (P = 0.009) (**Figure 5A**).

Correlation Analysis Between Different Vitamin D Levels and the Vitality of Choline Acetyltransferase

Correlation analysis of VD levels and ChAT viability in three groups [NS group, VD (+) group and VD (-) group] of aged mice treated with sevoflurane anesthesia showed, between VD level and ChAT, the Pearson correlation coefficient was 0.554 (P = 0.002), that is, VD levels are positively correlated with ChAT activity in the hippocampus (**Figure 5B**).

Inflammatory Markers Results

Expression of Inflammatory Factors in the Hippocampus

The results showed that the expression of TNF-α was significantly higher in the NS group, VD (+) group and VD (-) group compared to the NC group, but only the comparison of the VD (-) and NC groups showed significant differences ($P < 0.001$), there was no significant difference between the NC group and the NS group (P = 0.072), and with the VD (+) group (P = 0.794). A comparison of the NS, VD (+) and VD (-) groups treated with sevoflurane anesthesia showed that the TNF expression in the VD (-) group was much higher than that in the NS (P = 0.023) and VD (+) groups ($P < 0.001$), and also the difference between the NS and VD (+) groups was statistically significant (P = 0.030).

Analysis of IL-1β data showed that when comparing between groups, similar to TNF-α expression, the expression of IL-1β was significantly higher in the NS group, VD (+) group and VD (-) group compared to the NC group, but only the comparison of the VD (-) and NC groups showed significant differences (P = 0.002), there was no significant difference between the NC group and the NS group (P = 0.092), and with the VD (+) group (P = 0.568). Similarly, a comparison of the NS, VD (+) and VD (-) groups treated with sevoflurane anesthesia showed that the VD (+) group showed much lower IL expression than the NS (P = 0.043) and VD (-) groups (P = 0.001), while no significant difference was shown between the NS and VD (-) groups (P = 0.065) (**Figure 6**).

Correlation Analysis Between Different Vitamin D Levels and the Expression of Inflammatory Factors

Correlation analysis between VD level and inflammatory factor expression in aged mice in anesthesia treatment group [NS group, VD (+) group and VD (-) group] showed that: between VD level and TNF-α, the Pearson correlation coefficient was −0.453 (P = 0.012), that is, VD was negatively correlated with TNF-α expression; between VD level and IL-1β, the Pearson correlation coefficient was −0.516 (P = 0.003), that is, VD was negatively correlated with IL-1β expression. VD is more strongly correlated with IL-1β (**Figure 7**).

DISCUSSION

With the accelerated aging of the global population, the proportion of elderly patients undergoing various types of anesthesia is increasing year by year due to the need for medical treatment or physical examination. It has been reported that about one-fourth of elderly patients undergoing major surgery have significant cognitive decline, and nearly half of them may develop permanent cognitive impairment (Kotekar et al., 2018). Meanwhile, Research studies have shown that VD deficiency is very common in the elderly, with more than half of them having this problem (Anthony et al., 2007). Although the biological relationship between VD deficiency and cognitive function has been recognized by many scholars, the relevant theoretical mechanisms are still unclear, and most of the current studies focus on clinical correlation studies, lacking in-depth studies on the intrinsic mechanisms.

In this study, we investigated the possible mechanisms by which VD protects brain function in aged mice by establishing both VD deficiency and VD supplementation models and by comparing behavioral changes in aged mice with different VD levels after sevoflurane anesthesia, as well as changes in the expression of inflammatory factors and ChAT activity in the hippocampal region of aged mice in each group. Research shows that reducing VD levels in adult mice below the VD-deficient state (12 ng/ml) (Holick et al., 2011) can lead to severe abnormalities in calcium and phosphorus metabolism, as well as limb weakness, slow movement, and significantly reduced mobility (Chang et al., 2011), which would affect the experimental results of this study. Therefore, we considered the modeling successful when an aged VD (-) model was established with lower VD content than normal aged mice and the difference was statistically significant. Similarly, the VD (+) model was successfully established when the VD content of aged VD (+) mice was higher than that of normal aged mice and the difference was statistically significant. Animal studies have shown that female mice are more prone to cognitive dysfunction than male mice (Zhang et al., 2017). Therefore, female mice were selected in this study to improve the detection rate of neurocognitive disorders after anesthesia.

Delayed emergence refers to the state that 2 h after the cessation of general anesthesia administration, excluding cerebrovascular accidents, consciousness does not return and cannot respond to speech or stimulation with thought, which is one of the common complications of general anesthesia (Tzabazis et al., 2015). It has been shown that advanced age has become an independent influencing factor for delayed emergence (Tsai et al., 2011). In this study, we performed statistical analysis on the emergence time of aged mice with different levels of VD after

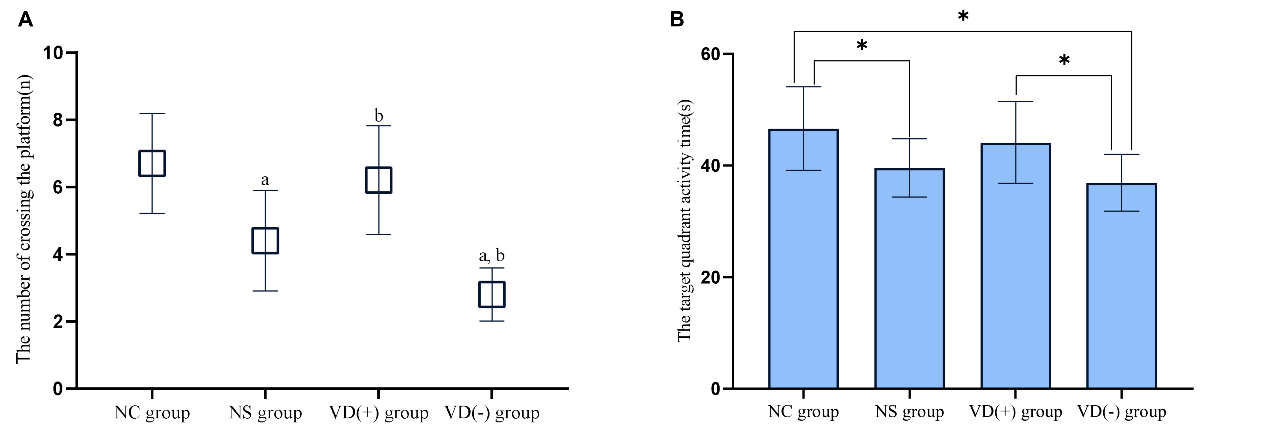

FIGURE 4 | Comparison of experimental results of spatial exploration. **(A)** Comparison of the times of crossing the platform: comparison with NC group: $^{a}P < 0.05$; comparison with NS group: $^{b}P < 0.05$. **(B)** Comparison of target quadrant activity time ratio: comparison between groups: $^{*}P < 0.05$.

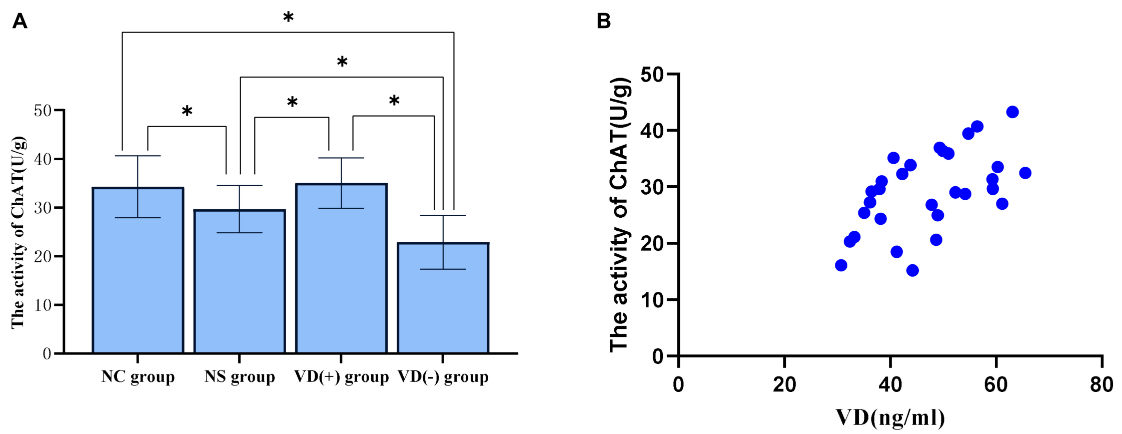

FIGURE 5 | Comparison of ChAT activity in hippocampal region between groups and correlation analysis between VD level and ChAT activity. **(A)** Comparison of the vitality of ChAT between the groups, $^{*}P < 0.05$. **(B)** Scatter plot of correlation analysis between VD and ChAT activity.

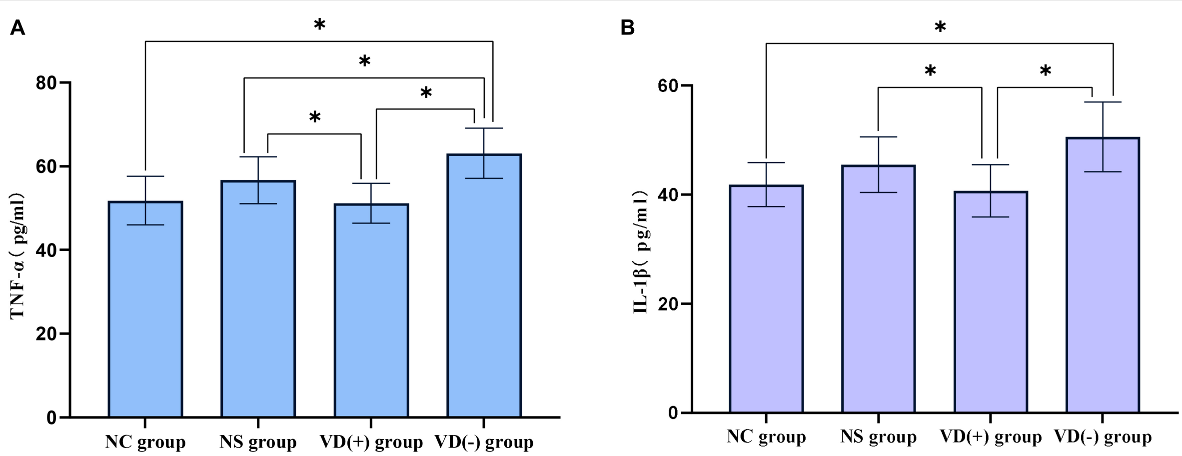

FIGURE 6 | Comparison of inflammatory factors between the control group and the anesthesia treatment group. **(A)** Comparison of TNF-α: between groups, $^{*}P < 0.05$. **(B)** IL-1β comparison: comparison between groups, $^{*}P < 0.05$.

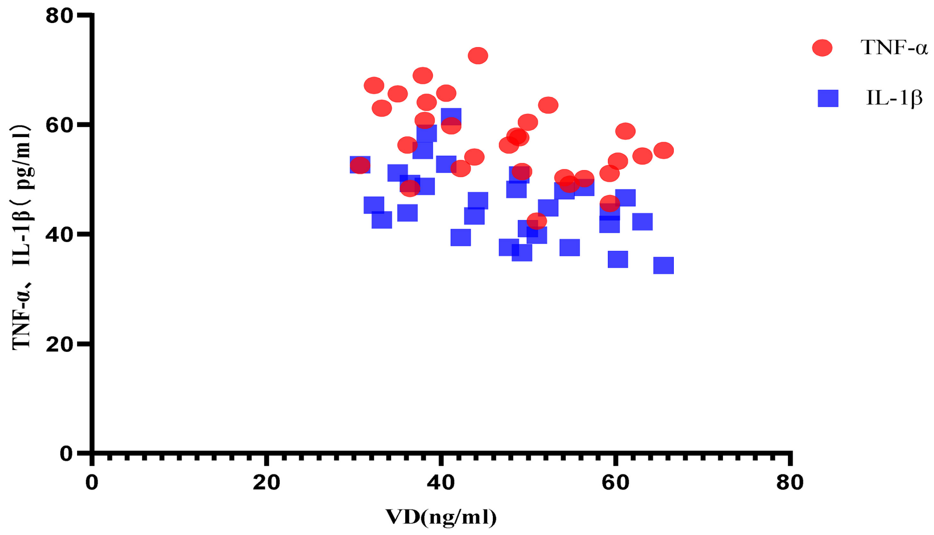

FIGURE 7 | Scatter plot of correlation analysis between VD and inflammatory factors.

sevoflurane anesthesia, and the results showed that the emergence time of the VD (+) group was significantly better than that of the NS and VD (-) groups, and the VD (-) group was the longest, suggesting that VD can play a certain role in promoting emergence after sevoflurane anesthesia.

Morris water maze test is divided into positioning navigation test and space exploration test. The former reflects the spatial learning ability of animals, and the latter reflects the spatial memory ability of animals. It is a classic method for evaluating long-term spatial learning and memory in rodents (Tian et al., 2019). The results of the water maze spatial exploration experiment showed that, after sevoflurane anesthesia treatment, the number of platform crossing was significantly decreased in the NS group compared to the NC group, demonstrating that sevoflurane anesthesia caused some impairment of cognitive function in aged mice, which is consistent with previous findings (Fei et al., 2020; Wang et al., 2021). And when comparing aged mice with different VD levels after sevoflurane anesthesia, it was found that VD (+) aged mice were significantly better than the NS and VD (-) groups, demonstrating that high serum levels of VD could reduce the cognitive impairment caused by sevoflurane. In the water maze positioning navigation test, the VD (+) group showed differences with the NC group only in the first two days, but in the third to fifth days, there was no significant difference between the two groups, and it was significantly lower than the NS and VD (-) groups, which showed that the elderly mice with high VD levels had better learning and memory abilities. In contrast, the VD (-) aged mice performed the worst in both the localized navigation test and the spatial exploration test, confirming that low levels of VD may aggravate the cognitive dysfunction caused by sevoflurane anesthesia.

In recent years, some scholars have proposed the "central cholinergic hypothesis" related to the occurrence of POCD (Urits et al., 2019). The central cholinergic system is an important neurotransmitter system involved in a variety of body behaviors, plays an important role in the regulation of arousal, attention, and related learning functions (Deibel et al., 2016; Hampel et al., 2018). As the most important neurotransmitter in the central cholinergic system, Ach plays an important role in learning, memory, and regulation of the sleep-wake cycle, and when its synthesis and metabolism are affected, it causes impairment of the cholinergic system, thus affecting cognitive function and sleep-wake transition (Mohr et al., 2015; Xiong et al., 2019). However, Ach is extremely unstable and easily hydrolyzed, so difficult to accurately determine its content. ChAT is a specific enzyme for Ach synthesis in cholinergic neurons and is consistent with the distribution of Ach in the Central Nervous System (CNS), so it is often used as a marker of cholinergic neurons or as an indirect response to Ach content (Luo et al., 2009).

The results of this study showed that sevoflurane anesthesia caused a decrease in ChAT activity in the hippocampal region of aged mice compared with normal aged mice, which is consistent with the results of previous studies (Yang et al., 2019b). And when comparing different levels of VD aged mice after sevoflurane anesthesia, it was found that ChAT vitality in the VD (+) group was significantly higher than that in the NS group, and ChAT vitality in the VD (-) group was the lowest, meanwhile, correlation analysis between VD levels and ChAT vitality after anesthesia revealed that there was a positive correlation between them, i.e., the higher the VD, the better the ChAT vitality, while the VD decreased, the ChAT vitality declined.

Previous clinical and animal studies have found that sevoflurane has some neurotoxicity and can cause cognitive decline by mediating the inflammatory response (Fan et al., 2018; Yin et al., 2019). Therefore, we analyzed the expression of inflammatory factors in hippocampal tissue. The results showed that there was no significant difference in the expression of TNF-α and IL-1β in the hippocampus of normal aged mice without anesthetic treatment and aged mice treated with sevoflurane, but why are there behavioral differences between the two? It is speculated that this may be due to the fact that the specimens were collected on the 8th day after anesthesia treatment and missed the acute phase of inflammatory factor expression, so the difference in inflammatory factor expression could not be detected, at the same time, sevoflurane anesthesia treatment can lead to the destruction of the cytoskeleton and synaptic structure of neurons in the hippocampus, and this change is relatively persistent (Xiao et al., 2016; Yang et al., 2019a), so resulting in this phenomenon seen in this study. However, when comparing aged mice with different levels of VD after sevoflurane anesthesia treatment, we found significant differences. It was found that the expression of inflammatory factors in VD (+) aged mice was significantly lower than that in NS aged mice and VD (-) aged mice, and the expression of inflammatory factors in VD (-) aged mice was significantly higher than that in NS aged mice. Similarly, we conducted a correlation analysis between the level of VD and the expression of inflammatory factors, and the results showed that the level of VD was negatively correlated with the expression of TNF-α and IL-1β, that is, the higher the level of VD, the lower the expression of inflammatory factors, and the lower the level of VD, the higher the expression of inflammatory factors.

In vivo and *in vitro* studies have shown that (Zhao et al., 2019; Yu, 2021), sevoflurane anesthetic treatment can lead to reduced ChAT activity in the hippocampus of aged mice, which in turn leads to cognitive dysfunction in aged mice, presumably due to reduced ChAT activity, resulting in reduced Ach synthesis, impaired central cholinergic system, and inhibition of cholinergic anti-inflammatory pathways, along with increased expression of inflammatory factors in the brain stimulated by sevoflurane (Yang et al., 2019a; Yin et al., 2019), ultimately leading to POCD, which is consistent with the results of the present study. The results of the present study showed that VD levels in aged mice were positively correlated with ChAT activity in the hippocampal region and, at the same time, negatively correlated with inflammatory factor expression in the hippocampal region. Therefore, we hypothesized that higher VD levels could enhance ChAT activity, activate the cholinergic anti-inflammatory system, reduce the inflammatory response in the brain, and thus reduce the occurrence of POCD. However, the mechanism by which VD enhances ChAT activity is unclear and needs to be further investigated.

A large body of evidence suggests that VD can exert potential biological functions in brain tissue and protect the nervous system, but the exact mechanism of action is unclear. It was found that pretreatment with VD ameliorated 6-hydroxydopamine-induced motor dysfunction and neuronal toxicity and greatly reduced the amount of neuronal apoptosis (Wang et al., 2001). In addition, similar to conventional antioxidants, VD inhibits the production of nitric oxide synthase (NOS), an enzyme whose expression is significantly elevated in CNS neurons and non-neurons in response to physical injury or disease, particularly in ischemic events, Alzheimer's disease, and Parkinson's disease (Chang et al., 2004). VD also increases γ-glutamyl transpeptidase levels by activating intrinsic antioxidant pathways (Garcion et al., 1999), thereby increasing glutathione levels and protecting the integrity of oligodendrocytes and neurotransmission pathways. Recent studies have shown that VD can elevate ACH levels and attenuate the resulting cognitive impairment by inhibiting the expression of neuroinflammatory factors including IL-1β, BDNF, and NF-κB caused by a high-fat diet (Farhangi et al., 2017).

In conclusion, our data show that sevoflurane-induced cognitive dysfunction in aged mice is associated with decreased cholinergic system viability and increased inflammatory factor expression in the hippocampal region, and that decreased VD levels *in vivo* can aggravate this impairment, which can be alleviated by pre-supplementation with VD, this may be related to the fact that VD increases ChAT activity, thereby activating central cholinergic anti-inflammatory pathways and inhibit the inflammatory factor expression in the brain. This finding may serve as a new therapeutic measure to clinically mitigate cognitive dysfunction in elderly patients after perioperative sevoflurane anesthesia, but until then, it still needs to be confirmed by numerous clinical trials, especially to qualify the optimal daily dose of VD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The experimental scheme was approved by the Ethics Committee of the Animal Experiment Center of Tianjin Medical University.

AUTHOR CONTRIBUTIONS

JiZ and YYu designed the study and wrote the manuscript. JiZ, XZ, YYa, and JuZ performed the experiments. JiZ, XZ, and WH analyzed the data. All authors contributed to the article and approved the submitted version.

REFERENCES

Anthony, W. N., Roger, B., Susan, J. W., Reinhold, V., and Paul, L. (2007). 13th Workshop consensus for vitamin D nutritional guidelines. *J. Steroid. Biochem. Mol. Biol.* 103, 204–205. doi: 10.1016/j.jsbmb.2006.12.071

Chang, J. M., Kuo, M. C., Kuo, H. T., Hwang, S. J., Tsai, J. C., Chen, H. C., et al. (2004). 1-alpha, 25- Dihydroxyvitamin D3 regulates inducible nitric oxide synthase messenger RNA expression and nitric oxide release in macrophage like RAW 264.7cells. *J. Lab. Clin. Med.* 143, 14–22. doi: 10.1016/j.lab.2003.08.002

Chang, Z., Zhang, Z., Luo, F., and Xu, F. (2011). Establish the animal model of vitamin D deficiency. *Chongqing Med.* 40, 1041–1043. doi: 10.3969/j.issn.1671-8348.2011.11.001

Deibel, S. H., Weishaupt, N., Regis, A. M., Hong, N. S., Keeley, R. J., and Balog, R. J. (2016). Subtle learning and memory impairment in an idiopathic rat model of

Alzheimer's disease utilizing cholinergic depletions and β-amyloid. *Brain Res.* 1646, 12–24. doi: 10.1016/j.brainres.2016.05.033

DeLuca, G. C., Kimball, S. M., and Kolasinski, J. (2013). Review:The role of vitamin d in nervous system health and disease. *Neuropathol. Appl. Neurobiol.* 39, 458–484. doi: 10.1111/nan.12020

Dringenberg, H. C., and Olmstead, M. C. (2003). Integrated contributions of basal forebrain and thalamus toneocortical activation elicited by pedunculopontine tegmental stimulation in urethane-anesthetized rats. *Neuroscience* 119, 839–853. doi: 10.1016/s0306-4522(03)00197-0

Fan, C. H., Peng, B., and Zhang, F. C. (2018). The postoperative effect of sevoflurane inhalational anesthesia on cognitive function and inflammatory response of pediatric patients. *Eur. Rev. Med. Pharmacol. Sci.* 22, 3971–3975. doi: 10.26355/eurrev_201806_15281

Farhangi, M. A., Mesgari-Abbasi, M., Nameni, G., Hajiluian, G., and Shahabi, P. (2017). The effects of vitaminD administration on brain inflammatory markers in high fat diet induced obese rats. *BMC Neurosci.* 18:81. doi: 10.1186/s12868-017-0400-1

Fei, X., Wang, J. X., Wu, Y., Dong, N., and Sheng, Z. Y. (2020). Sevoflurane-induced cognitive decline in aged mice: involvement of toll-like receptors 4. *Brain Res. Bull.* 165, 23–29. doi: 10.1016/j.brainresbull.2020.08.030

Garcion, E., Sindji, L., Leblondel, G., Brachet, P., and Darcy, F. (1999). 1,25-dihydroxyvitamin D3 regulates the synthesis of gamma-glutamyl transpeptidase and glutathione levels in rat primary astrocytes. *J. Neurochem.* 73, 859–866. doi: 10.1046/j.1471-4159.1999.0730859.x

Groves, N. J., McGrath, J. J., and Burne, T. H. (2014). Vitamin D as a neurosteroid affecting the developing and adult brain. *Annu. Rev. Nutr.* 34, 117–141. doi: 10.1146/annurev-nutr-071813-

Hampel, H., Mesulam, M. M., Cuello, A. C., Farlow, M. R., Giacobini, E., Grossberg, G. T., et al. (2018). The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain J. Neurol.* 141, 1917–1933. doi: 10.1093/brain/awy132

Holick, M. F., Hanley, D. A., Heaney, R. P., Murad, M. H., Weaver, C. M., Binkley, N. C., et al. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 96, 1911–1930. doi: 10.1210/jc.2011-0385

Jiang, P., Zhang, L. H., Cai, H. L., Li, H. D., Liu, Y. P., Tang, M. M., et al. (2014). Neurochemical effects of chronic administration of calcitriol in rats. *Nutrients* 6, 6048–6059. doi: 10.3390/nu6126048

Kotekar, N., Shenkar, A., and Nagaraj, R. (2018). Postoperative cognitive dysfunction -current preventive strategies. *Clin. Interv. Aging* 139, 2267–2273. S133896 doi: 10.2147/CIA

Kweder, H., and Eidi, H. (2018). Vitamin D deficiency in elderly:Risk factors and drugs impact on vitamin D status. *Avicenna J. Med.* 8, 139–146. doi: 10.4103/ajm.AJM-20-18

Luo, T. S., Tao, G. C., Yi, B., Li, P., and Shi, S. C. (2009). Effects of isoflurane on hippocampal ChAT expression and spatial learning and memory in aged rats. *J. Third Mil. Med. Univ.* 31, 2363–2366. doi: 10.3321/j.issn:1000-5404.2009.23.020

Mohr, F., Krejci, E., Zimmermann, M., and Klein, J. (2015). Dysfunctional Presynaptic M2 Receptors in the Presence of Chronically High Acetylcholine Levels: data from the PRiMA Knockout Mouse. *PLoS One* 10:e0141136. doi: 10.1371/journal.pone.0141136

Monk, T. G., Weldon, B. C., Garvan, C. W., Dede, D. E., van der Aa, M. T., and Heilman, K. M. (2008). Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 108, 18–30. doi: 10.1097/01.anes.0000296071.19434.1e

Rebuelto, M., Ambros, L., Waxman, S., and Montoya, L. (2004). Chronobiological Study of the Pharmacological Response of Rats to Combination Ketamine-Midazolam. *Chronobiol. Int.* 21:591. doi: 10.1081/CBI-200026466

Shin, Y. C., Jung, C. H., Kim, H. J., Kim, E. J., and Lim, S. W. (2016). The associations among vitamin D deficiency, C-reactive protein, and depressive symptoms. *J. Psychosom. Res.* 90, 98–104. doi: 10.1016/j.jpsychores.2016.10.001

Stewart, A. M., Wong, K., Cachat, J., Elegante, M., Gilder, T., Mohnot, S., et al. (2010). Neurosteroid vitamin D system as a nontraditional drug target in neuropsychopharmacology. *Behav. Pharmacol.* 21, 420–426. doi: 10.1097/FBP.0b013e32833c850f

Tian, H., Ding, N., Guo, M., Wang, S., Wang, Z., Liu, H., et al. (2019). Analysis of learning and memory ability in an alzheimer's disease mouse model using the morris water maze. *J. Vis. Exp.* 152. doi: 10.3791/60055

Tsai, H. J., Chen, C. C., and Chang, K. Y. (2011). Patients and surgery-related factors that affect time to recovery of consciousness in adult patients undergoing elective cardiac surgery. *J. Chin. Med. Assoc.* 74, 345–349. doi: 10.1016/j.jcma.2011.06.009

Tzabazis, A., Miller, C., Dobrow, M. F., Zheng, K., and Brock-Utne, J. G. (2015). Delayed emergence after anesthesia. *J. Clin. Anesth.* 27, 353–360. doi: 10.1016/j.jclinane.2015.03.023

Urits, I., Orhurhu, V., Jones, M., Hoyt, D., Seats, A., and Viswanath, O. (2019). Current perspectives on postoperative cognitive dysfunction in the ageing population. *Turk. J. Anaesthesiol. Reanim.* 47, 439–447. doi: 10.5152/TJAR.2019.75299

Vutskits, L., and Xie, Z. (2016). Lasting impact of general anaesthesia on the brain: mechanisms and relevance. *Nat. Rev. Neurosci.* 17, 705–717.

Wang, C. M., Chen, W. C., Zhang, Y., Lin, S., and He, H. F. (2021). Update on the mechanism and treatment of sevoflurane-induced postoperative cognitive dysfunction. *Front. Aging Neurosci.* 13:376. doi: 10.3389/fnagi.2021.702231

Wang, J. Y., Wu, J. N., Cherng, T. L., Hoffer, B. J., Chen, H. H., Borlongan, C. V., et al. (2001). VitaminD(3) attenuates 6-hydroxydopamine-induced neurotoxicity in rats. *Brain Res.* 904, 67–75. doi: 10.1016/s0006-8993(01)02450-7

Xiao, H., Liu, B., Chen, Y., and Zhang, J. (2016). Learning, memory and synaptic plasticity in hippocampus in rats exposed to sevoflurane. *Int. J. Dev. Neurosci.* 48, 38–49. doi: 10.1016/j.ijdevneu

Xiong, L., Duan, L., Xu, W., and Wang, Z. (2019). Nerve growth factor metabolic dysfunction contributes to sevoflurane-induced cholinergic degeneration and cognitive impairments. *Brain Res.* 1707, 107–116. doi: 10.1016/j.brainres.2018.11.033

Yang, Y., Zhong, Y. P., Zhao, P. C., Zhan, C., Zhu, Y. H., Lin, X. F., et al. (2019b). Changes in hippocampal α7nAChR, AChE and ChAT expression after sevoflurane anesthesia in neonatal rats. *Chin. J. Anesthesiol.* 39, 279–282.

Yang, Y., Wu, Z. Y., Lin, X. F., Zhang, C., and Zhu, Z. Q. (2019a). Effects of Sevoflurane on the Cognitive Function and Hippocampal Ultrastructure of Elderly Model Rats. *J. Sichuan Univ.* 50, 689–694. doi: 10.13464/j.scuxbyxb.2019.05.012

Yin, J., Zhao, X., Wang, L., Xie, X., Geng, H., Zhan, X., et al. (2019). Sevoflurane-induced inflammation development: involvement of cholinergic anti-inflammatory pathway. *Behav. Pharmacol.* 30, 730–737. doi: 10.1097/FBP.0000000000000507

Yu, Z. H. (2021). *The Effect Of Sevoflurane On The Expression Of Chat,Ache And A7nachr In Hippocampal Neurons*. China: Zunyi Medical University.

Zhang, C., Zhang, Y., Shen, Y., Zhao, G., Xie, Z., Dong, Y., et al. (2017). Anesthesia/surgery induces cognitive impairment in female Alzheimer's disease transgenic mice. *J. Alzheimers Dis.* 57, 505–518. doi: 10.3233/JAD-161268

Zhang, J. L., Zhang, X. L., Yang, Y. Y., Zhao, J., and Yu, Y. H. (2022). Correlation Analysis of Serum Vitamin D Levels and Postoperative Cognitive Disorder in Elderly Patients With Gastrointestinal Tumor. *Front. Psychiatry* 13:893309. doi: 10.3389/fpsyt.2022.893309

Zhao, P. C., Zhong, Y. P., and Zhu, Z. Q. (2019). Effects of sevoflurane anesthesia on the quantity of alpha 7 nicotinic acetylcholine receptor, cholinesterase and choline acetyl translocase in the rat hippocampus. *Chin. J. Anesthesiol.* 35, 160–164.

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Pre-operative Status of Gut Microbiota Predicts Post-operative Delirium in Patients With Gastric Cancer

*Meiru Jiang and Wenfei Tan**

Department of Anesthesiology, The First Hospital of China Medical University, Shenyang, China

Keywords: gut microbiota (GM), post-operative delirium (POD), 16S rRNA, principle coordinate analysis (PCoA), PCA, gastric cancer

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Edited by:
Diansan Su,
Shanghai Jiao Tong University, China

Reviewed by:
Fuzhou Hua,
Second Affiliated Hospital of Nanchang University, China
Xuesheng Liu,
First Affiliated Hospital of Anhui Medical University, China

Correspondence:
Wenfei Tan
winfieldtan@hotmail.com

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INTRODUCTION

We read with great interest the recent article by Liu et al. (1) and congratulate the authors for their innovative analysis of the pre-operative gut microbiota between patients with and without post-operative delirium (POD). This article included very important clinical data for early diagnosis and determination of the treatment for POD. However, there are some important points of concern.

First, we wonder about the sample size. Research on the correlation between gut microbiota and perioperative cognitive dysfunction, especially for humans, is still rare. Hence, the method used to determine the minimum sample size is yet to be ascertained. Therefore, using the distribution of that metric in published but related studies is the first step to estimating the sample size (2). Since we found that related studies included over 80 sample sizes (3) to increase the reliability of the results in most cases, we are concerned that only 20 fecal samples in each cohort may be unable to completely show the differences in gut microbiota between the two cohorts.

Moreover, all the patients in this trial underwent general anesthesia, but Hu Liu et al. limited the drugs in anesthesia induction and post-operation without during the operation-which could influence the morbidity of post-operative delirium significantly (4). Thus, we suggest that increasing the sample size or limiting the anesthetics during operation might higher the qualification of the results if the author chose not to determine the use of anesthetics during the operation.

Second, we are also curious about the incomplete β-diversity analysis results in Figure 2. We noticed that the author used Principal Component Analysis (PCA) in Figure 2A and Principal Co-ordinates Analysis (PCoA) in Figure 2B but missed the percent of PCA 1 and PCoA 1 and their quotiety of explanation on the X-axis equally and marked the PCA 2 and PCoA 2 on the Y-axis only, which should not be omitted (5). We expect the author to add these analyses in Figure 2 for the readers.

Furthermore, we searched the registration number (ChiCTR200030131) on the Chinese Clinical Trial Registry given by the author but failed to find any registered trail. We hope that the author could proofread this to confirm.

Our research team has been studying the "brain-gut" axis and submitted one similar study on clinicaltrails.gov in 2020 (NCT04316910), but it was unfortunate that the plan has been delayed because of funding issues. However, Hu Liu et al. derived a more original research study compared to ours. Therefore, we are very excited to read this article and sincerely hope that Hu Liu et al. can achieve greater academic success in this field in the future.

AUTHOR CONTRIBUTIONS

WT contributed to the conception and the review of the manuscript. MJ wrote the first draft and contributed to the editing of the manuscript. Both authors contributed to manuscript revision, read, and approved the submitted version.

REFERENCES

1. Liu H, Cheng G, Xu Y, Fang Q, Ye L, Wang C, et al. Pre-operative status of gut microbiota predicts post-operative delirium in patients with gastric cancer. *Front Psychiatry*. (2022) 13:852269. doi: 10.3389/fpsyt.2022.852269
2. Casals-Pascual C, González A, Vázquez-Baeza Y, Song SJ, Jiang L, Knight R. Microbial diversity in clinical microbiome studies: sample size and statistical power considerations. *Gastroenterology*. (2020) 158:1524–8. doi: 10.1053/j.gastro.2019.11.305
3. Yang Z, Tong C, Qian X, Wang H, Wang A. Mechanical bowel preparation is a risk factor for post-operative delirium as it alters the gut microbiota composition: a prospective randomized single-center study. *Front Aging Neurosci*. (2022) 14:847610. doi: 10.3389/fnagi.2022.847610
4. Mei X, Zheng H-L, Li C, Ma X, Zheng H, Marcantonio E, et al. The effects of propofol and sevoflurane on post-operative delirium in older patients: a randomized clinical trial study. *J Alzheimers Dis*. (2020) 76:1627–36. doi: 10.3233/JAD-200322
5. Zhang J, Bi JJ, Guo GJ, Yang L, Zhu B, Zhan GF, et al. Abnormal composition of gut microbiota contributes to delirium-like behaviors after abdominal surgery in mice. *CNS Neurosci Ther*. (2019) 25:685–96. doi: 10.1111/cns.13103

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EDITED BY
Mark Stecker,
Independent Practitioner, Fresno, CA, United States

REVIEWED BY
Ching-Fu Weng,
Hsinchu Cathay General Hospital, Taiwan
Birgitta Olofsson,
Umeå University, Sweden

*CORRESPONDENCE
Yun-feng Rui
ruiyunfeng@126.com
Jie Sun
dgsunjie@hotmail.com

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Risk factors for postoperative delirium in geriatric patients with hip fracture: A systematic review and meta-analysis

Yi-ming Qi[1,2,3,4], Ying-juan Li[2,4,5], Ji-hong Zou[2,4,5], Xiao-dong Qiu[2,4,6], Jie Sun[2,4,6]* and Yun-feng Rui[1,2,3,4,7]*

[1]Department of Orthopaedics, School of Medicine, Zhongda Hospital, Southeast University, Nanjing, China, [2]Multidisciplinary Team (MDT) for Geriatric Hip Fracture Comprehensive Management, School of Medicine, Zhongda Hospital, Southeast University, Nanjing, China, [3]Orthopaedic Trauma Institute, Southeast University, Nanjing, China, [4]School of Medicine, Southeast University, Nanjing, China, [5]Department of Geriatrics, School of Medicine, Zhongda Hospital, Southeast University, Nanjing, China, [6]Department of Anesthesiology, School of Medicine, Zhongda Hospital, Southeast University, Nanjing, China, [7]Trauma Center, Zhongda Hospital, Southeast University, Nanjing, China

Objectives: This systematic review and meta-analysis was conducted to identify the potential risk factors for postoperative delirium in geriatric patients with hip fracture.

Methods: PubMed, EMBASE, and Cochrane Library were searched from inception until December 31st, 2021. A combined searching strategy of subject words and free words was adopted. Studies involving risk factors for postoperative delirium in elderly patients undergoing hip fracture surgeries were reviewed. Qualities of included studies were assessed using the Newcastle–Ottawa Scale. Data were pooled and a meta-analysis was performed using Review Manager 5.3.

Results: A total of 37 studies were included. The following risk factors were significant: advanced age (per year increase) (OR: 1.05, 95% CI 1.04–1.07), age>80 years (OR: 2.26, 95% CI 1.47–3.47), male (OR: 1.53, 95% CI 1.37–1.70), preoperative cognitive impairment (OR:3.20, 95% CI 2.12–4.83), preoperative dementia (OR: 2.74, 95% CI 2.18–3.45), preoperative delirium (OR: 9.23, 95% CI 8.26–10.32), diabetes (OR: 1.18, 95% CI 1.05–1.33), preoperative functional dependence (OR: 1.31, 95% CI 1.11–1.56), ASA level (per level increase) (OR: 1.63, 95% CI 1.04–2.57), ASA level≥3(OR: 1.76, 95% CI 1.39–2.24), low albumin (OR: 3.30, 95% CI 1.44–7.55), medical comorbidities (OR: 1.15, 95% CI 1.06–1.25), Parkinson's disease (OR: 4.17, 95% CI 1.68–10.31) and surgery delay>48 h (OR: 1.90, 95% CI 1.36–2.65).

Conclusions: Clinicians should be alert to patients with those risk factors. To identify the risk factors more precisely, more research studies with larger sample size and better design should be conducted.

KEYWORDS

risk factors, postoperative delirium, geriatric, hip fracture, systematic review, meta-analysis

Introduction

The incidence of hip fracture is increasing concurrently with the aging of the population. It has been estimated that in many countries, the number of hip fractures will rise from 1.7 million in 1990 to 6.3 million in 2050 (Gullberg et al., 1997). One of the complications associated with hip fracture is postoperative delirium.

Delirium is a common neuropsychiatric syndrome that can happen in hospitalized patients from different settings. It has three notable characteristics: acute onset of altered mental status, difficulty in sustaining attention or changing attention and a fluctuating course (Greer et al., 2011). In surgical departments, the incidence is particularly high, especially in geriatric patients undergoing surgery with hip fracture, where the prevalence can reach as high as around 50% (Goldenberg et al., 2006; Shin et al., 2016; Jeon and Sohng, 2021). Significant negative consequences concerned about postoperative delirium in hip fracture patients include higher postoperative complications, poorer functional recovery, more readmissions and reoperations and even higher mortality (Haynes et al., 2021; Jeon and Sohng, 2021). The good news is that delirium is referred to be preventable in about 40% of patients, which makes it meaningful and attractive to take proactive measures to prevent the process of delirium (None, 2015). Given these negative consequences, the high incidence and preventability of delirium following hip fracture surgery in this population, the identification of those patients at risk of postoperative delirium is of great significance.

Risk factors in terms of delirium after hip fracture surgeries have been researched in many studies, while they have not reached an agreement (Kim et al., 2020; Wang et al., 2021; Ahn and Bang, 2022). Former meta-analysis have explored some potential risk factors for delirium in hip fracture patients (Yang et al., 2017; Wu et al., 2021), however, the patients in some included studies are not all geriatric patients, and the risk factors reported in some included studies are not merely for postoperative delirium, but for preoperative or perioperative delirium. Besides, many articles have been published after those meta-analysis were published, which may provide some new evidences for or against previous outcomes. Therefore, this meta-analysis was conducted to identify the potential risk factors for postoperative delirium in geriatric in patients with hip fracture.

Methods

This meta-analysis is conducted according to the Preferred Reporting Items for systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009).

Search strategy

PubMed, EMBASE, and Cochrane Library were searched from inception until December 31st, 2021. A combined searching strategy of subject words and free words was adopted. The concrete searching strategy for PUBMED is as follows:("femur neck fractures"[Title/Abstract] OR "fractures, femur neck"[Title/Abstract] OR "fractures, femoral neck"[Title/Abstract] OR "Femoral neck fractures"[Title/Abstract] OR "fractures, subtrochanteric"[Title/Abstract] OR "subtrochanteric fractures"[Title/Abstract] OR "fractures, intertrochanteric"[Title/Abstract] OR "intertrochanteric fractures"[Title/Abstract] OR "fractures, trochanteric"[Title/Abstract] OR "trochanteric fractures"[Title/Abstract] OR "fractures, pertrochanteric"[Title/Abstract] OR "pertrochanteric fractures"[Title/Abstract] OR "fractures, hip"[Title/Abstract] OR "Hip Fractures"[Title/Abstract] OR "hip surgery"[Title/Abstract] OR "Femoral neck fractures"[MeSH Terms] OR "Hip Fractures"[MeSH Terms]) AND ("Risk Factors"[MeSH Terms] OR ["correlat*"[Title/Abstract] OR "factor*"[Title/Abstract] OR "risk"[Title/Abstract] OR "predict*"[Title/Abstract])] AND ("Delirium"[MeSH Terms] OR ["deliri*"[Title/Abstract] OR "confus*"[Title/Abstract] OR "pocd"[Title/Abstract] OR "postoperative cognitive disorder"[Title/Abstract])].

Eligibility criteria

The inclusion criteria were as follows: (1) Types of studies: retrospective or prospective cohort design; (2) Types of participants: all the patients are older than 60 years old and undergo surgeries for hip fracture; (3) Outcomes: risk factors merely for postoperative delirium, and the risk factors are reported in ≥2 studies. (4) Data: available odds ratio (OR) or relative risk (RR) with 95% confidence interval (95% CI) as a result of a multivariate logistic regression.

The exclusion criteria were as follows: (1) Types of studies: those studies that are not cohort design or whose concrete description could not be extracted, editorial reviews, systematic reviews, conference abstracts, letters and comments; (2) Types of participants: including patients younger than 60 years old or undergoing other types of surgeries; (3) Outcomes: assessed risk factors for postoperative delirium are reported in less than 2 studies or risk factors for preoperative delirium or perioperative delirium; (4) Data: no available odds ratio (OR) or relative risk (RR) with 95% confidence interval (95% CI) as a result of a multivariate logistic regression.

Data extraction and quality assessment

Two reviewers independently scanned the titles and abstracts of potentially included studies. Once the studies met the inclusion criteria, full texts of articles were reviewed thoroughly. The following variables were extracted from each study: first author's name, publication year, country, diagnosis of delirium and numbers of cases and controls, mean age of cases and controls, numbers of males and females in cases and controls, and significant risk factors. The extracted data were entered in a standardized data collection form. Any discrepancy about the data were resolved by discussion or consulting a senior reviewer.

The quality of included studies was assessed by 2 reviewers with the Newcastle–Ottawa Scale (NOS) (Wells et al., 2014) based on the three main items: the selection of the study groups (0–4 points), the comparability of the groups (0–2 points) and the determination of either the exposure or the outcome of interest (0–3 points). The NOS score ranges from 0 to 9. A study with a score more than 7 was considered to be of high quality.

Statistical analysis

The meta-analysis was conducted with the Review Manager 5.3 software (The Cochrane Collaboration, Oxford, UK). Odds ratios (ORs) and 95% confidence intervals (CIs) were pooled across the studies to estimate the risk factors of postoperative delirium. In studies where the incidence of delirium is low, the RR could be regarded as equal to the OR. Statistical heterogeneity was assessed with the P and I^2 values using the standard Chi-square test. When $I^2 > 50\%$, or $P < 0.1$, significant heterogeneity was indicated and a random-effects model was applied for the meta-analysis. Otherwise, a fixed-effects model was used. To assess the publication bias, a funnel plot of the primary outcome will be utilized. When it is necessary, sensitive analysis will be conducted by excluding outlier studies one by one to verify the source of heterogeneity.

Results

One thousand seven hundred ten articles were identified from the search of the databases and 1 paper was identified from other sources. One thousand two hundred sixty-two studies remained when the duplicates were removed. Then, the title and the abstracts of the 1262 citations were scanned to exclude those which did not meet the inclusion criteria. As a consequence, 1175 citations were excluded. Next, the 87 remained studies were carefully full-text-reviewed to recognize those which could reach the inclusion criteria. At last 37 citations (Kagansky et al., 2004; Goldenberg et al., 2006; Juliebø et al., 2009; Chrispal et al., 2010; Lee et al., 2011; Vochteloo et al., 2011; Nie et al., 2012; Kim et al., 2013, 2020; Chen et al., 2014; Guo et al., 2016; Oh et al., 2016; Shin et al., 2016; van der Zanden et al., 2016; Zheng et al., 2016; Choi et al., 2017; Koskderelioglu et al., 2017; Mazzola et al., 2017; Arshi et al., 2018; Flikweert et al., 2018; Levinoff et al., 2018; Wang et al., 2018, 2021; Agrawal et al., 2019; Harris et al., 2019; Ravi et al., 2019; Zhang et al., 2019; Aldwikat et al., 2020; Cho et al., 2020; He et al., 2020; Uzoigwe et al., 2020; Xing et al., 2020; Davani et al., 2021; Haynes et al., 2021; Jeon and Sohng, 2021; Oberai et al., 2021; Ahn and Bang, 2022) were included for further qualitative and quantitative synthesis (Figure 1).

The general characteristics of the included studies

In the included 37 studies, 17 studies were conducted in Asia (9 in China, 6 in Korea, 1 in India and 1 in Israel), 11 studies were conducted in North America (9 in the USA and 2 in Canada), 7 studies were conducted in Europe (3 in Netherlands, 1 in UK, 1 in Italy, 1 in Turkey and 1 in Norway) and the remaining 2 were conducted in Australia and New Zealand. The Confusion Assessment Scale (CAM) was the most frequently used scale (in 20 studies) for the diagnosis of postoperative delirium in hip fracture patients. The incidence of postoperative delirium varies among the range from 10.09% to 51.28%. In eight studies, the mean age in delirium patients an non-delirium patients are both older than 80, and in almost all of the studies, female patients are more than male patients in both groups (Additional File 1 in Supplementary material).

Methodological quality assessment

The result of methodological quality assessment of the included studies are as follows: 20 studies scored 8 points, 13 studies scored 7 points and 4 studies scored 6 points (Additional File 2 in Supplementary material).

Outcomes for meta-analysis

Age and gender

Eleven papers (Lee et al., 2011; Vochteloo et al., 2011; Chen et al., 2014; Guo et al., 2016; Oh et al., 2016; Zheng et al., 2016; Mazzola et al., 2017; Arshi et al., 2018; Ravi et al., 2019; He et al., 2020; Davani et al., 2021) reported advanced age (per year increase) as a significant risk factor for POD. A random-effects model was applied because significant heterogeneity was found among these studies ($P = 0.0003$, $I^2 = 69\%$). The meta-analysis of the pooled studies suggest that advanced age (per year increase) is a significant risk factor for the development of POD in geriatric patients after hip fracture surgeries (OR: 1.05, 95% CI 1.04–1.07, $P < 0.00001$, Figure 2). The funnel plot for age (per year increase) was employed to evaluate publication bias. The

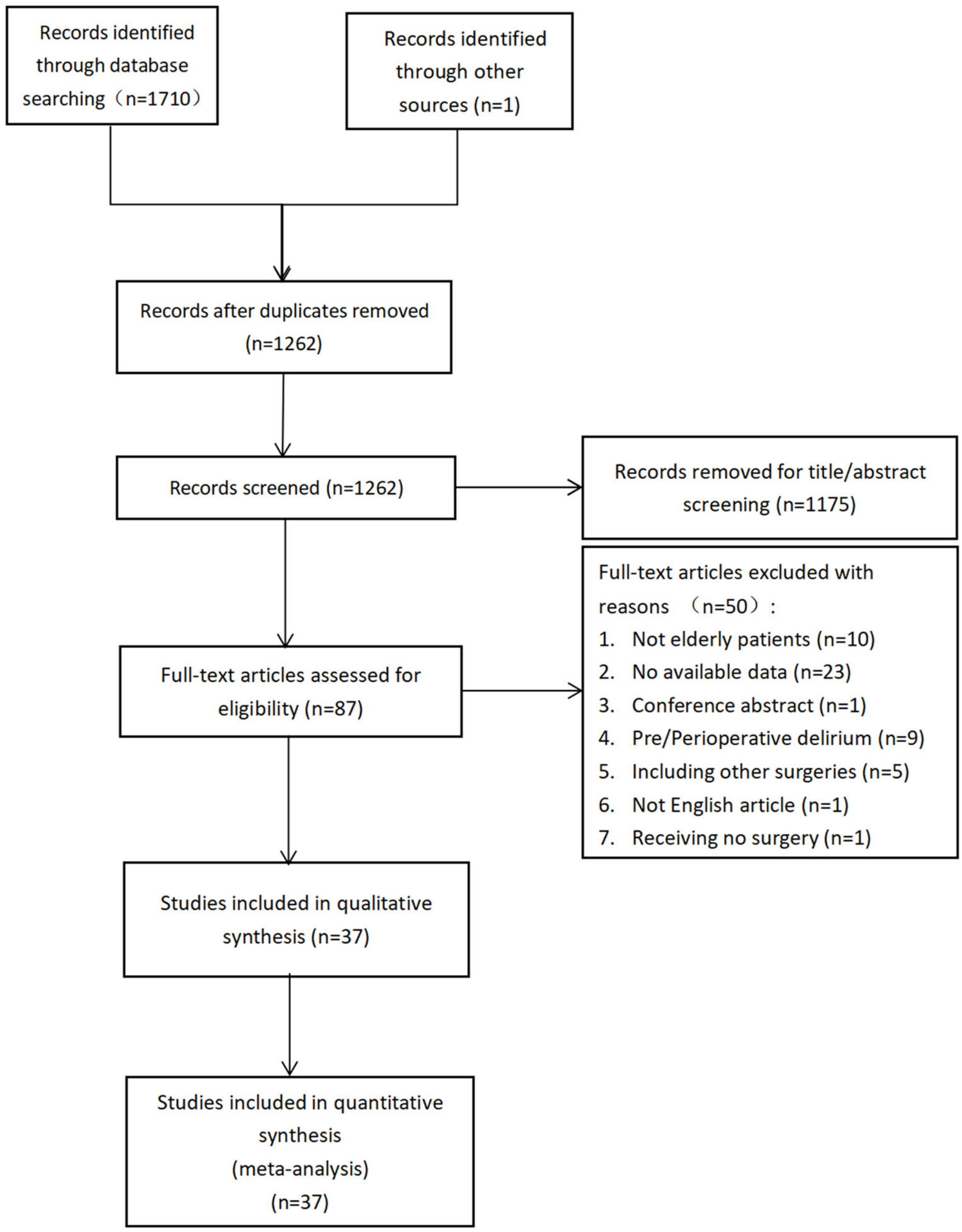

FIGURE 1
The flow diagram of the search process of the literature and the result of the literature search.

funnel plot shows that all the dots are generally symmetrically distributed on both sides of the dotted line, which suggests little publication bias for the meta-analysis of advanced age (Figure 3). Another 4 studies (Goldenberg et al., 2006; Kim et al., 2013; Harris et al., 2019; Oberai et al., 2021) reported age>80 years as a significant risk factor for POD. A random-effects model was applied because significant heterogeneity was found among these studies ($P = 0.03$, $I^2 = 67\%$). The meta-analysis of the pooled studies suggests that age>80 years is a significant risk factor for the development of POD in geriatric patients after hip fracture surgeries (OR: 2.26, 95% CI 1.47–3.47, $P = 0.0002$, Figure 4). This means that the incidence of POD in patients older than 80 years Is 2.26 times the incidence of POD in patients younger than 80 years.

9 Papers (Lee et al., 2011; Vochteloo et al., 2011; Kim et al., 2013; Oh et al., 2016; Mazzola et al., 2017; Ravi

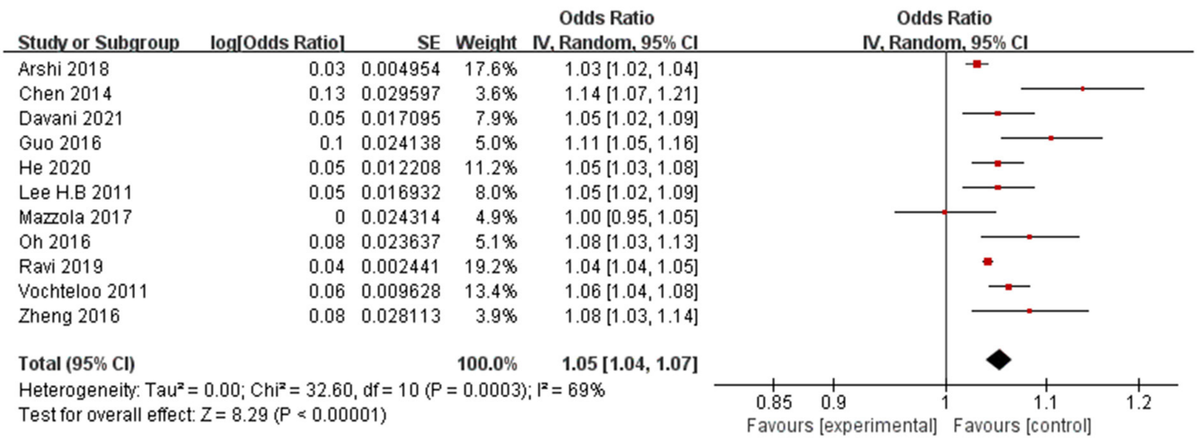

FIGURE 2
Forest plot for age (per year increase).

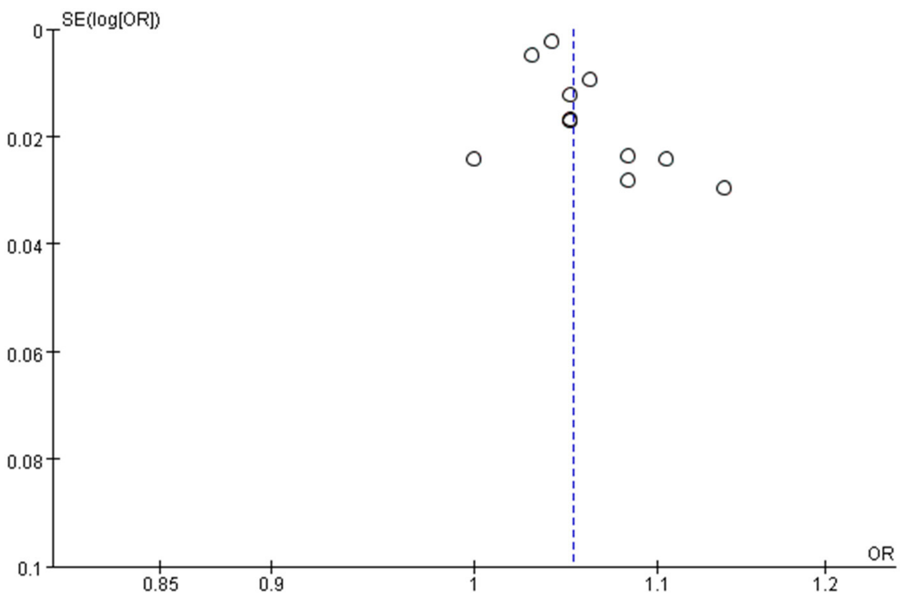

FIGURE 3
Funnel plot for age (per year increase) for the investigation of publication bias.

et al., 2019; Haynes et al., 2021; Oberai et al., 2021; Ahn and Bang, 2022) reported male as a significant risk factor for POD. A random-effects model was applied because significant heterogeneity was found among these studies ($P < 0.0001$, $I^2 = 78\%$). The meta-analysis of the pooled studies suggests that male is a significant risk factor for the development of POD (OR: 1.53, 95% CI 1.37–1.70, $P < 0.00001$, Figure 5).

Preoperative cognitive impairment

Ten papers (Kagansky et al., 2004; Goldenberg et al., 2006; Juliebø et al., 2009; Nie et al., 2012; Koskderelioglu et al., 2017; Mazzola et al., 2017; Levinoff et al., 2018; Zhang et al., 2019; Aldwikat et al., 2020; Oberai et al., 2021) reported preoperative cognitive impairment as a significant risk factor for POD. A random-effects model was applied because significant heterogeneity was found among these studies ($P < 0.00001$, I^2

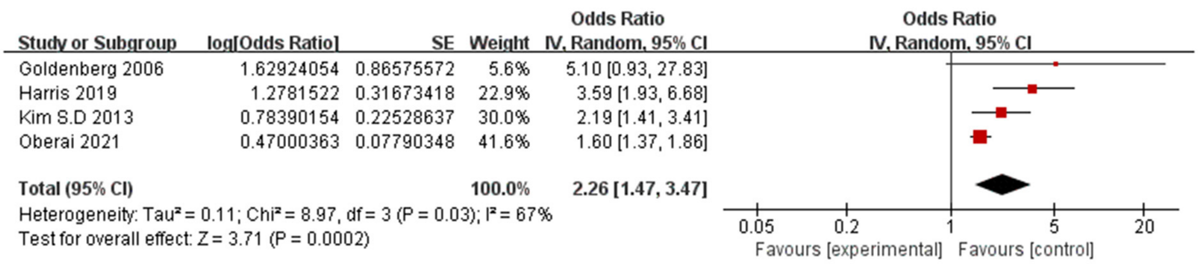

FIGURE 4
Forest plot for age>80 years.

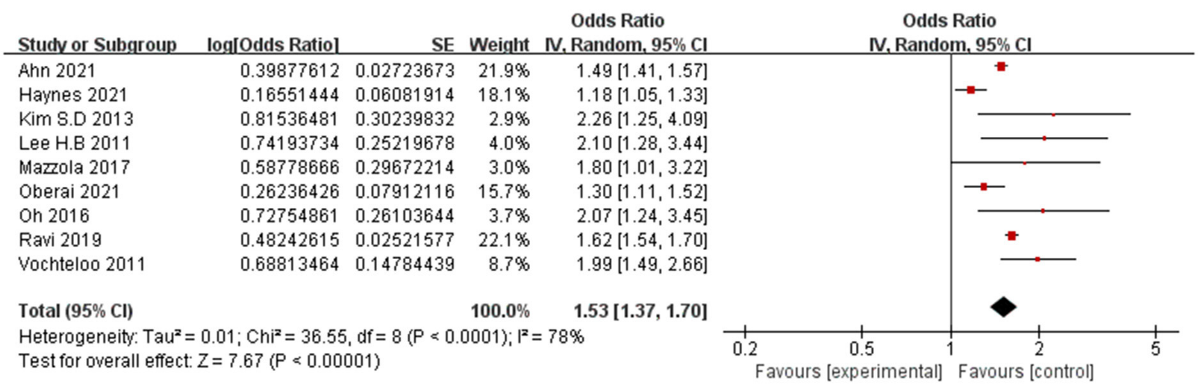

FIGURE 5
Forest plot for male.

= 83%). The meta-analysis of the pooled studies suggest that preoperative cognitive impairment is a significant risk factor for the development of POD (OR: 3.20, 95% CI 2.12–4.83, $P < 0.00001$, Figure 6).

Preoperative dementia

Ten papers (Chrispal et al., 2010; Lee et al., 2011; Oh et al., 2016; Choi et al., 2017; Arshi et al., 2018; Cho et al., 2020; Kim et al., 2020; Davani et al., 2021; Haynes et al., 2021; Oberai et al., 2021) reported preoperative dementia as a significant risk factor for POD. A random-effects model was applied because significant heterogeneity was found among these studies ($P < 0.00001$, $I^2 = 85\%$). The meta-analysis of the pooled studies suggest that preoperative dementia is a significant risk factor for the development of POD (OR: 2.74, 95% CI 2.18–3.45, $P < 0.00001$, Figure 7).

Preoperative delirium

Three papers (Arshi et al., 2018; Agrawal et al., 2019; Kim et al., 2020) reported preoperative delirium as a significant risk factor for POD. A fixed-effects model was applied because no significant heterogeneity was found among these studies ($P = 0.44$, $I^2 = 0\%$). The meta-analysis of the pooled studies suggest that preoperative delirium is a significant risk factor for the development of POD (OR: 9.23, 95% CI 8.26–10.32, $P < 0.00001$, Figure 8). This means that the incidence of POD in patients with preoperative delirium Is 9.23 times the incidence of pod in patients without preoperative delirium.

Diabetes

Five papers (Wang et al., 2018, 2021; He et al., 2020; Haynes et al., 2021; Ahn and Bang, 2022) reported preoperative diabetes as a significant risk factor for POD. A random-effects model was applied because significant heterogeneity was found among these studies ($P < 0.00001$, $I^2 = 87\%$). The meta-analysis of the pooled studies suggest that preoperative diabetes is a significant risk factor for the development of POD (OR: 1.18, 95% CI 1.05–1.33, $P = 0.006$, Additional File 3 in Supplementary material).

Preoperative functional dependence

Five papers (van der Zanden et al., 2016; Flikweert et al., 2018; Kim et al., 2020; Haynes et al., 2021; Jeon and Sohng, 2021) reported preoperative functional dependence as a significant risk factor for POD. A random-effects model was applied because

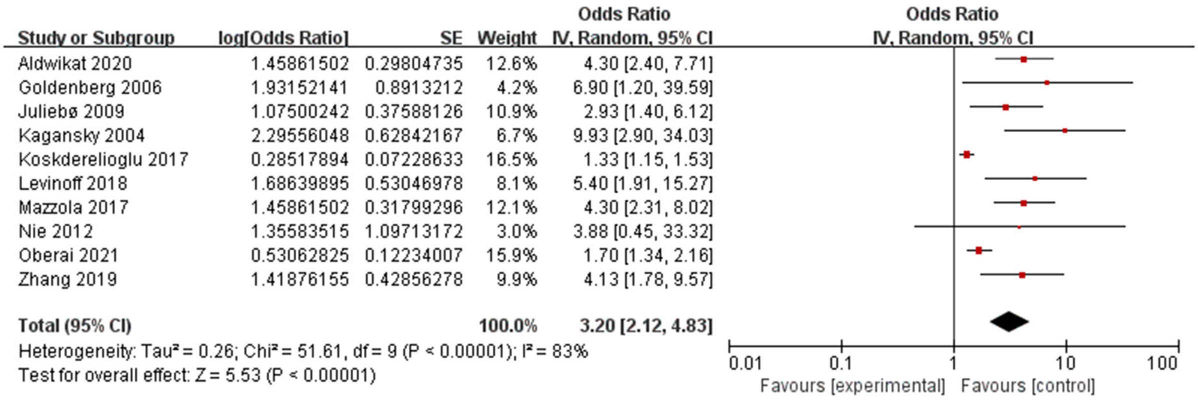

FIGURE 6
Forest plot for preoperative cognitive impairment.

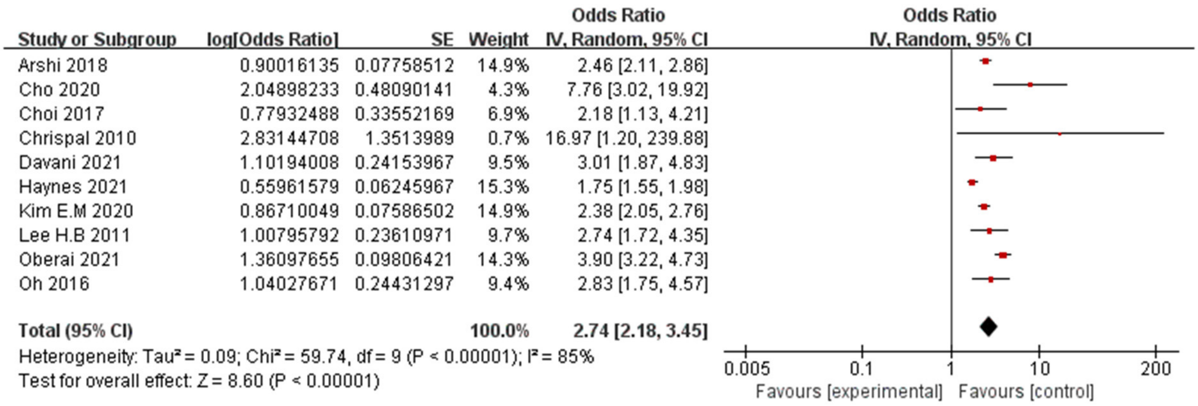

FIGURE 7
Forest plot for preoperative dementia.

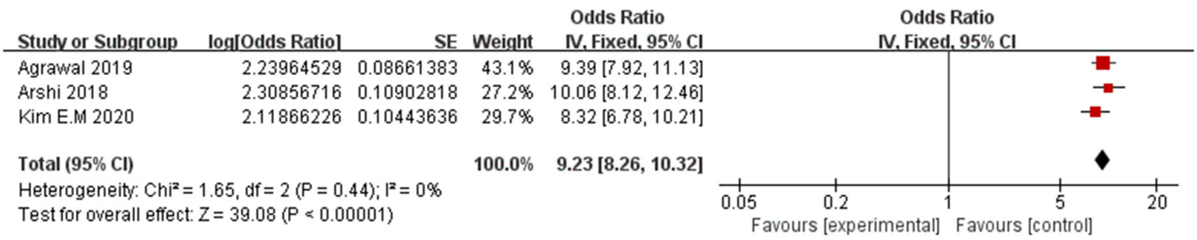

FIGURE 8
Forest plot for preoperative delirium.

significant heterogeneity was found among these studies ($P = 0.008$, $I^2 = 71\%$). The meta-analysis of the pooled studies suggests that preoperative functional dependence is a significant risk factor for the development of POD (OR: 1.31, 95% CI 1.11–1.56, $P = 0.002$, Additional File 4 in Supplementary material).

ASA level

Three papers (Oh et al., 2016; Arshi et al., 2018; Davani et al., 2021) reported higher ASA level (per level increase) as a significant risk factor for POD. A random-effects model was applied because significant heterogeneity was found among

TABLE 1 Results of meta-analysis of other factors.

Factor	Number of study	OR	95% CI	*p* value	I^2 (%)	Test(p)	Statistical method
General anesthesia	2	1.44	0.71–2.94	0.32	80	0.03	IV, Random
Longer surgical duration	2	2.82	0.69–11.50	0.15	57	0.13	IV, Random
Low albumin	2	3.30	1.44–7.55	0.005	0	0.38	IV, fixed
Medical comorbidities	2	1.15	1.06–1.25	0.0006	0	0.66	IV, fixed
Parkinson's disease	2	4.17	1.68–10.31	0.002	0	0.72	IV, fixed
Smoking	2	1.80	0.88–3.65	0.11	69	0.07	IV, Random
Surgery delay>48 h	2	1.90	1.36–2.65	0.0002	48	0.16	IV, fixed

these studies ($P = 0.003$, $I^2 = 83\%$). The meta-analysis of the pooled studies suggests that higher ASA level (per level increase) is a significant risk factor for the development of POD in geriatric patients after hip fracture surgeries (OR: 1.63, 95% CI 1.04–2.57, $P = 0.03$, Additional File 5 in Supplementary material). Another 8 studies (Vochteloo et al., 2011; Kim et al., 2013, 2020; Wang et al., 2018, 2021; Zhang et al., 2019; Uzoigwe et al., 2020; Haynes et al., 2021) reported ASA level≥3 as a significant risk factor for POD. A random-effects model was applied because significant heterogeneity was found among these studies ($P = 0.003$, $I^2 = 68\%$). The meta-analysis of the pooled studies suggest that ASA level≥3 is a significant risk factor for the development of POD in geriatric patients after hip fracture surgeries (OR: 1.76, 95%CI 1.39–2.24, $P < 0.00001$, Additional File 6 in Supplementary material).

Other factors

Another 7 factors including general anesthesia, medical comorbidities, Parkinson's disease, smoking, surgery delay>48 h, longer surgical duration were analyzed. The results in Table 1 indicate that low albumin (OR: 3.30, 95% CI 1.44–7.55, $P = 0.005$), medical comorbidities (OR: 1.15, 95% CI 1.06–1.25, $P = 0.0006$), Parkinson's disease (OR: 4.17, 95% CI 1.68–10.31, $P = 0.002$) and surgery delay>48 h (OR: 1.90, 95% CI 1.36–2.65, $P = 0.0002$) are significant risk factors for POD in geriatric patients undergoing hip fracture surgeries, while general anesthesia (OR: 1.44, 95%CI 0.71–2.94, $P = 0.32$), smoking (OR: 1.80, 95% CI 0.88–3.65, $P = 0.11$), longer surgical duration (OR: 2.82, 95% CI 0.69–11.50, $P = 0.15$) are not significant risk factors.

Sensitivity analysis

A sensitivity analysis was conducted respectively for the analysis of age (per year increase), male, preoperative dementia and ASA level≥3. We excluded each study one by one to explore whether a single study significantly impacts the heterogeneity or the results. Overall, we found that when it comes to factors including age (per year increase), male, preoperative dementia, the heterogeneity and the results were not significantly affected by any single study and that although when analyzing the ASA level≥3, after we excluding the study by Wang Y et al., the heterogeneity decreased significantly, the result changed little. Therefore, the result of our meta-analysis was relatively robust.

Discussion

POD is prevalent among geriatric patients undergoing hip fracture surgeries. POD is a common, acute, under-recognized adverse event and is associated with significant morbidity and mortality in hospitalized elderly patients, Considering these serious complications, it is essential to recognize the risk factors of delirium to prevent it after surgery (Yang et al., 2021). Therefore we conducted this meta-analysis to investigate the potential risk factors for the occurrence of POD. Compared with previous meta-analysis (Yang et al., 2017; Wu et al., 2021), our systematic review and meta-analysis included newly-published articles in the latest 2 years and studies concerning risk factors for preoperative delirium, perioperative delirium or younger patients were excluded.

Postoperative delirium assessment

From the results of the meta-analysis we found that the incidence of POD varies from 10.09 to 51.28%, which is similar to the former meta-analysis (Yang et al., 2017). In some institutes, the incidence of delirium is relatively high. The wide range may result from the differences including the differences in inclusion and exclusion criteria, diagnosis of POD, time and frequency of screening for POD.

The most frequently used scale is CAM. Developed by Inouye et al. based on the DSM-III for delirium, CAM has 4 remarkable features: acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness (Inouye et al., 1990). In former studies, its sensitivities ranged from 77 to 92% and specificity ranged from 96 to 100% (Hestermann et al., 2009; Wongpakaran et al., 2011; Martins et al., 2015). Its performance in the diagnosis of delirium is excellent. However, CAM is inferior to other screening methods such as CAM-ICU and Nu-DESC in terms of time consuming. CAM-ICU and Nu-DESC can be conducted within around 5 minutes, which makes it more feasible for daily use by nurses (Han et al., 2014; Pipanmekaporn et al., 2014; Zastrow et al., 2021).

Risk factors

The age limit of susceptibility to delirium remains controversial. From this meta-analysis, we found that when people grow older, the risk for POD is increasing year by year. For those older than 80 years old, the incidence of POD is 2.26 times that in patients younger than 80. This is comparable to previous meta-analysis (Yang et al., 2017; Wu et al., 2021). The result may be due to the fact that elderly patients were more likely influenced by age-related physical and psychical changes, such as poor organ compensative capacity, reduced body adaptability, and declined adjustment ability (van der Mast, 1998).

Patients who developed postoperative delirium were more often males. Zhu et al. (2017) deemed that women could deal with postoperative psychological stress better than male and thus was associated with less delirium. Interestingly, although in most of the included studies, female patients make up the majority, those who are markedly more likely to develop POD are male patients. Factors that may contribute to the strong association between male sex and POD include underlying disease severity, more comorbidities, and more postoperative complications (Oh et al., 2016; Oberai et al., 2021).

Preoperative cognitive impairment, as measured often by the Mini-Mental State Exam (MMSE) (Goldenberg et al., 2006; Koskderelioglu et al., 2017; Mazzola et al., 2017), has been found to be an important predictor for POD. Many studies (Liang et al., 2015; Chu et al., 2016; Yang et al., 2017) have proved the feasibility of preoperative cognitive testing in emergencies. It should become a part of the standardized program for preoperative clinical assessment for orthopedic surgeries.

Cole et al. (2009) elucidated the relationship between preoperative dementia and delirium, indicating that both had similar symptoms and pathogenesis, including metabolic rates and impaired cholinergic function, and similar causative factors, such as excitotoxic neuronal damage and neuron death (Blass and Gibson, 1999; Cole et al., 2002). Elucidation of the link between delirium and dementia could lead to the development of decided strategies for early detection, prevention and intervention strategies in patients with preoperative dementia undergoing hip fracture surgery.

For patients diagnosed with preoperative delirium, the risk of the occurrence of POD is about 10 times the risk for patients without preoperative delirium. Thus, early diagnosis and treatment of delirium is crucial to prevent the occurrence of POD.

We found a significant correlation between preoperative low albumin and POD, which appeared to indicate that a poor nutritional condition might be a potential risk factor (Lee and Park, 2010). Patients with diabetes or preoperative functional dependence also need more attention.

Our evaluation showed that the risk of POD was 1.76 times higher in patients undergoing hip surgeries with ASA≥3 than in patients with ASA <3. ASA classification is a commonly used index for pre-anesthesia risk assessment of patients formulated by the American Medical association, and the higher the rating, the worse the health status of patients (Allen, 2016). Patients with ASA ≥ 3 classification often have more serious systemic diseases and limited physical activities. The preoperative status of the patient is a key determinant of postoperative recovery. Therefore, the physical condition of a patient plays an important role in the recovery after hip surgeries.

Several previous reports compared the use of general anesthesia and regional anesthesia to reduce morbidity and mortality, including delirium. They reported that regional anesthesia yielded more favorable outcomes than general anesthesia (Mauermann et al., 2006; Guay et al., 2018). However, our meta-analysis shows that the General anesthesia is not a relevant risk factor for POD.

In our study, surgical delay was identified as a significant risk factor for POD. In previous study, Lefaivre KA.et al and Rizk.et al had proposed that, for patients with hip fracture, a surgical delay of more than 24 h was a significant predictor for POD and fast-track pathway was needed to reduce the POD incidence (Lefaivre et al., 2009; Rizk et al., 2016). Similarly, many counties had developed guidelines to support the fast-track pathway of hip surgery.

Strengths and limitations of this meta-analysis

The present meta-analysis has strengths over the previous systematic reviews because it contains more cohort studies and more severe inclusion and exclusion criteria. To our knowledge, this is the first meta-analysis concerning the risk factors for POD in geriatric patients undergoing hip fracture surgeries, for former meta-analysis included studies of younger patients or concerning risk factors for preoperative delirium or perioperative delirium. Besides, only available odds ratio (OR) or relative risk (RR) with 95% confidence interval (95% CI) as a result of a multivariate logistic regression was extracted.

There are several limitations in this meta-analysis: (1) significant heterogeneity was found within the selected studies. (2) only articles published in English were included. (3) different assessment time and assessment scale for delirium may introduce bias. (4) for certain identified factors, only small numbers of included studies were available, and as a result, the statistical power might not be enough to detect potential associations.

Conclusions

Based on all the relevant studies, some risk factors for POD in geriatric inpatients with hip fracture were identified. Possible significant risk factors include advance age, male, preoperative cognitive impairment, preoperative delirium, preoperative dementia, diabetes, preoperative functional dependence, high ASA level, low albumin, medical comorbidities, Parkinson's disease and surgical delay. Clinicians should be alert to patients with those factors. To identify the risk factors more precisely, more research studies with larger sample size and better design should be conducted.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.960364/full#supplementary-material

References

Agrawal, S., Turk, R., Burton, B., and Gabriel, R. (2019). Association of Preoperative Delirium with Postoperative Outcomes after Hip Surgery in the Elderly. *J. Am. Coll. Surgeons.* 229, e107. doi: 10.1016/j.jamcollsurg.2019.08.1009

Ahn, E. J., and Bang, S. R. (2022). Risk factors associated with treatment of hyperactive postoperative delirium in elderly patients following hip fracture surgery under regional anesthesia: a nationwide population-based study. *Braz. J. Anesthesiol.* 72, 213–219. doi: 10.1016/j.bjane.2021.03.020

Aldwikat, R. K., Manias, E., and Nicholson, P. (2020). Incidence and risk factors for acute delirium in older patients with a hip fracture: a retrospective cohort study. *Nurs. Health Sci.* 22, 958–966. doi: 10.1111/nhs.12753

Allen, G. C. (2016). American society of anesthesiologist classification-higher incentives for higher scores. *JAMA Intern. Med.* 176, 1578. doi: 10.1001/jamainternmed.2016.5448

Arshi, A., Lai, W. C., Chen, J. B., Bukata, S. V., Stavrakis, A. I., and Zeegen, E. N. (2018). Predictors and sequelae of postoperative delirium in geriatric hip fracture patients. *Geriatr. Orthop. Surg. Rehabil.* 9, 2151459318814823. doi: 10.1177/2151459318814823

Blass, J. P., and Gibson, G. E. (1999). Cerebrometabolic aspects of delirium in relationship to dementia. *Dement. Geriatr. Cogn. Disord.* 10, 335–338. doi: 10.1159/000017165

Chen, X. W., Shi, J. W., Yang, P. S., and Wu, Z. Q. (2014). Preoperative plasma leptin levels predict delirium in elderly patients after hip fracture surgery. *Peptides.* 57, 31–35. doi: 10.1016/j.peptides.2014.04.016

Cho, M. R., Song, S. K., and Ryu, C. H. (2020). Sleep Disturbance Strongly Related to the Development of Postoperative Delirium in Proximal Femoral Fracture Patients Aged 60 or Older. *Hip Pelvis.* 32, 93–98. doi: 10.5371/hp.2020.32.2.93

Choi, Y. H., Kim, D. H., Kim, T. Y., Lim, T. W., Kim, S. W., and Yoo, J. H. (2017). Early postoperative delirium after hemiarthroplasty in elderly patients aged over 70 years with displaced femoral neck fracture. *Clin. Interv. Aging.* 12, 1835–1842. doi: 10.2147/CIA.S147585

Chrispal, A., Mathews, K. P., and Surekha, V. (2010). The clinical profile and association of delirium in geriatric patients with hip fractures in a tertiary care hospital in India. *J. Assoc. Physicians India.* 58, 15–19.

Chu, C. S., Liang, C. K., Chou, M. Y., Lin, Y. T., Hsu, C. J., Chou, P. H., et al. (2016). Short-Form Mini Nutritional Assessment as a useful method of predicting the development of postoperative delirium in elderly patients undergoing orthopedic surgery. *Gen. Hosp. Psychiatry.* 38, 15–20. doi: 10.1016/j.genhosppsych.2015.08.006

Cole, M. G., Ciampi, A., Belzile, E., and Zhong, L. (2009). Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing.* 38, 19–26. doi: 10.1093/ageing/afn253

Cole, M. G., Mccusker, J., Dendukuri, N., and Han, L. (2002). Symptoms of delirium among elderly medical inpatients with or without dementia. *J. Neuropsychiatry Clin. Neurosci.* 14, 167–175. doi: 10.1176/jnp.14.2.167

Davani, A. B., Snyder, S. H., Oh, E. S., Mears, S. C., Crews, D. C., Wang, N. Y., et al. (2021). Kidney function modifies the effect of intraoperative opioid dosage on postoperative delirium. *J. Am. Geriatr. Soc.* 69, 191–196. doi: 10.1111/jgs.16870

Flikweert, E. R., Wendt, K. W., Diercks, R. L., Izaks, G. J., Landsheer, D., Stevens, M., et al. (2018). Complications after hip fracture surgery: are they preventable? *Eur. J. Trauma Emerg. Surg.* 44, 573–580. doi: 10.1007/s00068-017-0826-2

Goldenberg, G., Kiselev, P., Bharathan, T., Baccash, E., Gill, L., Madhav, V., et al. (2006). Predicting post-operative delirium in elderly patients undergoing surgery for hip fracture. *Psychogeriatrics.* 6, 43–48. doi: 10.1111/j.1479-8301.2006.00146.x

Greer, N., Rossom, R., Anderson, P., Macdonald, R., Tacklind, J., Rutks, I., et al. (2011). *Delirium: Screening, Prevention, and Diagnosis - A Systematic Review of the Evidence*. Washington (DC): Department of Veterans Affairs (US).

Guay, J., Parker, M. J., Griffiths, R., and Kopp, S. L. (2018). Peripheral nerve blocks for hip fractures: a cochrane review. *Anesth. Analg.* 126, 1695–1704. doi: 10.1213/ANE.0000000000002489

Gullberg, B., Johnell, O., and Kanis, J. A. (1997). World-wide projections for hip fracture. *Osteoporos. Int.* 7, 407–413. doi: 10.1007/PL00004148

Guo, Y., Jia, P., Zhang, J., Wang, X., Jiang, H., and Jiang, W. (2016). Prevalence and risk factors of postoperative delirium in elderly hip fracture patients. *J. Int. Med. Res.* 44, 317–327. doi: 10.1177/0300060515624936

Han, J. H., Wilson, A., Graves, A. J., Shintani, A., Schnelle, J. F., Dittus, R. S., et al. (2014). Validation of the confusion assessment method for the intensive care unit in older emergency department patients. *Acad. Emerg. Med.* 21, 180–187. doi: 10.1111/acem.12309

Harris, M. J., Brovman, E. Y., and Urman, R. D. (2019). Clinical predictors of postoperative delirium, functional status, and mortality in geriatric patients undergoing non-elective surgery for hip fracture. *J. Clin. Anesth.* 58, 61–71. doi: 10.1016/j.jclinane.2019.05.010

Haynes, M. S., Alder, K. D., Toombs, C., Amakiri, I. C., Rubin, L. E., and Grauer, J. N. (2021). Predictors and sequelae of postoperative delirium in a geriatric patient population with hip fracture. *J. Am. Acad. Orthop. Surg. Glob. Res. Rev.* 5, e20. doi: 10.5435/JAAOSGlobal-D-20-00221

He, R., Wang, F., Shen, H., Zeng, Y., and Lijuanzhang (2020). Association between increased neutrophil-to-lymphocyte ratio and postoperative delirium in elderly patients with total hip arthroplasty for hip fracture. *BMC Psychiatry.* 20, 496. doi: 10.1186/s12888-020-02908-2

Hestermann, U., Backenstrass, M., Gekle, I., Hack, M., Mundt, C., Oster, P., et al. (2009). Validation of a German version of the Confusion Assessment Method for delirium detection in a sample of acute geriatric patients with a high prevalence of dementia. *Psychopathology.* 42, 270–276. doi: 10.1159/000224151

Inouye, S. K., van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P., and Horwitz, R. I. (1990). Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann. Intern. Med.* 113, 941–948. doi: 10.7326/0003-4819-113-12-941

Jeon, E. J., and Sohng, K. Y. (2021). Risk factors and clinical outcomes of delirium after hip fracture surgery in Korean older adults: a retrospective study. *Int. J. Gerontol.* 15, 25–29. doi: 10.6890/IJGE.202101_15(1).0005

Juliebø, V., Bjøro, K., Krogseth, M., Skovlund, E., Ranhoff, A. H., and Wyller, T. B. (2009). Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. *J. Am. Geriatr. Soc.* 57, 1354–1361. doi: 10.1111/j.1532-5415.2009.02377.x

Kagansky, N., Rimon, E., Naor, S., Dvornikov, E., Cojocaru, L., and Levy, S. (2004). Low incidence of delirium in very old patients after surgery for hip fractures. *Am. J. Geriatr. Psychiatry.* 12, 306–314 doi: 10.1097/00019442-200405000-00010

Kim, E. M., Li, G., and Kim, M. (2020). Development of a risk score to predict postoperative delirium in patients with hip fracture. *Anesth. Analg.* 130, 79–86. doi: 10.1213/ANE.0000000000004386

Kim, S. D., Park, S. J., Lee, D. H., and Jee, D. L. (2013). Risk factors of morbidity and mortality following hip fracture surgery. *Korean J. Anesthesiol.* 64, 505–510. doi: 10.4097/kjae.2013.64.6.505

Koskderelioglu, A., Onder, O., Gucuyener, M., Altay, T., Kayali, C., and Gedizlioglu, M. (2017). Screening for postoperative delirium in patients with acute hip fracture: assessment of predictive factors. *Geriatr. Gerontol. Int.* 17, 919–924. doi: 10.1111/ggi.12806

Lee, H. B., Mears, S., Leoutsakos, J., Rosenberg, P., Gottschalk, A., and Sieber, F. (2011). Predisposing factors for post-operative delirium after hip fracture repair among patients with and without dementia. *J. Am. Geriatr. Soc.* 59, S158. doi: 10.1111/j.1532-5415.2011.03725.x

Lee, J. K., and Park, Y. S. (2010). Delirium after spinal surgery in Korean population. *Spine.* 35, 1729–1732. doi: 10.1097/BRS.0b013e3181c423fc

Lefaivre, K. A., Macadam, S. A., Davidson, D. J., Gandhi, R., Chan, H., and Broekhuyse, H. M. (2009). Length of stay, mortality, morbidity and delay to surgery in hip fractures. *J. Bone. Joint Surg. Br.* 91, 922–927. doi: 10.1302/0301-620X.91B7.22446

Levinoff, E., Try, A., Chabot, J., Lee, L., Zukor, D., and Beauchet, O. (2018). Precipitants of delirium in older inpatients admitted in surgery for post-fall hip fracture: an observational study. *J. Frailty Aging.* 7, 34–39. doi: 10.14283/jfa.2017.37

Liang, C. K., Chu, C. L., Chou, M. Y., Lin, Y. T., Lu, T., Hsu, C. J., et al. (2015). Developing a prediction model for post-operative delirium and long-term outcomes among older patients receiving elective orthopedic surgery: a prospective cohort study in Taiwan. *Rejuvenation Res.* 18, 347–355. doi: 10.1089/rej.2014.1645

Martins, S., Lourenço, C., Pinto-De-Sousa, J., Conceição, F., Paiva, J. A., Simões, M. R., et al. (2015). Validation study of the European Portuguese version of the Confusion Assessment Method (CAM). *Int. Psychogeriatr.* 27, 777–784. doi: 10.1017/S1041610214001926

Mauermann, W. J., Shilling, A. M., and Zuo, Z. (2006). A comparison of neuraxial block versus general anesthesia for elective total hip replacement: a meta-analysis. *Anesth. Analg.* 103, 1018–1025. doi: 10.1213/01.ane.0000237267.75543.59

Mazzola, P., Ward, L., Zazzetta, S., Broggini, V., Anzuini, A., Valcarcel, B., et al. (2017). Association between preoperative malnutrition and postoperative delirium after hip fracture surgery in older adults. *J. Am. Geriatr. Soc.* 65, 1222–1228. doi: 10.1111/jgs.14764

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 6, e1000097. doi: 10.1371/journal.pmed.1000097

Nie, H., Zhao, B., Zhang, Y. Q., Jiang, Y. H., and Yang, Y. X. (2012). Pain and cognitive dysfunction are the risk factors of delirium in elderly hip fracture Chinese patients. *Arch. Gerontol. Geriatr.* 54, e172–e174. doi: 10.1016/j.archger.2011.09.012

None (2015). Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. *J. Am. Coll. Surg.* 220, 136–48.e1. doi: 10.1016/j.jamcollsurg.2014.10.019

Oberai, T., Oosterhoff, J., Woodman, R., Doornberg, J. N., Kerkhoffs, G., and Jaarsma, R. (2021). Development of a postoperative delirium risk scoring tool using data from the Australian and New Zealand Hip Fracture Registry: an analysis of 6672 patients 2017-2018. *Arch. Gerontol. Geriatr.* 94, 104368. doi: 10.1016/j.archger.2021.104368

Oh, E. S., Sieber, F. E., Leoutsakos, J. M., Inouye, S. K., and Lee, H. B. (2016). Sex differences in hip fracture surgery: preoperative risk factors for delirium and postoperative outcomes. *J. Am. Geriatr. Soc.* 64, 1616–1621. doi: 10.1111/jgs.14243

Pipanmekaporn, T., Wongpakaran, N., Mueankwan, S., Dendumrongkul, P., Chittawatanarat, K., Khongpheng, N., et al. (2014). Validity and reliability of the Thai version of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Clin. Interv. Aging.* 9, 879–885. doi: 10.2147/CIA.S62660

Ravi, B., Pincus, D., Choi, S., Jenkinson, R., Wasserstein, D. N., and Redelmeier, D. A. (2019). Association of duration of surgery with postoperative delirium among patients receiving hip fracture repair. *JAMA Netw. Open.* 2, e190111. doi: 10.1001/jamanetworkopen.2019.0111

Rizk, P., Morris, W., Oladeji, P., and Huo, M. (2016). Review of postoperative delirium in geriatric patients undergoing hip surgery. *Geriatr. Orthop. Surg. Rehabil.* 7, 100–105. doi: 10.1177/2151458516641162

Shin, J. E., Kyeong, S., Lee, J. S., Park, J. Y., Lee, W. S., Kim, J. J., et al. (2016). A personality trait contributes to the occurrence of postoperative delirium: a prospective study. *BMC Psychiatry.* 16, 371. doi: 10.1186/s12888-016-1079-z

Uzoigwe, C. E., O'Leary, L., Nduka, J., Sharma, D., Melling, D., Simmons, D., et al. (2020). Factors associated with delirium and cognitive decline following hip fracture surgery. *Bone Joint J.* 102-B, 1675–1681. doi: 10.1302/0301-620X.102B12.BJJ-2019-1537.R3

van der Mast, R. C. (1998). Pathophysiology of delirium. *J. Geriatr. Psychiatry Neurol.* 11, 138–45; discussion 157–8. doi: 10.1177/089198879801100304 van der Zanden, V., Beishuizen, S. J., Scholtens, R. M., de Jonghe, A., de Rooij, S. E., and van Munster, B. C. (2016). The effects of blood transfusion on delirium incidence. *J. Am. Med. Dir. Assoc.* 17, 748–753. doi: 10.1016/j.jamda.2016.04.008

Vochteloo, A. J. H., Borger Van Der Burg, B. L., Mertens, B. J. A., Niggebrugge, A. H. P., De Vries, M. R., Tuinebreijer, W. E., et al. (2011). Outcome in hip fracture patients related to anemia at admission and allogeneic blood transfusion: an analysis of 1262 surgically treated patients. *BMC Musculoskel. Dis.* 12, 262. doi: 10.1186/1471-2474-12-262

Wang, C. G., Qin, Y. F., Wan, X., Song, L. C., Li, Z. J., and Li, H. (2018). Incidence and risk factors of postoperative delirium in the elderly patients with hip fracture. *J. Orthop. Surg. Res.* 13, 186. doi: 10.1186/s13018-018-0897-8

Wang, Y., Zhao, L., Zhang, C., An, Q., Guo, Q., Geng, J., et al. (2021). Identification of risk factors for postoperative delirium in elderly patients with hip fractures by a risk stratification index model: a retrospective study. *Brain Behav.* 11, e32420. doi: 10.1002/brb3.2420

Wells, G. A., Shea, B. J., O'Connell, D., Peterson, J., and Tugwell, P. (2014). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Available online at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed January 15, 2022).

Wongpakaran, N., Wongpakaran, T., Bookamana, P., Pinyopornpanish, M., Maneeton, B., Lerttrakarnnon, P., et al. (2011). Diagnosing delirium in elderly Thai patients: utilization of the CAM algorithm. *BMC Fam. Pract.* 12, 65. doi: 10.1186/1471-2296-12-65

Wu, J., Yin, Y., Jin, M., and Li, B. (2021). The risk factors for postoperative delirium in adult patients after hip fracture surgery: a systematic review and meta-analysis. *Int. J. Geriatr. Psychiatry.* 36, 3–14. doi: 10.1002/gps.5408

Xing, H., Xiang, D., Li, Y., Ji, X., and Xie, G. (2020). Preoperative prognostic nutritional index predicts postoperative delirium in elderly patients after hip fracture surgery. *Psychogeriatrics.* 20, 487–494. doi: 10.1111/psyg.12511

Yang, Y., Zhao, X., Dong, T., Yang, Z., Zhang, Q., and Zhang, Y. (2017). Risk factors for postoperative delirium following hip fracture repair in elderly patients: a systematic review and meta-analysis. *Aging Clin. Exp. Res.* 29, 115–126. doi: 10.1007/s40520-016-0541-6

Yang, Y., Zhao, X., Gao, L., Wang, Y., and Wang, J. (2021). Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. *Aging Clin. Exp. Res.* 33, 1493–1506. doi: 10.1007/s40520-020-01674-1

Zastrow, I., Tohsche, P., Loewen, T., Vogt, B., Feige, M., Behnke, M., et al. (2021). Comparison of the '4-item assessment test' and 'nursing delirium screening scale' delirium screening tools on non-intensive care unit wards: a prospective mixed-method approach. *Eur. J. Anaesthesiol.* 38, 957–965. doi: 10.1097/EJA.0000000000001470

Zhang, X., Tong, D. K., Ji, F., Duan, X. Z., Liu, P. Z., Qin, S., et al. (2019). Predictive nomogram for postoperative delirium in elderly patients with a hip fracture. *Injury.* 50, 392–397. doi: 10.1016/j.injury.2018.10.034

Zheng, Y. B., Ruan, G. M., Fu, J. X., Su, Z. L., Cheng, P., and Lu, J. Z. (2016). Postoperative plasma 8-iso-prostaglandin F2α levels are associated with delirium and cognitive dysfunction in elderly patients after hip fracture surgery. *Clin. Chim. Acta.* 455, 149–153. doi: 10.1016/j.cca.2016.02.007

Zhu, Y., Wang, G., Liu, S., Zhou, S., Lian, Y., Zhang, C., et al. (2017). Risk factors for postoperative delirium in patients undergoing major head and neck cancer surgery: a meta-analysis. *Jpn. J. Clin. Oncol.* 47, 505–511. doi: 10.1093/jjco/hyx029

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EDITED BY
Yiying Zhang,
Massachusetts General Hospital and Harvard Medical School, United States

REVIEWED BY
Wenyu Song,
Brigham and Women's Hospital and Harvard Medical School, United States
Zhongyong Shi,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Jianli Li
hblijianli@163.com

†These authors have contributed equally to this work and share first authorship

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The Age-adjusted Charlson Comorbidity Index predicts post-operative delirium in the elderly following thoracic and abdominal surgery: A prospective observational cohort study

Jing Liu[1,2†], Jianli Li[1*†], Jinhua He[1], Huanhuan Zhang[1], Meinv Liu[1] and Junfang Rong[1]

[1]Department of Anesthesiology, Hebei General Hospital, Shijiazhuang, China, [2]Graduate Faculty, Hebei North University, Zhangjiakou, China

Background: Post-operative delirium (POD) presents as a serious neuropsychiatric syndrome in the elderly undergoing thoracic and abdominal surgery, which is mostly associated with poor prognosis. The Age-adjusted Charlson Comorbidity Index (ACCI) has been widely recognized as an independently predictive factor for overall survival rate and mortality in various surgeries. However, no studies demonstrated the potential relationship between ACCI and POD. The current study was to explore the correlation between ACCI and POD, and determine the predictive effect of ACCI on POD in the elderly after thoracic and abdominal surgery.

Materials and methods: Total 184 patients (≥60 years) who underwent thoracic and abdominal surgery from 2021.10 to 2022.5 were enrolled in this prospective observational cohort study. ACCI was calculated by weighting comorbidities and age. POD was diagnosed using Confusion Assessment Method (CAM) twice a day in the first 3 days after surgery. The Visual Analog Scale (VAS) was applied to measure pre-operative and post-operative pain at rest and in motion. All demographic and perioperative data were compared in patients with POD and without POD. ACCI and other variables were analyzed by univariate and multivariate logistic regression analysis. The characteristic curve of receiver operating characteristic (ROC) was used to further evaluate the accuracy of ACCI to predict POD.

Results: Post-operative delirium was diagnosed in 36 of 184 patients included in our study. The prevalence of POD in the elderly after thoracic and abdominal surgery was 19.6%. The outcomes by multivariate regression analysis showed the independent risk factors for POD were ACCI (OR: 1.834; 95%CI: 1.434–2.344; $P < 0.001$), pre-operative Mini-Mental State Examination

(MMSE) scores (OR: 0.873; 95%CI: 0.767–0.994; P = 0.040), serum albumin (OR: 0.909; 95%CI: 0.826–1.000; P = 0.049) and pain scores in the post-operative third day (OR: 2.013; 95%CI: 1.459–2.778; P < 0.001). ACCI can predict POD more accurately with the largest area under curve (AUC) of 0.794 and sensitivity of 0.861, respectively.

Conclusion: Age-adjusted Charlson Comorbidity Index, pre-operative MMSE scores, serum albumin and post-operative pain were independently associated with POD in geriatric patients following thoracic and abdominal surgery. Moreover, ACCI may become an accurate indicator to predict POD early.

KEYWORDS

elderly, Age-adjusted Charlson Comorbidity Index, thoracic and abdominal surgery, observational study, post-operative delirium

Introduction

With the aging of population, the proportion of surgeries in the elderly is increasing. It is reported that thoracic and abdominal surgery accounted for 54.8% of all surgeries among the elderly in China (Han et al., 2019). The incidences of post-operative complications in elderly patients after thoracic and abdominal surgery range from 12 to 47% and from 13 to 39%, respectively (Revenig et al., 2015; Mosquera et al., 2016). Post-operative delirium (POD), a common complication in the elderly after thoracic and abdominal surgery, exerts an acute and transient neurological disorder, mainly characterized by inattention and cognitive function decline within 1 week after surgery (Robinson et al., 2009). It is estimated that 11.1–45.6% of elderly patients can develop POD (Ho et al., 2021). In addition, the risk for POD is increasing with the aging of the population. POD can lead to various adverse consequences, such as prolonged hospitalization, higher economic costs, and an increased risk for Alzheimer's disease (Kinchin et al., 2021; Richardson et al., 2021). Moreover, it may be even strongly associated with high mortality and morbidity (Aung Thein et al., 2020). Therefore, it is crucial to prevent POD for improving the long-term prognosis and the life quality of patients. POD is multifactorial and complex, depending on the interaction between predisposing and precipitating factors (Janssen et al., 2019; Seiler et al., 2020). As a previous meta-analysis reported, some potentially related risk factors can induce POD, such as advanced age, comorbidities, and others (Rong et al., 2021). Since 30–40% of the onset of delirium can be prevented (Ishibashi et al., 2022), it might play a prominent role in reducing POD by early identifying associated risk factors.

Charlson Comorbidity Index (CCI) was firstly proposed by Charlson et al. (1987), which has become an indicator to estimate mortality risk owing to comorbidity (Charlson et al., 2022). A meta-analysis has demonstrated that CCI $\geq$ 2 was independently associated with the development of POD (Mevorach et al., 2022). After adjusting age as a correction variable, Age-adjusted Charlson Comorbidity Index (ACCI) is regarded as a new index to evaluate prognosis, which is calculated ultimately by integrating age and all underlying diseases, namely, cerebrovascular disease, liver or kidney disease, and heart disease, etc., and a higher ACCI can lead to worse survival rate and more mortality (Aoyama et al., 2020). Currently, ACCI is applied to standardize the evaluation of surgical patients and to predict the post-operative mortality of patients undergoing surgery (Asano et al., 2017; González Quevedo et al., 2017). Moreover, ACCI played a remarkable role in predicting post-surgical complications such as arrhythmia, delirium, stroke, and other diseases in the orthopedic surgery (Marya et al., 2016; Amit and Marya, 2022), and the incidence and severity of post-operative complications were higher in patients with high ACCI score than those with low ACCI score (Nagata et al., 2021). Nonetheless, the direct relationship between ACCI and POD in thoracic and abdominal surgery remains obscure to date.

Given this context, we aimed to analyze ACCI and other risk factors associated with POD and determine the predictive value of ACCI on POD in the elderly after thoracic and abdominal surgery, to provide guidance for clinical management of patients.

Materials and methods

Study population

This prospective observational cohort study was approved by the Medical Ethics Committee of Hebei

General Hospital. Elderly patients aged ≥60 years who scheduled for thoracic and abdominal surgery were screened for eligibility. The study included the participants meeting the eligibility criteria in Hebei General Hospital from October, 2021 to May, 2022. The inclusion criteria were as follows: regardless of gender and nationality, American Society of Anesthesiologists (ASA) grade II ∼ III, operation time ≥1 h, surgical procedures under general anesthesia including thoracic, gastrointestinal, urinary, hepatobiliary surgery. Patients who developed delirium before surgery, refused to participate, lacked of cooperation or communication abilities, were unable to read Chinese before surgery and entered intensive care unit (ICU) after surgery were excluded.

Data collection

Demographic and clinical characteristics

Demographic data [age, ASA grade, and Body Mass Index (BMI), etc.,] and comorbidities (hypertension, cardiac arrhythmia, and coronary disease) were recorded in a medical chart. Clinical data obtained from the electronic anesthesia record included operation and anesthesia time, surgical types, drugs usage (remifentanil and sufentanil), and others. Mini-Mental State Examination (MMSE) was adopted to assess the pre-operative cognitive condition, and MMSE score of less than 27 indicated cognitive impairment (Segernäs et al., 2022). Anxiety or depression was diagnosed by Hospital Anxiety and Depression Scale (HADS) (Pais-Ribeiro et al., 2018). Pre-operative and post-operative pain was frequently described by Visual Analogue Scale (VAS) (da Costa et al., 2021).

Pre-operative laboratory indicators

Laboratory data included neutrophils, hemoglobin, serum albumin, D-dimer, prognostic nutrition index (PNI), and albumin to fibrinogen ratio (AFR), etc. AFR was calculated as serum albumin divided by fibrinogen. PNI was calculated by the following formula: [10 × serum albumin value (g/dl)] + [0.005 × total lymphocyte count in the peripheral blood (per mm^3)] (Cadwell et al., 2020).

All data were acquired independently from the medical records by two researchers, which were regarded as potential variables to result in POD.

The Age-adjusted Charlson Comorbidity Index

Evaluation and definition of comorbidities were performed prior to thoracic and abdominal surgery. The CCI score included 19 different medical conditions, with a score range of 1–6 for each comorbidity to sum an index score. Each decade over the age of 40 years was assigned a comorbidity score of 1. ACCI was calculated by adding the CCI score and age, where a higher score indicated a poorer physical condition (Aoyama et al., 2020). Since all patients were 60 years old or over, ACCI score was not less than 2 points (**Supplementary Table 1**).

Post-operative delirium assessment and determination

Confusion Assessment Method (CAM) was used to assess POD twice a day (08:00–10:00 a.m. and 18:00–20:00 p.m.) during the post-operative first 3 days by a trained anesthesiologist who was unaware of this study. All subjects were finally divided into POD group and non-POD group according to the diagnostic criterion, based on observations in four aspects, including: (1) changes in level of consciousness, (2) an acute fluctuation in mental status, (3) disordered thinking, (4) inattention. Delirium was defined as the presence of (1) and (2), accompanied by (3) or (4) or both (González et al., 2004). At the same time, patients discharged within 3 days can be followed up by telephone.

Statistical analyses

In our study, at least 6–10 patients per independent variable events are necessary to adequately produce estimates of effect with binary regression models (Peduzzi et al., 1996). Based on the reported incidence of POD after major abdominal surgery of approximately 17.8% (Li et al., 2021), a least sample size of 141 individuals will allow 4 variables to be assessed in the regression model. Data analyses were conducted by IBM SPSS statistics software version 25.0 (SPSS Inc., Chicago, IL, United States). Quantitative data were described as mean and standard deviation ($\bar{x} \pm s$) or as median and interquartile ranges [M (IQR)], depending on the normality of the variables checked by Shapiro–Wilk (SW) test. For continuous variables, differences in both groups can be compared either by independent sample *t*-test or Mann–Whitney *U* test. On the other hand, categorical variables were represented as number (n) or rate (%), which can be tested by chi-square test or Fisher test. $P < 0.05$ was identified as statistically significant. Using tolerance (Tol) and variance inflation factor (VIF) examined multicollinearity among variables. The arguments with *P*-value < 0.1 by univariate regression analysis were performed a forward stepwise multivariate logistic regression analysis, thus controlling the confounding bias and screening out related risk factors for POD. The odds ratio (OR) with 95% confidence interval (CI) and the *P*-values were used to express the effects of related variables. Moreover, we implemented Hosmer and Lemeshow goodness-of-fit test to verify the model fitness for the logistic regression. In addition, the characteristic curve of receiver operating characteristic (ROC) was applied as a descriptive tool to further evaluate the accuracy of ACCI in predicting POD in terms of the area under curve (AUC).

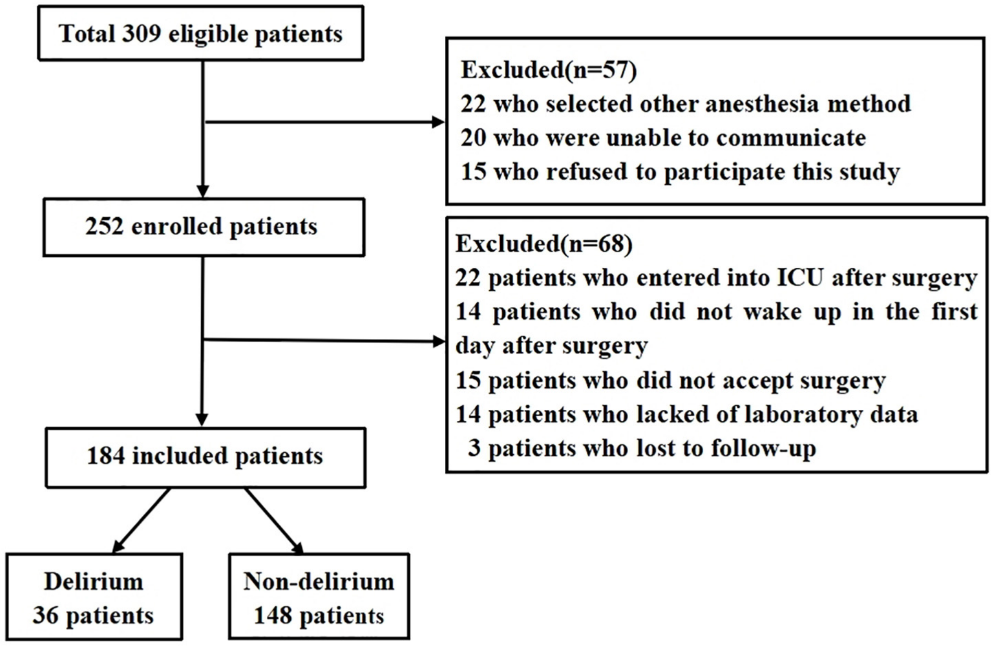

FIGURE 1
Flow chart of study population.

Results

Comparison of patients characteristics

Initially, total 309 elderly patients were included in this study, of whom 125 patients were excluded because of poor communication, data loss, refusal surgery, and other reasons, and 184 patients were enrolled to analyze ultimately (**Figure 1**). The incidence of POD in the elderly following thoracic and abdominal surgery was 19.6%. All demographic and clinical data were displayed in **Table 1**, where the median (interquartile ranges) age was 68 (64–72) years and males were 102 cases (54.4%). Among demographic data, there were statistic differences in age ($P = 0.004$), educational level ($P = 0.022$), ASA grade ($P = 0.004$), BMI ($P = 0.028$), and pre-operative MMSE scores ($P = 0.010$) between POD group and non-POD group. The level of ACCI [7 (6–8) vs. 5 (4–6), $P < 0.001$] was higher in patients with POD, in comparison with that without POD. Pain scores in the first 3 days after surgery had significant differences in two groups (all $P < 0.05$).

Comparison of pre-operative laboratory relevant indicators

As indicated in **Table 2**, subjects with POD had lower levels of serum albumin (36.0 ± 5.5 vs. 38.0 ± 4.8, $P = 0.030$), AFR [10.5 (8.6–13.6) vs. 12.7 (9.9–14.9), $P = 0.026$] and total cholesterol [4.3 (3.7–4.9) vs. 4.8 (3.9–5.5), $P = 0.037$], compared to those without POD. Patients with a higher level of D-dimer had an increased risk to develop POD ($P = 0.009$).

Multicollinearity among variables by linear analysis

Our results demonstrated that there was no severe collinearity among variables included in multivariate logistic regression analysis (all Tol >0.1, VIF <10). Details were shown in **Supplementary Table 2**.

Independent risk factors for post-operative delirium by logistic regression analyses

Originally, all variables with $P < 0.05$ were performed univariate logistic regression analysis, and unadjusted outcomes that differed significantly between two groups were age, ASA grade, BMI, pre-operative MMSE scores, ACCI, serum albumin, AFR, D-dimer, total cholesterol, and pain scores within the post-operative first 3 days (all $P < 0.1$). Finally, the adjusted results by multivariate logistic regression analysis showed the independent predictors for POD were ACCI (OR: 1.834; 95%CI: 1.434–2.344; $P < 0.001$), pre-operative MMSE scores (OR: 0.873; 95%CI: 0.767–0.994; $P = 0.040$), serum albumin (OR: 0.909;

TABLE 1 Comparison of demographic and clinical data between two groups.

Variables	Total (N = 184)	Delirium (n = 36)	Non-delirium (n = 148)	P-value
Age (years)	68 (64–72)	70.5 (67–75)	67 (64–72)	0.004
Gender (male)	102 (55.4)	20 (55.6)	82 (55.4)	0.987
Educational level (n%)				**0.022**
Low degree (Illiteracy and primary school)	72 (39.1)	12 (33.3)	60 (40.5)	–
Medium degree (Middle and senior school)	90 (48.9)	23 (63.9)	67 (45.3)	–
High degree (College and above)	22 (12.0)	1 (2.8)	21 (14.2)	–
BMI (kg/m^2)	25.3 ± 3.2	24.2 ± 2.6	25.5 ± 3.3	**0.028**
ASA grade (n%)				**0.004**
II	86 (46.7)	9 (25.0)	77 (52.0)	–
III	98 (53.3)	27 (75.0)	71 (48.0)	–
Smoking history (n%)	44 (23.9)	13 (36.1)	31 (20.9)	0.056
Alcohol consumption (n%)	21 (11.4)	6 (16.7)	15 (10.1)	0.269
Pre-operative MMSE scores (0–30)	27 (24–28)	25 (21.3–28)	27 (25–28)	**0.010**
Cognitive impairment (n%)	90 (48.9)	69 (46.6)	21 (58.3)	0.207
Anxiety (n%)	31 (16.8)	6 (16.7)	25 (16.9)	0.974
Depression (n%)	4 (11.1)	2 (5.6)	2 (1.4)	0.361
ACCI	5 (4–7)	7 (6–8)	5 (4–6)	**<0.001**
Comorbidities				
Hypertension (n%)	89 (48.4)	19 (52.8)	70 (47.3)	0.555
Cardiac arrhythmia (n%)	29 (15.8)	6 (16.7)	23 (15.5)	0.701
Coronary heart disease (n%)	24 (13.0)	4 (11.1)	20 (13.5)	0.914
Pre-operative pain scores	0 (0–0)	0 (0–0)	0 (0–0)	0.185
Operation time (min)	152.5 (100–217.5)	175 (101.2–233.8)	145 (98.5–200)	0.147
Anesthesia time (min)	195 (145–263.8)	234 (146.3–278.8)	190 (141.3–253.8)	0.065
Surgical methods (endoscopic) (n%)	152 (82.6)	30 (83.3)	122 (82.4)	0.898
Type of surgery (n%)				0.422
Thoracic	95 (51.6)	23 (63.9)	72 (48.6)	–
Gastrointestinal	44 (23.9)	6 (16.7)	38 (25.7)	–
Urinary	34 (18.5)	5 (13.9)	29 (19.6)	–
Hepatobiliary	11 (6.0)	2 (5.5)	9 (6.1)	–
Dosage of opioids				
Remifentanil (mg)	1.5 (1.1–2.4)	1.8 (1.1–2.9)	1.5 (1–2.4)	0.185
Sufentanil (μg)	25 (20–30)	25 (20–30)	25 (20–30)	0.507
Norepinephrine usage (mg)	0 (0–0.1)	0 (0–0.3)	0 (0–0.1)	0.653
Estimated blood loss volume (ml)	121.4 (72.5–229.6)	151.4 (99.4–231.4)	113.1 (53.6–226.7)	0.103
Infusion of blood products				
Red blood cells (U)	0 (0–0)	0 (0–0)	0 (0–0)	0.389
Plasma (ml)	0 (0–0)	0 (0–0)	0 (0–0)	0.249
Minimum body temperature (°C)	36.3 (36.1–36.4)	36.3 (36.1–36.4)	36.3 (36.1–36.4)	0.942
Pain scores within the first 3 days post-operatively (0–10)				
The first day post-operatively	5 (3–6)	6 (4–6.8)	4.5 (3–6)	**0.005**
The second day post-operatively	4 (3–5)	5 (4–6)	3 (2–5)	**<0.001**
The third day post-operatively	3 (2–4)	4 (3–5.8)	3 (2–4)	**<0.001**
Use of post-operative analgesic pump (n%)	129 (70.1)	24 (66.7)	105 (70.9)	0.615
Total times of analgesics used within the first 3 days post-operatively	1 (0–1)	1 (1–1)	1 (0–1)	0.051
Total times of analgesics used in the first day post-operatively	1 (0–1)	1 (1–1)	1 (0–1)	0.083
Total times of analgesics used in the second day post-operatively	0 (0–0)	0 (0–0)	0 (0–0)	0.193
Total times of analgesics used in the third day post-operatively	0 (0–0)	0 (0–0)	0 (0–0)	0.244
Post-surgical stay (days)	7 (5–9)	7.5 (5–10)	7 (5–9)	0.333
Length of hospital stay (days)	12 (8–16.8)	13.5 (9–19.5)	12 (8–15)	0.333

Bold values indicated statistical significances.
Abbreviation: BMI, Body Mass Index; ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; ACCI, Age-adjusted Charlson Comorbidity Index.

TABLE 2 Pre-operative laboratory variables in older patients with or without post-operative delirium (POD).

Variables	Total (*N* = 184)	Delirium (*n* = 36)	Non-delirium (*n* = 148)	*P*-value
Neutrophil count ($\times 10^9$/L)	4.4 (3–7)	4.9 (3.2–9)	4.3 (3–6.8)	0.187
Platelets count ($\times 10^9$/L)	213.5 (170.8–255.5)	226.5 (161–252.8)	212 (170.8–259.5)	0.859
Total lymphocyte count ($\times 10^9$/L)	1.3 (1–1.9)	1.5 (1–2.3)	1.3 (1–1.8)	0.249
White blood cell count ($\times 10^9$/L)	6.6 (5.3–8.6)	7.6 (6.1–10.1)	6.4 (5.1–8.4)	0.062
Hemoglobin (g/L)	126.2 ± 16.1	121.8 ± 13.7	127.3 ± 16.4	0.063
Serum albumin (g/L)	37.6 ± 5.0	36.0 ± 5.5	38.0 ± 4.8	**0.030**
Creatinine (μmol/L)	67.3 (56.6–77.9)	71.5 (59.9–83.2)	66.1 (55.6–77.7)	0.064
Blood type (*n*%)				0.769
A	49 (26.6)	9 (25.0)	40 (27.0)	–
B	65 (35.3)	12 (33.3)	53 (35.8)	–
AB	13 (7.1)	4 (11.1)	9 (6.1)	–
O	57 (31.0)	11 (30.6)	46 (31.1)	–
Fibrinogen (g/L)	3.1 (2.7–3.8)	3.2 (2.7–4.1)	3.1 (2.6–3.7)	0.248
CK-MB (U/L)	15.6 (13.1–17.9)	15.3 (13–17.3)	15.7 (13.2–17.9)	0.455
AST/ALT	1.3 (1–1.7)	1.4 (1–1.8)	1.3 (1–1.7)	0.636
Uric acid (μmol/L)	289.7 ± 78.4	284.0 ± 63.7	291.1 ± 81.7	0.629
D-dimer (mg/L)	0.5 (0.3–0.9)	0.7 (0.5–1.3)	0.5 (0.3–0.9)	**0.009**
AFR	12.4 (9.6–14.6)	10.5 (8.6–13.6)	12.7 (9.9–14.9)	**0.026**
PNI	44.4 (40.4–49.3)	43.4 (38.6–50.2)	44.6 (40.9–49.9)	0.352
BUN (mmol/L)	4.9 (4–5.8)	5.3 (4–6.3)	4.8 (3.9–5.8)	0.300
Calcium (mmol/L)	2.2 (2.1, 2.3)	2.1 (2.0, 2.3)	2.2 (2.1, 2.3)	0.093
Sodium (mmol/L)	140 (138–141)	140 (138–141.8)	140 (138–141)	0.796
Total cholesterol (mmol/L)	4.7 (3.9–5.5)	4.3 (3.7–4.9)	4.8 (3.9–5.5)	**0.037**

Bold values indicated statistical significances.
Abbreviation: CK-MB, Creatine kinase-MB; AST/ALT, Aspartate transaminase/Alanine aminotransferase; AFR, Albumin to Fibrinogen Ratio; PNI, Prognostic Nutrition Index; BUN, Blood Urea Nitrogen.

TABLE 3 Univariate and multivariate logistic regression analyses of clinical associated risk factors for post-operative delirium (POD).

Variables	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (years)	1.096	1.027–1.170	0.006	–	–	–
ASA grade	0.307	0.135–0.698	0.005	–	–	–
BMI (kg/m^2)	0.874	0.774–0.987	0.030	–	–	–
Pre-operative MMSE scores	0.834	0.749–0.929	0.001	0.873	0.767–0.994	**0.040**
ACCI	1.513	1.262–1.814	<0.001	1.834	1.434–2.344	**<0.001**
Educational level (*n*%)	0.829	0.616–1.115	0.215	–	–	–
Serum albumin (g/L)	0.920	0.852–0.993	0.032	0.909	0.826–1.000	**0.049**
D-dimer (mg/L)	1.340	1.014–1.771	0.040	–	–	–
Total cholesterol (mmol/L)	0.709	0.500–1.005	0.054	–	–	–
Pain scores in the first day post-operatively	1.305	1.079–1.579	0.006	–	–	–
Pain scores in the second day post-operatively	1.451	1.178–1.787	<0.001	–	–	–
Pain scores in the third day post-operatively	1.658	1.288–2.135	<0.001	2.013	1.459–2.778	**<0.001**
AFR	0.897	0.809–0.994	0.038	–	–	–

Hosmer and Lemeshow goodness-of-fit test: χ^2 value = 12.536, P = 0.129. Bold values indicated statistical significances.
Abbreviation: ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; ACCI, Ageadjusted Charlson Comorbidity Index; BMI, Body Mass Index; AFR, Albumin to Fibrinogen Ratio; CI, Confidence Interval; OR, Odds Ratio.

95%CI: 0.826–1.000; P = 0.049) and pain scores in the post-operative third day (OR: 2.013; 95%CI: 1.459–2.778; $P < 0.001$), as demonstrated in Table 3.

Additionally, the predictable model fitted very well by Hosmer and Lemeshow goodness-of-fit test with a χ^2 value 12.536 and P-value of 0.129.

TABLE 4 The accuracy of risk factors to predict post-operative delirium (POD) by ROC curve analysis.

Variables	Area under the curve (95% confidence interval)	Sensitivity	Specificity	Cut-off value	*P*-value
ACCI	0.794 (0.724, 0.863)	0.861	0.358	5.5	<0.001
Pre-operative MMSE scores	0.637 (0.532, 0.743)	0.770	0.556	24.5	0.011
Serum albumin (g/L)	0.609 (0.501, 0.717)	0.777	0.556	34.65	0.043
Pain scores in the third day post-operatively	0.706 (0.612, 0.800)	0.889	0.595	2.5	<0.001

Abbreviation: ACCI, Age-adjusted Charlson Comorbidity Index.

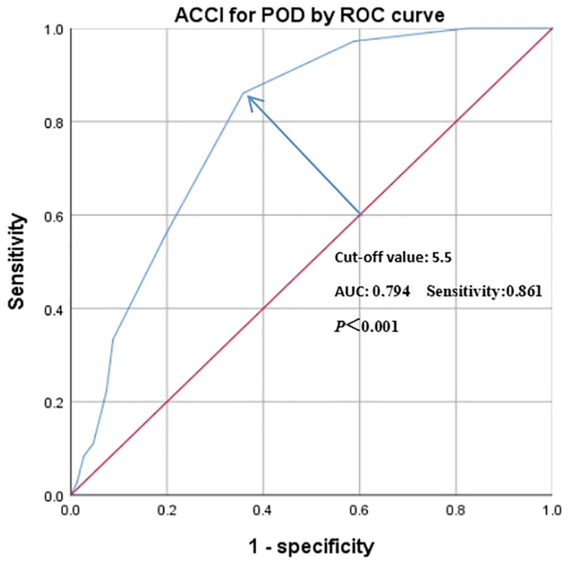

FIGURE 2
The predictive value of ACCI for POD by ROC analysis. Abbreviations: ACCI, Age-adjusted Charlson Comorbidity Index; POD, post-operative delirium; ROC, receiver operating characteristic; AUC, area under the curve.

The predictive value of Age-adjusted Charlson Comorbidity Index for post-operative delirium by receiver operating characteristic analysis

The characteristic curve of ROC was applied to further evaluate the accuracy of all predictive factors. As presented in Table 4, ACCI had the largest AUC with 0.794 and sensitivity with 0.861, compared to others predictive risk factors (pre-operative MMSE scores AUC: 0.637 sensitivity: 0.770; serum albumin AUC: 0.609 sensitivity: 0.777; post-operative pain AUC: 0.706, sensitivity: 0.889). Also, based on ROC analysis, the optimal cut-off value of ACCI was 5.5 to predict POD (Figure 2).

Discussion

Post-operative delirium is a serious post-surgical complication in the elderly and contributes to various adverse effects, such as longer hospital stays, increased economic burden and decrease in life quality (Park and Lee, 2019). It has been reported that multiple related factors increased the risk of POD including advanced age, diabetes mellitus, and others (Lee et al., 2020). Early identification of related factors plays a significant role in preventing and treating POD. This prospective observational cohort study firstly explored the predictive value of ACCI on POD in geriatric patients after thoracic and abdominal surgery. Our results revealed that ACCI, pre-operative MMSE scores, serum albumin and post-operative pain were independently correlated with POD, and ACCI was regarded as a predictor for POD.

In the present study, the prevalence of POD in the elderly undergoing thoracic and abdominal surgery was 19.6%. Similar to our finding, an observational retrospective cohort study analyzed 1,055 cases of elderly patients undergoing major abdominal surgery and observed that 17.8% of patients developed POD (Li et al., 2021). Additionally, a previous study showed that POD occurred in 22.4% of elderly patients after esophagectomy (Jung et al., 2018). However, other studies revealed the incidence of POD was a little lower than that in our study, such as the 3.3% by Ishibashi et al. (2022) and

7.3% by Ida et al. (2020), which might be related to baseline characteristics, sample size, diagnostic criteria, and different interventions in patients.

Our univariate logistic regression analysis has demonstrated that 12 related variables were potential risk factors for POD, including age, ASA grade, ACCI, and others. After adjusting related factors by multivariate logistic regression analysis, ACCI was identified as an independent predictor for POD. ACCI, as a weighting index to measure the burden of comorbidities, has become a predictive factor for post-operative complications (Amit and Marya, 2022). Numerous studies have reported that elderly cancer patients with high ACCI scores had decreased progression-free survival and overall survival (Aoyama et al., 2020; Zhou et al., 2022). Our study firstly focused on the predictive role of ACCI for POD in geriatric patients undergoing thoracic and abdominal surgery. ACCI was calculated by total points based on age and 19 medical conditions, including cerebrovascular, immune systems diseases, and others (Aoyama et al., 2020). Some reports have proved that comorbidities were independently correlated with POD, such as hypertension and dementia etc. (Pérez-Ros et al., 2019; Ramos et al., 2022). Moreover, it has been well-established that patients with advanced age were more prone to develop POD (Lee et al., 2020). Conversely, our results did not support the predictive effect of age on POD. Although univariate regression analysis indicated a statistic difference in age in two groups ($P = 0.006$), the multivariate regression analysis indicated no difference ($P = 0.273$). The possible reason for the discrepancy may be related to the small age range [68, IQR: (64–72)] and insufficient sample size in this study. While age was not an independent risk factor for POD, our results confirmed that ACCI was highly related to POD. Also, increased per one-point of ACCI scores can add 1.834-fold risk of POD (OR: 1.834; 95%CI: 1.434–2.344; $P < 0.001$), which was likely that ACCI combined the effect of both age and comorbidity and probably gived true measure of the physiologic reserve. In addition, ACCI can predict cumulative minor or major post-operative complications among geriatric patients following orthopedic surgery, including delirium and stroke in the nervous system and other systems (Marya et al., 2016; Amit and Marya, 2022). Therefore, we deemed that ACCI might have a predictive value in POD in other surgeries. Besides, the cut-off values of ACCI have been widely investigated in cancer survival (Aoyama et al., 2020; Takahara et al., 2020). However, the optimal cut-off value of ACCI to predict POD in the elderly after thoracic and abdominal surgery was hardly explored. In this study, we set the optimal intercept value of ACCI as 5.5 by ROC analysis and ACCI was regarded as a better predictive factor for POD with the largest AUC of 0.794 and sensitivity of 0.861, respectively, compared with other related variables. Nevertheless, a great deal of studies should be performed to further verify whether ACCI can better predict POD in other surgeries.

Mini-Mental State Examination has been generally accepted as a simple scale to evaluate cognitive function, including 30 lists of decline symptoms totally, and lower scores represented worse cognitive condition in patients (Segernäs et al., 2022). Our results showed that pre-operative MMSE scores in POD group were two points lower than those in non-POD group and were negatively associated with POD *via* multivariate regression analysis, which suggested that patients may have some impaired brain function pre-operatively, and thus increasing the probability to develop POD (Pettemeridou et al., 2021). In line with our study, previous studies have confirmed that patients who experienced POD had lower baseline MMSE scores before surgery (Pan et al., 2019; Humbert et al., 2021). Interestingly, there was no statistic difference in cognitive impairment assessed by MMSE between two groups in our study ($P = 0.207$), which may likely that educational attainment played a confounding effect on MMSE score. Some recent studies have suggested the educational level was positively associated with MMSE score, and the threshold of MMSE for diagnosing cognitive impairment was different among patients with different educational levels (Wu et al., 2021; Cardoso et al., 2022). Even so, pre-operative assessment of cognitive status by MMSE can contribute to early preventing POD, which deserved more attention.

Additionally, serum albumin, as an indicator representing patients' nutritional and immune status, has been verified to be closely associated with POD in orthopedic and urological surgery (Matsuki et al., 2020; Qi et al., 2020). Moreover, a meta-analysis further evidenced that serum albumin was an independent risk factor for POD in colorectal cancer surgery (Lee and Lim, 2020). Our regression analysis result concluded that the a low level of albumin prior to surgery was relevant to an increased risk of POD, which was accordance with previous studies. Unfortunately, we did not measure the difference between pre-operative and post-operative albumin (ΔAlb), which may better explain its relationship with POD.

Our study also demonstrated that another potential risk factor that affected the onset of POD was post-operative pain. As previous studies reported, post-operative pain might exert a certain promoting influence on developing POD (Denny and Such, 2018; Ding et al., 2021). Similarly, our study showed post-operative pain had a remarkable effect on POD even though adjusting several potential factors by multiple regression analysis. Meanwhile, the risk of POD added 2.421 times when per one-point of pain scores increased (OR: 2.013; 95%CI: 1.459–2.778; $P < 0.001$). With respect to analgesic remedies, there were no statistical significance in post-operative analgesic pumps usage and analgesic drugs including flurbiprofen, ketorolac tromethamine, dezocine, pentazocine between two groups, which might be due to the fact that some patients refused to take analgesics for fear of its side effects according to surgeons' feedback.

There are also some limitations that need to be addressed. First, since the sample size of this single-center prospective observational study is small, internal bias cannot be avoided. Second, the time of evaluating delirium is only within 3 days after surgery, which may lead to a lower incidence of POD. Finally, some other factors with an early vigilant role in POD in elderly patients, such as frailty, malnutrition and depth of anesthesia, are not fully considered in this study.

Conclusion

Taken together, delirium was common among geriatric patients undergoing thoracic and abdominal surgery in our study. We found that ACCI, pre-operative MMSE scores, serum albumin, and post-operative pain became the independent risk factors for POD, and ACCI can better predict the development of POD. This study provides evidence supporting ACCI as a part of clinical assessments for delirium risk in elderly patients following thoracic and abdominal surgery. In order to provide evidence-based prevention strategies, clinicians should regard ACCI as an early detection to identify older patients at risk of delirium.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Hebei General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JL, JFR, and JLL: design or idea of the study and drafting of manuscript. JL and JHH: data collection. HHZ and MNL: data monitoring and analysis. All authors contributed to revision and agreed with this manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.979119/full#supplementary-material

References

Amit, P., and Marya, S. K. S. (2022). Age-adjusted Charlson comorbidity index as a novel guideline for patient selection between unilateral versus bilateral simultaneous total knee arthroplasty. *Arch. Orthop. Trauma Surg.* 142, 657–663. doi: 10.1007/s00402-021-03841-z

Aoyama, T., Atsumi, Y., Kawahara, S., Tamagawa, H., Tamagawa, A., Ozawa, Y., et al. (2020). The clinical impact of the age-adjusted charlson comorbidity index on esophageal cancer patients who receive curative treatment. *In Vivo* 34, 2783–2790. doi: 10.21873/invivo.12103

Asano, T., Yamada, S., Fujii, T., Yabusaki, N., Nakayama, G., and Sugimoto, H. (2017). The Charlson age comorbidity index predicts prognosis in patients with resected pancreatic cancer. *Int. J. Surg.* 39, 169–175. doi: 10.1016/j.ijsu.2017.01.115

Aung Thein, M. Z., Pereira, J. V., Nitchingham, A., and Caplan, G. A. (2020). A call to action for delirium research: Meta-analysis and regression of delirium associated mortality. *BMC Geriatr.* 20:325. doi: 10.1186/s12877-020-01723-4

Cadwell, J. B., Afonso, A. M., and Shahrokni, A. (2020). Prognostic nutritional index (PNI), independent of frailty is associated with six-month postoperative mortality. *J. Geriatr. Oncol.* 11, 880–884. doi: 10.1016/j.jgo.2020.03.013

Cardoso, S., Barros, R., Marôco, J., de Mendonça, A., and Guerreiro, M. (2022). Different MMSE domains are associated to cognitive decline and education. *Appl. Neuropsychol. Adult* 1–7. doi: 10.1080/23279095.2022.2041018

Charlson, M. E., Carrozzino, D., Guidi, J., and Patierno, C. (2022). Charlson comorbidity index: A critical review of clinimetric properties. *Psychother. Psychosom.* 91, 8–35. doi: 10.1159/000521288

Charlson, M. E., Pompei, P., Ales, K. L., and MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic. Dis.* 40, 373–383. doi: 10.1016/0021-9681(87)90171-8

da Costa, B. R., Saadat, P., Basciani, R., Agarwal, A., Johnston, B. C., and Jüni, P. (2021). Visual Analogue Scale has higher assay sensitivity than WOMAC pain in detecting between-group differences in treatment effects: A meta-epidemiological study. *Osteoarthritis Cartilage* 29, 304–312. doi: 10.1016/j.joca.2020.10.004

Denny, D. L., and Such, T. L. (2018). Exploration of relationships between postoperative pain and subsyndromal delirium in older adults. *Nurs. Res.* 67, 421–429. doi: 10.1097/NNR.0000000000000305

Ding, X., Gao, X., Chen, Q., Jiang, X., Li, Y., Xu, J., et al. (2021). Preoperative acute pain is associated with postoperative delirium. *Pain Med.* 22, 15–21. doi: 10.1093/pm/pnaa314

González Quevedo, D., Mariño, I. T., Sánchez Siles, J. M., Escribano, E. R., Granero Molina, E. J., Enrique, D. B., et al. (2017). Patient survival and surgical re-intervention predictors for intracapsular hip fractures. *Injury* 48, 1831–1836. doi: 10.1016/j.injury.2017.06.014

González, M., de Pablo, J., Fuente, E., Valdés, M., Peri, J. M., Nomdedeu, M., et al. (2004). Instrument for detection of delirium in general hospitals: Adaptation of the confusion assessment method. *Psychosomatics* 45, 426–431. doi: 10.1176/appi.psy.45.5.426

Han, B., Li, Q., and Chen, X. (2019). Frailty and postoperative complications in older Chinese adults undergoing major thoracic and abdominal surgery. *Clin. Interv. Aging* 14, 947–957. doi: 10.2147/CIA.S201062

Ho, M. H., Nealon, J., Igwe, E., Traynor, V., Chang, H. R., Chen, K. H., et al. (2021). Postoperative delirium in older patients: A systematic review of assessment and incidence of postoperative delirium. *Worldviews Evid. Based Nurs.* 18, 290–301. doi: 10.1111/wvn.12536

Humbert, M., Büla, C. J., Muller, O., Krief, H., and Monney, P. (2021). Delirium in older patients undergoing aortic valve replacement: Incidence, predictors, and cognitive prognosis. *BMC Geriatr.* 21:153. doi: 10.1186/s12877-021-02100-5

Ida, M., Takeshita, Y., and Kawaguchi, M. (2020). Preoperative serum biomarkers in the prediction of postoperative delirium following abdominal surgery. *Geriatr. Gerontol. Int.* 20, 1208–1212. doi: 10.1111/ggi.14066

Ishibashi, H., Wakejima, R., Asakawa, A., Sugita, Y., Ishikawa, Y., Hanafusa, M., et al. (2022). Postoperative delirium in lung cancer anatomical resection-analysis of risk factors and prognosis. *World J. Surg.* 46, 1196–1206. doi: 10.1007/s00268-022-06442-y

Janssen, T. L., Alberts, A. R., Hooft, L., Mattace-Raso, F., Mosk, C. A., and van der Laan, L. (2019). Prevention of postoperative delirium in elderly patients planned for elective surgery: Systematic review and meta-analysis. *Clin. Interv. Aging* 14, 1095–1117. doi: 10.2147/CIA.S201323

Jung, D. M., Ahn, H. J., Yang, M., Kim, J. A., Kim, D. K., Lee, S. M., et al. (2018). Hydroxyethyl starch is associated with early postoperative delirium in patients undergoing esophagectomy. *J. Thorac. Cardiovasc. Surg.* 155, 1333–1343. doi: 10.1016/j.jtcvs.2017.10.077

Kinchin, I., Mitchell, E., Agar, M., and Trépel, D. (2021). The economic cost of delirium: A systematic review and quality assessment. *Alzheimers Dement.* 17, 1026–1041. doi: 10.1002/alz.12262

Lee, S. H., and Lim, S. W. (2020). Risk factors for postoperative delirium after colorectal surgery: A systematic review and meta-analysis. *Int. J. Colorectal. Dis.* 35, 433–444. doi: 10.1007/s00384-019-03498-6

Lee, S., Gottlieb, M., Mulhausen, P., Wilbur, J., Reisinger, H. S., Han, J. H., et al. (2020). Recognition, prevention, and treatment of delirium in emergency department: An evidence-based narrative review. *Am. J. Emerg. Med.* 38, 349–357. doi: 10.1016/j.ajem.2019.158454

Li, G. H., Zhao, L., Lu, Y., Wang, W., Ma, T., Zhang, Y. X., et al. (2021). Development and validation of a risk score for predicting postoperative delirium after major abdominal surgery by incorporating preoperative risk factors and surgical Apgar score. *J. Clin. Anesth.* 75:110408. doi: 10.1016/j.jclinane.2021.110408

Marya, S. K., Amit, P., and Singh, C. (2016). Impact of Charlson indices and comorbid conditions on complication risk in bilateral simultaneous total knee arthroplasty. *Knee* 23, 955–959. doi: 10.1016/j.knee.2016.05.013

Matsuki, M., Tanaka, T., Takahashi, A., Inoue, R., Hotta, H., Itoh, N., et al. (2020). Incidence and risk factors of postoperative delirium in elderly patients undergoing urological surgery: A multi-institutional prospective study. *Int. J. Urol.* 27, 219–225. doi: 10.1111/iju.14172

Mevorach, L., Forookhi, A., Farcomeni, A., Romagnoli, S., and Bilotta, F. (2022). Perioperative risk factors associated with increased incidence of postoperative delirium: Systematic review, meta-analysis, and grading of recommendations assessment, development, and evaluation system report of clinical literature. *Br. J. Anaesth.* doi: 10.1016/j.bja.2022.05.032 [Epub ahead of print].

Mosquera, C., Spaniolas, K., and Fitzgerald, T. L. (2016). Impact of frailty on surgical outcomes: The right patient for the right procedure. *Surgery* 160, 272–280. doi: 10.1016/j.surg.2016.04.030

Nagata, T., Adachi, Y., Taniguchi, A., Kimura, Y., Iitaka, D., Iwata, G., et al. (2021). [Impact of the age-adjusted charlson comorbidity index on postoperative complications after gastric cancer surgery]. *Gan To Kagaku Ryoho* 48, 1567–1569.

Pais-Ribeiro, J. L., Martins da Silva, A., Vilhena, E., Moreira, I., Santos, E., and Mendonça, D. (2018). The hospital anxiety and depression scale, in patients with multiple sclerosis. *Neuropsychiatr. Dis. Treat.* 14, 3193–3197. doi: 10.2147/NDT.S184260

Pan, Z., Huang, K., Huang, W., Kim, K. H., Wu, H., Yu, Y., et al. (2019). The risk factors associated with delirium after lumbar spine surgery in elderly patients. *Quant. Imaging Med. Surg.* 9, 700–710. doi: 10.21037/qims.2019.04.09

Park, S. Y., and Lee, H. B. (2019). Prevention and management of delirium in critically ill adult patients in the intensive care unit: A review based on the 2018 PADIS guidelines. *Acute Crit. Care* 34, 117–125. doi: 10.4266/acc.2019.00451

Peduzzi, P., Concato, J., Kemper, E., Holford, T. R., and Feinstein, A. R. (1996). A simulation study of the number of events per variable in logistic regression analysis. *J. Clin. Epidemiol.* 49, 1373–1379. doi: 10.1016/s0895-4356(96)00236-3

Pérez-Ros, P., Martínez-Arnau, F. M., Baixauli-Alacreu, S., Caballero-Pérez, M., García-Gollarte, J. F., and Tarazona-Santabalbina, F. (2019). Delirium predisposing and triggering factors in nursing home residents: A Cohort trial-nested case-control study. *J. Alzheimers Dis.* 70, 1113–1122. doi: 10.3233/JAD-190391

Pettemeridou, E., Kallousia, E., and Constantinidou, F. (2021). Regional brain volume, brain reserve and MMSE performance in healthy aging from the NEUROAGE Cohort: Contributions of sex, education, and depression symptoms. *Front. Aging Neurosci.* 13:711301. doi: 10.3389/fnagi.2021.711301

Qi, J., Liu, C., Chen, L., and Chen, J. (2020). Postoperative serum albumin decrease independently predicts delirium in the elderly subjects after total joint arthroplasty. *Curr. Pharm. Des.* 26, 386–394. doi: 10.2174/1381612826666191227153150

Ramos, M. D., Vergara, F. H., Shackleford, J., Briggs, C., Gomez, C., Mofazali, M., et al. (2022). Risk for post-operative delirium related to comorbidities in older adult cardiac patients: An integrative review. *J. Clin. Nurs.* doi: 10.1111/jocn.16389 Epub ahead of print.

Revenig, L. M., Canter, D. J., Kim, S., Liu, Y., Sweeney, J. F., Sarmiento, J. M., et al. (2015). Report of a simplified frailty score predictive of short-term postoperative morbidity and mortality. *J. Am. Coll. Surg.* 220, 904–911.e1. doi: 10.1016/j.jamcollsurg.2015.01.053

Richardson, S. J., Davis, D. H. J., Stephan, B. C. M., Robinson, L., Brayne, C., Barnes, L. E., et al. (2021). Recurrent delirium over 12 months predicts dementia: Results of the delirium and cognitive impact in dementia (DECIDE) study. *Age Ageing.* 50, 914–920. doi: 10.1093/ageing/afaa244

Robinson, T. N., Raeburn, C. D., Tran, Z. V., Angles, E. M., Brenner, L. A., and Moss, M. (2009). Postoperative delirium in the elderly: Risk factors and outcomes. *Ann. Surg.* 249, 173–178. doi: 10.1097/SLA.0b013e31818e4776

Rong, X., Ding, Z. C., Yu, H. D., Yao, S. Y., and Zhou, Z. K. (2021). Risk factors of postoperative delirium in the knee and hip replacement patients: A systematic review and meta-analysis. *J. Orthop. Surg. Res.* 16, 76. doi: 10.1186/s13018-020-02127-1

Segernäs, A., Skoog, J., Ahlgren Andersson, E., Almerud Österberg, S., Thulesius, H., and Zachrisson, H. (2022). Prediction of postoperative delirium after cardiac surgery with a quick test of cognitive speed, mini-mental state examination and hospital anxiety and depression scale. *Clin. Interv. Aging* 17, 359–368. doi: 10.2147/CIA.S350195

Seiler, A., Schubert, M., Hertler, C., Schettle, M., Blum, D., Guckenberger, M., et al. (2020). Predisposing and precipitating risk factors for delirium in palliative care patients. *Palliat. Support. Care* 18, 437–446. doi: 10.1017/S1478951519000919

Takahara, N., Nakai, Y., Saito, K., Sasaki, T., Suzuki, Y., Inokuma, A., et al. (2020). The impact of age and comorbidity in advanced or recurrent biliary tract cancer receiving palliative chemotherapy. *J. Gastroenterol. Hepatol.* 35, 1828–1835. doi: 10.1111/jgh.15066

Wu, Y., Zhang, Y., Yuan, X., and Guo, J. (2021). Gao X. Influence of education level on MMSE and MoCA scores of elderly inpatients. *Appl. Neuropsychol. Adult* 1–5. doi: 10.1080/23279095.2021.1952588

Zhou, S., Zhang, X. H., Zhang, Y., Gong, G., Yang, X., and Wan, W. H. (2022). The age-adjusted charlson comorbidity index predicts prognosis in elderly cancer patients. *Cancer Manag. Res.* 14, 1683–1691. doi: 10.2147/CMAR.S361495

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EDITED BY
Zhanqi Zhao,
Furtwangen University, Germany

REVIEWED BY
Tian-Long Wang,
Capital Medical University, China
Nobuhiro Tanaka,
Nara Medical University, Japan

*CORRESPONDENCE
Di Wang
di.wang@ustc.edu.cn

†These authors have contributed equally to this work and share first authorship

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Flurbiprofen used in one-lung ventilation improves intraoperative regional cerebral oxygen saturation and reduces the incidence of postoperative delirium

Liang Shen[1,2†], Jia-qi Chen[2†], Xin-lu Yang[2†], Ji-cheng Hu[2], Wei Gao[2], Xiao-qing Chai[2] and Di Wang[2*]

[1]Department of Anesthesiology, Anhui Provincial Hospital Affiliated to Anhui Medical University, Hefei, China, [2]Pain Clinic, Department of Anesthesiology, First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China (USTC), Hefei, China

Background: We previously demonstrated that flurbiprofen increased arterial oxygen partial pressure and reduced intrapulmonary shunts. The present study aims to investigate whether flurbiprofen improves intraoperative regional cerebral oxygen saturation ($rScO_2$) and reduces the incidence of postoperative delirium (POD) in elderly patients undergoing one-lung ventilation (OLV).

Methods: One hundred and twenty patients undergoing thoracoscopic lobectomy were randomly assigned to the flurbiprofen-treated group ($n = 60$) and the control-treated group ($n = 60$). Flurbiprofen was intravenously administered 20 minutes before skin incision. The $rScO_2$ and partial pressure of arterial oxygen (PaO_2) were recorded during the surgery, and POD was measured by the Confusion Assessment Method (CAM) within 5 days after surgery. The study was registered in the Chinese Clinical Trial Registry with the number ChiCTR1800020032.

Results: Compared with the control group, treatment with flurbiprofen significantly improved the mean value of intraoperative $rScO_2$ as well as the PaO_2 value ($P < 0.05$, both) and significantly reduced the baseline values of the $rScO_2$ area under threshold (AUT) ($P < 0.01$) at 15, 30, and 60 min after OLV in the flurbiprofen-treated group. After surgery, the POD incidence in the flurbiprofen-treated group was significantly decreased compared with that in the control group ($P < 0.05$).

Conclusion: Treatment with flurbiprofen may improve $rScO_2$ and reduce the incidence of POD in elderly patients undergoing thoracoscopic one-lung ventilation surgery for lung cancer.

Clinical trial registration: http://www.chictr.org/cn/, identifier ChiCTR1800020032.

KEYWORDS

flurbiprofen, one-lung ventilation, regional cerebral oxygen saturation, postoperative delirium, thoracic surgery

Introduction

One-lung ventilation (OLV) refers to the mechanical separation of the two lungs to allow ventilation of only one lung, while the other lung is compressed by the surgeon or allowed to passively deflate (1). This non-physiological ventilation approach is a standard approach to facilitate surgical exposure for pulmonary and other thoracic surgeries by using either a double-lumen tube or bronchial blocker (2). However, hypoxemia is one of the most common complications associated with OLV, occurring in 7–28% of individuals subjected to OLV (3, 4). It is thought that hypoxemia during OLV is related to ventilation/perfusion disturbance due to intrapulmonary shunts (5, 6). Although hypoxic pulmonary vasoconstriction (HPV) allows redirection of blood flow into the ventilated lung, approximately 4–10% of patients still experience an oxygen saturation of <90% (1, 7, 8).

Brain cellular function may be impaired or damaged by the reduction in oxygen delivery under this level of peripheral oxygen desaturation (9). Brain oximetry based on cerebral near-infrared spectroscopy (NIRS) enables continuous and noninvasive measurement of cerebral tissue oxygen saturation ($SctO_2$) or regional cerebral oxygen saturation ($rScO_2$) (10, 11). The incidence of cerebral oxygen desaturation, depicted as a decrease in $SctO_2$ of more than 15% from the baseline level, has been reported to be as high as 70–100% in thoracic surgical patients undergoing OLV (7, 12). Cerebral hypoxia is a well-established risk factor for postoperative delirium (POD), which is an acute fluctuating brain dysfunction characterized by inattention, disorganized thinking, and altered levels of consciousness (13, 14). The reported incidence of POD ranges from 7 to 23% in patients who receive OLV (15, 16). It has been reported that cerebral desaturation, defined by 90% baseline for left $SctO_2$, may be associated with an increased risk of POD in thoracotomy with OLV (17).

We have demonstrated that treatment with flurbiprofen reduced the Qs/Qt ratio and further increased the PaO_2 level during OLV, possibly due to the upregulation of the vasoactive agent thromboxane B2 (TXB2)/6-keto-prostaglandin F1α (6-K-PGF1α) ratio (18). However, whether flurbiprofen can further alleviate cerebral desaturation and reduce POD incidence is largely unclear. In the present study, we aimed to determine whether flurbiprofen alleviates the reduction in the intraoperative $rScO_2$ value and decreases the incidence of POD.

Abbreviations: $rScO_2$, regional cerebral oxygen saturation; POD, postoperative delirium; OLV, one-lung ventilation; PaO_2, partial pressure of arterial oxygen; CAM, Confusion Assessment Method; AUT, the area under threshold; HPV, hypoxic pulmonary vasoconstriction; NIRS, near-infrared spectroscopy; $SctO_2$, cerebral tissue oxygen saturation; VATS, video-assisted thoracoscopic surgery; ASA, American Society of Anesthesiologists; MMSE, Mini-mental State Examination; BIS, bispectral index; PCA, patient-controlled analgesia; HR, heart rate; MBP, mean blood pressure; PEEP, positive end-expiratory pressure.

Patients and methods

Trial design

This is a prospective, randomized, double-blind and controlled trial implemented in First Affiliated Hospital, University of Science and Technology of China (USTC). This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee. All the patients were informed of the full details of the study protocol and signed the informed consent from. The study was registered in the Chinese Clinical Trial Registry with the number ChiCTR1800020032.

Randomization and blinding

The patients were randomized to either the flurbiprofen treatment group (Group F) or the control group (Group C) before entering the operation room. An allocation sequence was created by a computer-generated list. Allocation concealment was implemented by using sequentially numbered, opaque, sealed envelopes. Randomization and drug preparation were performed by an independent investigator who was not involved in the administration of anesthesia. Flurbiprofen and fat emulsions of the same appearance were sent to the anesthesiologist in an unmarked syringe before intravenous injection. Data collection was performed by another independent researcher involved in the administration of anesthesia. Data were collected in a blinded manner by the study patients, anesthesiologists, other researchers, and statisticians.

Patients

From June 2020 to April 2021, patients who were scheduled for elective pulmonary lobectomy and underwent video-assisted thoracoscopic surgery (VATS) were assessed before the study. Figure 1 shows the flow diagram of participant recruitment. The inclusion criteria were as follows: (1) age between 65 and 75 years; (2) American Society of Anesthesiologists (ASA) status II-III; and (3) anticipated duration of one-lung ventilation >60 min.

Exclusion criteria were as follows: (1) severe impairment of respiratory function (forced expiratory volume in 1 s of <50% of the predicted values); (2) presence of contraindications for using flurbiprofen or intralipid; (3) treatment with NSAIDs drugs within 1 month before surgery; (4) scored<24 on the

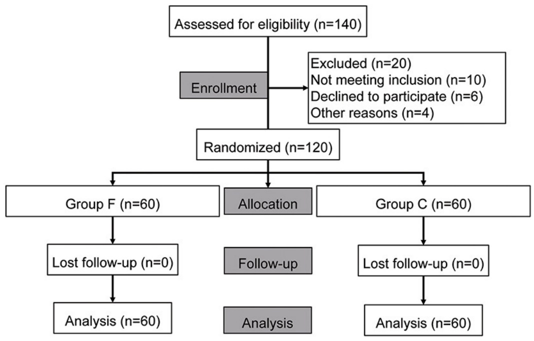

FIGURE 1
Flow chart of study.

Mini-mental State Examination (MMSE) or who were unable to complete baseline cognitive assessment; (5) history of smoking, alcohol or drug abuse; (6) difficulty to maintain oxygenation with one-lung ventilation intraoperatively; (7) duration of one-lung ventilation was smaller than 60 min; (8) unable to collect data due to the cerebral oximeter machine malfunction; (9) researchers believe that other situations do not meet the conditions of this study. For example, VATS was intraoperatively converted to an open thoracotomy procedure.

Treatment

The participants were randomized to either the flurbiprofen treatment group (Group F) or the control group (Group C). Flurbiprofen 100 mg (50 mg/5 ml, Beijing Tide Pharmaceutical, China) was in Group F, and the placebo (Intralipid, Chengdu Huarui Pharmaceutical, China) was in Group C. The trial drug was dissolved in 100 ml of normal saline and intravenous drip within 15 min. All subjects received the drug (flurbiprofen or placebo) 20 min before incision. The length of the trial drug to OLV start was approximately 30 min.

General anesthesia

No premedication was used prior to surgery. General anesthesia was initiated with intravenous 0.05 mg/kg midazolam, 2 mg/kg propofol, 0.4 μg/kg sufentanil, and 1.0 mg/kg rocuronium. After the induction of anesthesia, an endobronchial tube was inserted and confirmed by bronchoscopy. Intubation was performed using a double-lumen tube. An additional 0.15 μg/kg sufentanil was given before the incision. Subsequently, intraoperative anesthesia was maintained with a continuous infusion of propofol (4–8 mg/kg/h) and remifentanil (0.05–0.2 μg/kg/min) to achieve a target bispectral index (BIS) value between 40 and 50. Cisatracurium was administered intermittently as required during the surgery. All patients were mechanically ventilated to maintain 35–45 mmHg $ETCO_2$. Patients were mechanically ventilated in constant-flow volume-controlled mode following the protocol with a tidal volume of 6 to 8 mL/kg (two-lung ventilation) or 4–6 mL/kg (one-lung ventilation), inspiratory-to-expiratory time ratio of 1:2, and positive end-expiratory pressure 5 cm H_2O. Pulse oxygen saturation was maintained above 92%. All surgical operations were performed by the same surgeon team, without any additional administration of local anesthetic by surgeons. Postoperative analgesia was regularly conducted using patient-controlled analgesia (PCA): Sufentanil was delivered at a rate of 2 μg/hr, with a 1.5 μg bolus and lockout interval of 15 min for breakthrough pain. Tramadol (50 mg) was provided for rescue analgesia if the visual analog scale (VAS) score was ≥4.

Monitoring indicators

Throughout the perioperative period, electrocardiography (ECG), heart rate (HR), SpO_2, blood pressure, and CVP were continuously monitored. A bispectral index (BIS) sensor (Aspect Medical Systems, Inc., USA) applied to the forehead was used to monitor the depth of anesthesia, and the BIS value was kept at 40–50. The nasopharyngeal temperature was maintained at 36.3–37.2°C. Phenylephrine was given at a bolus of 25 μg if mean blood pressure (MBP) decreased to <80% of the preoperative baseline or systolic blood pressure decreased to <90 mmHg; atropine (0.3 mg) was given if HR decreased to <50 beats/min. If MBP or HR increased by >20% of the preoperative baseline, patients received fentanyl (0.05 mg) followed by perdipine (0.2 mg) or esmolol (10 mg). These treatments were repeated if necessary.

$rScO_2$ monitoring

All patients were monitored with the INVOS 5100C cerebral oximeter before anesthesia induction until extubation. A fiberoptic sensor was positioned on each side on the forehead of the patients and covered by an opaque plastic patch to prevent ambient light. Baseline absolute $rScO_2$ values were taken in the awake patient after 2 min of breathing 100% oxygen through a face mask. The screen of the cerebral oximeter was covered with an opaque bag to blind the $rScO_2$ data to anesthesia providers and surgeons for monitoring. The $rScO_2$ data were recorded at 30-s intervals on the device's accessory disk drive for later analysis. With the whole $rScO_2$ data of each subject, the baseline, mean and minimum absolute $rScO_2$ values of both sides during surgery were recorded, calculated and sifted. According to reference, cerebral desaturation was defined as either of the following two situations: (1) a baseline absolute value over 50%, $rScO_2$ reduced to <75 percent of baseline; (2) or a baseline absolute value <50%, $rScO_2$ reduced to <80 percent of baseline (19). Thus, in this trial, the $rScO_2$ threshold was defined as 75% of the baseline absolute value if the baseline value was ≥50%, and if the baseline value was <50%, the $rScO_2$ threshold was defined as 75% of the baseline value. The area under the threshold (AUT-$rScO_2$) was also calculated. AUT was based on the following formula: AUT (present) = AUT (past)+($rScO_2$ threshold- $rScO_2$ value) × sample rate. The AUT was 0 if the rScO2 value was above the defined $rScO_2$ threshold (20).

Neuropsychological tests

The Confusion Assessment Method (CAM) is a widely used and well-validated screening tool for delirium with a sensitivity of 94% (95% confidence interval [CI] = 91–97%) and specificity of 89% (95% CI = 85–94%) and has been successfully adapted for use in the intensive care unit (ICU) setting (the CAM-ICU was used where appropriate) (21, 22). POD was defined as any episode of delirious symptoms within five postoperative days. Delirium was assessed twice daily, between 06:00–08:00 and 18:00–20:00, using the Chinese version of the Confusion Assessment Method (CAM) in non-intubated patients and the CAM-ICU in intubated patients. (17). The research personnel who were responsible for delirium assessment participated in a 4-h training session with the following agenda: (1) an introduction to the symptoms, diagnosis, and treatment of delirium, (2) a lecture on how to use CAM and CAM-ICU for delirium assessments, and (3) a simulation training course with a quiz at the end of training. All trainees were required to answer all quiz questions correctly. Research personnel who were responsible for out-come assessment were not allowed to access patient data collected during surgery (17).

Sample collection

Blood samples were collected from arterial catheters before anesthesia, 15 min after double-lung ventilation (supine position), 15, 30, and 60 min after OLV, and 30 min after re-expansion of the collapsed lung. The samples were tested by blood gas analyses. The Qs/Qt ratio was determined from the following formula: (CCO_2 – arterial oxygen content)/ (CCO_2 – mixed venous oxygen content), where CCO_2 = end-pulmonary capillary oxygen content.

Other outcomes

Baseline blood pressure, baseline heart rate, operation time, anesthesia time, OLV time, intraoperative blood loss, urine volume, infusion volume, length of hospital stay, length of stay in the ICU, pulmonary infection rate, chest tube removal time, visual analog score, and death rate 1 month after surgery were recorded for every patient.

Sample capacity

Few studies have tested the effect of flurbiprofen on cerebral oxygen saturation in one-lung ventilation. However, based on our pre-experiment outcome, we considered a difference of 3% for the mean $rScO_2$ between both groups and a pooled SD of 7% of the means. With a power (β) of 0.95 and a 5% significance level, a minimum sample size of 59 patients for each group was estimated. Considering a drop-out rate of 20%, 70 subjects whose elective pulmonary lobectomy was undergoing VATS with an ASA status of II-III were registered in each group (140 patients in total).

Statistical analysis

Data were analyzed using SPSS 16.0 software. Values are expressed as the mean ± standard deviation (SD) or n (%). The comparison of the two groups of normal data was performed using one-way analysis, the comparison of two groups of nonnormal data was performed using the independent sample *t*-test and the Mann–Whitney *U* test, and the comparison of count data was performed by the chi-square test. Multiple reading data were analyzed by repeated-measures analysis of variance. A $P < 0.05$ was considered statistically significant, and a $P < 0.01$ was considered highly statistically significant.

Results

Patient demographics

One hundred and twenty patients aged between 65 and 75 years underwent elective pulmonary lobectomy for this study. There were 60 patients in each group. The characteristics of the 120 patients are summarized in Table 1. There were no significant differences in age, sex, ASA grade, year of education, MMSE score, hemoglobin before surgery, clinical characteristics, or surgery side between the two groups ($P > 0.05$).

Cerebral oxygen saturation values

In terms of the baseline values of $rScO_2$ measured before anesthesia induction and the minimum values of $rScO_2$ during a surgical operation, our findings showed that there were no significant differences between the flurbiprofen-treated group and the control group in either the right or left hemisphere (*P*

TABLE 1 Patient characteristics.

Characteristic	Group C ($n = 60$)	Group F ($n = 60$)	p Value[a]
Age (years)	68.38 ± 3.08	68.63 ± 2.91	0.9310
Gender		0.6011	
Male	38 (63.3%)	40 (66.7%)	
Female	22 (36.7%)	20 (33.3%)	
ASA physical status			0.7158
II	11 (18.3%)	13 (21.7%)	
III	49 (81.7%)	47 (78.3%)	
BMI (kg/m^2)	24.78 ± 2.48	25.28 ± 2.29	0.4299
Education (years)			0.4324
≤9 years	52 (86.7)	52 (83.3)	
>9 years	8 (13.3)	10 (16.7)	
MMSE before surgery	27.52 ± 2.018	27.19 ± 1.966	0.8032
Clinical characteristics			
History of stroke	8 (13.3%)	10 (16.7%)	0.6291
Hypertension	26 (43.3%)	24 (40.0%)	0.6932
Diabetes	15 (25.0%)	18 (30.0%)	0.5294
Surgery side			0.5104
Left	25 (41.7%)	28 (46.7%)	
Right	35 (58.3%)	32 (53.3%)	
Hemoglobin (g/dl)	12.64 ± 1.42	12.62 ± 1.74	0.9742

Values are n (%) or mean ± SD.
[a]The comparison among the two groups of normal data using one-way analysis, the comparison of count data by chi-square test.
ASA, American Society of Anesthesiologists; BMI, body mass index; MMSE, Minimum Mental State Examination.

> 0.05) (Figure 2). The mean value of $rScO_2$ on both sides in the flurbiprofen-treated group was significantly higher than that in the control group (right hemisphere, $P < 0.05$; left hemisphere, $P < 0.01$) (Figure 2). In the flurbiprofen-treated group, the area under the threshold (AUT) of baseline $rScO_2$, either in the right hemisphere or left hemisphere, was less than that in the control group, with significant differences ($P < 0.01$ both) (Figure 3). PaO_2 levels throughout the intraoperative period in the flurbiprofen-treated group were higher than those in the control group ($P < 0.05$) (Figure 4).

**P < 0.01 vs Group C.

POD incidence and other outcomes

Throughout the follow-up period after surgery, there were significant differences in POD development between the flurbiprofen-treated group and the control group at postoperative day 1 (7 vs. 14, $P < 0.05$), postoperative day 2 (5 vs. 12, $P < 0.05$), postoperative day 3 (4 vs. 8, $P < 0.05$), postoperative day 4 (1 vs. 5, $P < 0.05$), and postoperative day 5 (1 vs. 2, $P < 0.05$). The overall incidence of POD in the flurbiprofen-treated group was significantly lower than that in the control group (7 vs. 15, $P < 0.05$) (Figure 5). There were no significant differences in the baseline mean blood pressure, baseline heart rate, duration of anesthesia, duration of surgery, duration of OLV, phenylephrine and blood loss, urine output, fluid infusion during the surgery, chest tube removal time, lung infection rate, visual analog scale score, or ICU stay. However, the hospital stay of Group F was significantly shorter than that of Group C. No patient died at the one-month postoperative follow-up (Table 2). There were no significant differences in the intraoperative arterial blood oxygen saturation (SaO_2) and arterial blood partial pressure of carbon dioxide (pCO_2), as shown in Table 3.

Discussion

Hypoxemia remains challenging for intraoperative management, despite intervention including an increase in the inspired fraction of oxygen followed by a recruitment maneuvered and escalation of positive end-expiratory pressure (PEEP) to the ventilated lung (3, 6). Our study previously reported that intraoperative use of flurbiprofen increased arterial oxygen partial pressure and reduced intrapulmonary shunt (18). In the present study, our findings indicate that flurbiprofen may improve intraoperative $rScO_2$ and further reduce the POD incidence in patients undergoing OLV. To the best of our knowledge, this is the first report to demonstrate the effects of flurbiprofen on intraoperative $rScO_2$ and POD in elderly patients undergoing OLV.

Recently, an increasing number of published works have suggested NSAIDs (such as parecoxib, and flurbiprofen) that are commonly used for postoperative analgesia and can reduce POD after major noncardiac surgery in elderly patients (23, 24). However, the pharmacological mechanism underlying this beneficial action of NSAIDs on neuropsychiatric function is not entirely understood. It may involve the NSAID-elicited reduction of proinflammatory cytokines (TNF-α, IL-1β, and IL-6), which is thought to be primarily triggered by surgical operation and damage synapses and neurons and ultimately lead to POD *via* vagal afferents and by crossing the blood-brain barrier (25, 26). In addition to neuroinflammation, there are many other risk factors contributing to POD, such as age, sex, hypothermia, category of surgery, surgical position, duration of surgery, and mechanical ventilation. Given the complex etiology of POD, it is largely unknown whether flurbiprofen can in particular impact cerebral homeostasis, which has been shown to be closely related to the high risk of developing POD.

A variety of studies have indicated that the incidence of cerebral desaturation, defined as a decrease in $SctO_2$ of more than 15% from the baseline level, can be as high as 70–100% in thoracic surgical patients (7). The cerebral desaturation during thoracic surgery might be due to a reduction in cerebral oxygen delivery that could be caused by an impairment

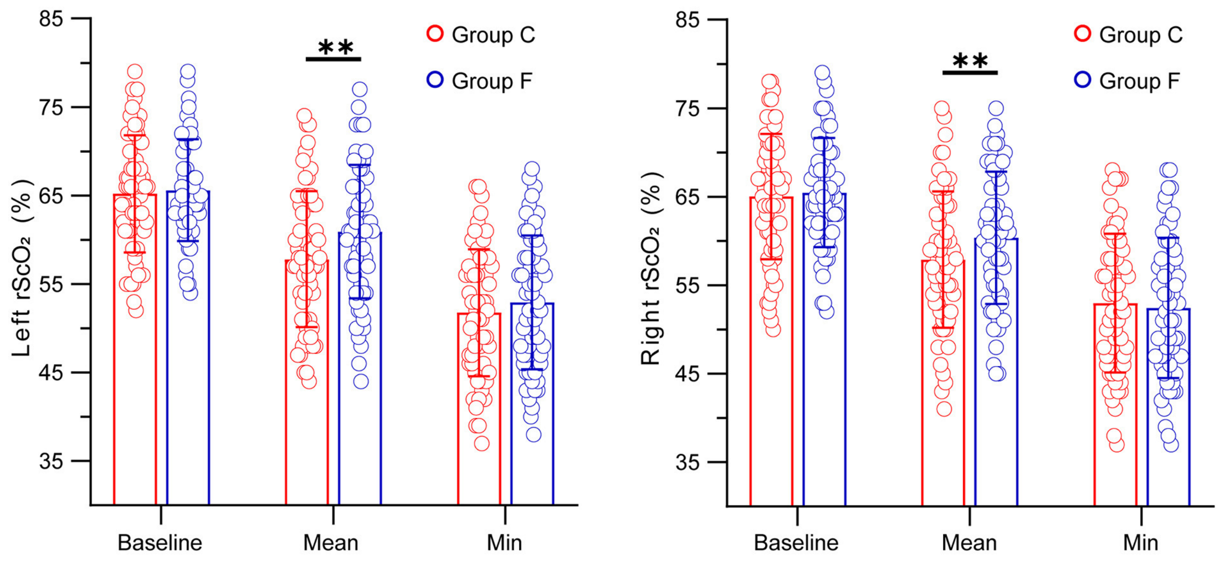

FIGURE 2
Baseline, mean and minimum of the left and right rScO_2 values in Group F and Group C. All data are presented as mean ± SD, $^{**}P < 0.01$ vs Group C.

either in arterial oxygen content or in cerebral blood flow that might also be related to a decrease in cardiac output. OLV together with the lateral decubitus position which is required for most cases of thoracic surgery, is accompanied by substantial physiological disturbances, including increases in pulmonary vascular resistance and pulmonary arteriovenous shunt, hypoxic pulmonary vasoconstriction, and reduction in alveolar-arterial oxygen tension. With the increase in pulmonary resistance during the collapse of the operated lung, the right ventricular cardiac output would be expected to decrease, especially under anesthesia where compensatory reflex mechanisms may be blunted (17). Furthermore, with impaired right ventricular performance, an increase in right-sided filling pressures could increase cerebral venous blood volume and affect cerebral saturation in this manner. Thus, these mechanisms could contribute to the decreases seen in cerebral oxygen saturation. It has been well-documented that flurbiprofen alleviates inflammation and pain by inhibiting cyclooxygenase (COX) activity and the synthesis of thromboxane A2 (TXA2)/prostaglandin I2 (PGI2), which are vasoactive agents that affect pulmonary arterial pressure, the Qs/Qt ratio, and PaO_2. In the present study, flurbiprofen improved intraoperative rScO_2 by increasing PaO_2, probably owing to flurbiprofen-elicited adequate oxygen delivery.

Many studies have shown that the alteration of cerebral oxygen saturation is also of great clinical significance. For example, a study implied that once the maximum percentage decrease in rScO_2 was more than 11%, the sensitivity and specificity of postoperative cognitive dysfunction occurrence were 86.5 and 77.8%, respectively. This suggests that if

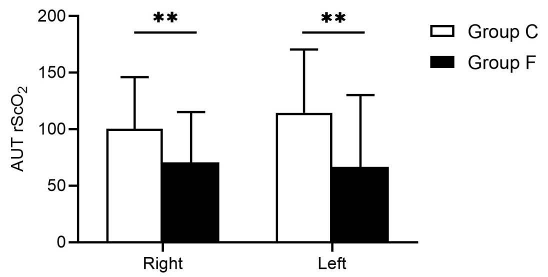

FIGURE 3
The left and right AUT rScO_2 of baseline rScO_2 values in Group F and Group C. All data are presented as mean ± SD, $^{**}P < 0.01$ vs. Group C. AUT rScO_2, the area under the threshold of rScO_2 readings.

the maximum percentage decrease in rScO_2 exceeds 11%, appropriate measures should be taken to increase rScO_2 to prevent the risk of developing cerebral ischemia (27). Our study found that the maximum percentage decrease in rScO_2 in single-lung ventilation was more than 11%. Furthermore, among patients undergoing coronary artery bypass grafting, maintenance of intraoperative monitored rScO_2 values above a "safety threshold" was associated with a lower incidence of major organ dysfunction and a shorter hospital stay (28). Another study by Plachky et al. showed a positive relationship between decreased rScO_2 during the anhepatic phase and a hypoxia/ischemia-induced increase in neuron-specific enolase, which is used as an index of cerebral damage,

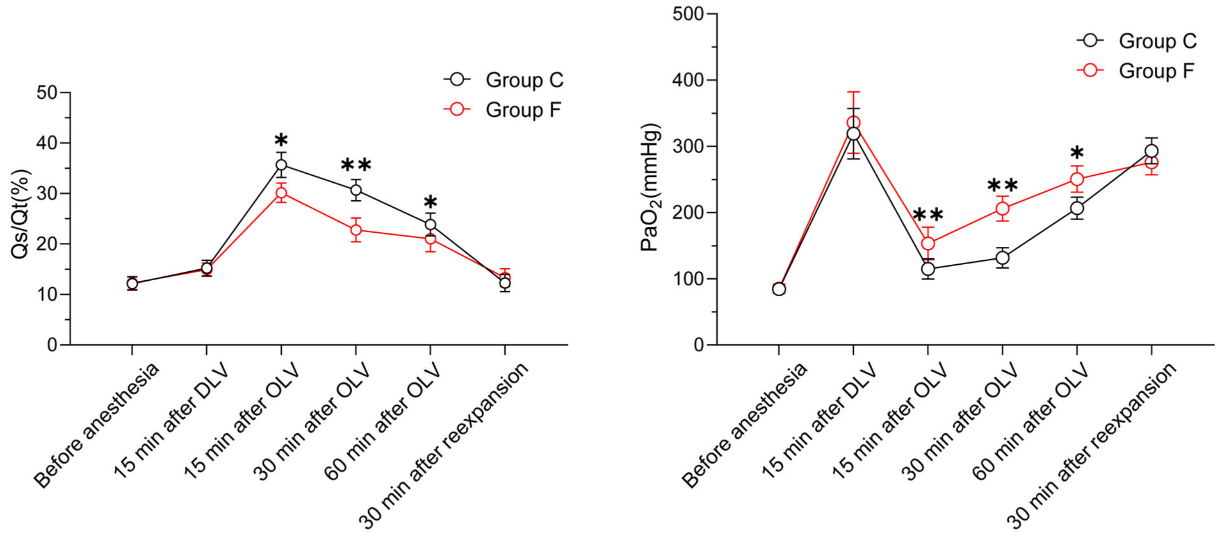

FIGURE 4
PaO_2 and Qs/Qt values in Group F and Group C. All data are presented as mean ± SD, $^*P < 0.05$ and $^{**}P < 0.01$ vs. Group C.

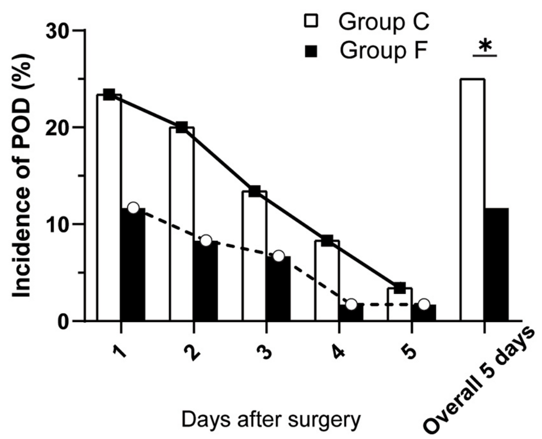

FIGURE 5
Incidence of POD in the two groups on postoperative days 1, 2, 3, 4, 5 and overall. All data are presented as n (%), $^*P < 0.05$ vs. Group C. POD, postoperative delirium.

during orthotopic liver transplantation (29). Collectively, even a small improvement in cerebral oxygen saturation is clinically significant, and near-infrared spectroscopy determination has strong potential with clinical utility in differing settings. Therefore, we also cautiously compared the differences in hemoglobin, phenylephrine use, and intraoperative partial pressure of carbon dioxide, which may affect cerebral oxygen saturation, in the two groups, and the results were not significantly different. We consider that flurbiprofen may have improved the decrease in cerebral oxygen saturation during one-lung ventilation and this may contribute to the improvement of postoperative cognitive dysfunction.

TABLE 2 Perioperative data and postoperative outcomes.

Information	Group C ($n = 60$)	Group F ($n = 60$)	p Value[a]
Baseline MBP (mmHg)	92.25 ± 6.428	93.18 ± 5.792	0.4425
Baseline HR (beats/min)	69.37 ± 4.215	67.12 ± 6.14	0.5914
Duration of anesthesia (min)	247.73 ± 48.12	250.14 ± 45.73	0.9048
Duration of surgery (min)	186.17 ± 40.23	187.20 ± 46.56	0.9209
Duration of OLV (min)	129.33 ± 17.62	135.60 ± 21.20	0.5055
Phenylephrine (µg)	267.47 ± 129.77	283.23 ± 79.45	0.6831
Blood loss (ml)	287.83 ± 84.45	284.50 ± 58.34	0.8448
Urine output (ml)	480.33 ± 139.12	467.67 ± 114.64	0.7503
Fluid infusion (ml)	1,953.33 ± 257.95	2,015.17 ± 277.71	0.6897
Hospital-stay (days)	7.38 ± 2.27	6.52 ± 2.43	0.043
Chest tube removal (days)	4.11 ± 1.17	3.98 ± 1.30	0.574
visual analog scale	2.76 ± 0.87	2.45 ± 1.01	0.597
Lung infection[b]	10(16.66)	7(11.66)	0.198
1st month postoperative mortality rate	0	0	-
ICU-stay (days)	0.88 ± 2.37	0.87 ± 2.42	0.820

Values are n (%) or mean±SD.
[a]The comparison among the two groups of normal data using one-way analysis, the comparison of count data by chi-square test.
[b]Lung infection was defined through imaging and clinical manifestations 1 week after surgery.
MBP, mean blood pressure; HR, heart rate; OLV, one-lung ventilation.

Hypoxemia during one-lung ventilation triggers a concern that organ cellular function may be impaired or injured by the reduction in oxygen delivery (9, 12). Initially, perioperative cerebral oximetry monitoring primarily focused on cardiac

TABLE 3 Intraoperative data.

Information	Group C ($n = 60$)	Group F ($n = 60$)	p Value[a]
Oxygen saturation (%)			
Before anesthesia	98.3 ± 1.4	98.2 ± 0.8	0.9957
15 min after DLV	99.2 ± 0.5	99.3 ± 0.7	0.9957
15 min after OLV	97.1 ± 1.8	96.9 ± 1.5	0.8714
30 min after OLV	97.4 ± 1.1	97.3 ± 0.9	0.9957
60 min after OLV	97.8 ± 0.9	97.6 ± 0.6	0.8714
30 min after re-expansion	99.3 ± 0.4	98.9 ± 0.8	0.1894
Partial pressure of carbon dioxide (mmHg)			
Before anesthesia	40.1 ± 3.5	41.4 ± 2.4	0.1888
15 min after DLV	37.7 ± 4.7	37.8 ± 4.1	0.9899
15 min after OLV	43.5 ± 3.1	44.0 ± 3.7	0.9599
30 min after OLV	44.4 ± 2.3	44.1 ± 2.8	0.9972
60 min after OLV	45.3 ± 3.5	45.6 ± 2.6	0.9972
30 min after re-expansion	41.1 ± 2.1	42.0 ± 4.3	0.6023

Values are the mean±SD.
[a]The comparison among the two groups of normal data using One-way analysis, the comparison of count data by chi-square test.
DLV, double-lung ventilation; OLV, one-lung ventilation.

surgery patients as this cohort had a known significant incidence of postoperative neurocognitive disorder and cerebral vascular incidents (22). As there was a growing recognition of the potential for intraoperative monitoring with cerebral oximetry, it was applied to non-cardiac surgery scenarios such as thoracic surgery, which often has an increased risk of intraoperative hypoxemia, and was one potential application of great interest. Although the validity needs to be further tested, multiple studies have shown a relationship between cerebral oxygen desaturations and neurocognitive deficits in patients undergoing thoracic surgical procedures (17, 30, 31). For example, Monique Roberts and colleagues indicated that intraoperative cerebral oxygen desaturations, frequent during one-lung ventilation, are significantly associated with worse early cognitive recovery, and a high risk of POD (31). Furthermore, it is important to understand how the severity of cerebral desaturation and POD is related and if there is a $SctO_2$ threshold below which the risk of delirium is increased. In another study performed by Fan Cui and colleagues, cerebral desaturation defined by <90% baseline for left $SctO_2$ and <85% baseline for right $SctO_2$, may be associated with an increased risk of post-thoracotomy delirium (17). Our findings may support an additional mechanism by which flurbiprofen-elicited cerebral oxygen saturation might, at least in part, contribute to a reduction in POD.

There are several limitations. First, oxygen delivery is not solely dependent on saturation but rather must be considered in concert with hemoglobin level and, more importantly, cardiac output (8). Thus, whether hypoxemia reflected through peripheral oxygen saturation results in hypoxia is patient-dependent. Additionally, due to a lack of direct evidence, we do not know whether the participation of neuroinflammation underlies the beneficial actions of flurbiprofen (25, 26). Finally, this was a single-center study. The same team of performing surgeons and anesthetists ensured the standardization and consistency of the work. To add more evidence, multicenter studies are warranted to test the results and conclusions of our trial.

Conclusions

Collectively, premedication with flurbiprofen may improve intraoperative $rScO_2$ and reduce the incidence of POD in elderly patients undergoing thoracoscopic surgery with one-lung ventilation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The Ethics Committee at the First Affiliated Hospital of USTC approved this prospective trial. Written informed consent was obtained from all patients recruited to the study, in accordance with the code of the Declaration of Helsinki.

Author contributions

LS and J-qC: data curation and writing-original draft preparation. X-lY: writing-review and editing. J-cH and WG: analyze or synthesize study data. X-qC and DW: development or design of methodology. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Bernasconi F, Piccioni F. One-lung ventilation for thoracic surgery: current perspectives. *Tumori.* (2017) 103:495–503. doi: 10.5301/tj.5000638

2. Mcgrath B, Tennuci C, Lee G. The history of one-lung anesthesia and the double-lumen tube. *J Anesth Hist.* (2017) 3:76–86. doi: 10.1016/j.janh.2017.05.002

3. Ishikawa S, Lohser J. One-lung ventilation and arterial oxygenation. *Curr Opin Anaesthesiol.* (2011) 24:24–31. doi: 10.1097/ACO.0b013e3283415659

4. Yoon S, Kim BR, Min SH, Lee J, Bahk JH, Seo JH. Repeated intermittent hypoxic stimuli to operative lung reduce hypoxemia during subsequent one-lung ventilation for thoracoscopic surgery: A randomized controlled trial. *PLoS ONE.* (2021) 16:e0249880. doi: 10.1371/journal.pone.0249880

5. Lohser J, Slinger P. Lung injury after one-lung ventilation: a review of the pathophysiologic mechanisms affecting the ventilated and the collapsed lung. *Anesth Analg.* (2015) 121:302–18. doi: 10.1213/ANE.0000000000000808

6. Campos JH, Feider A. Hypoxia during one-lung ventilation-a review and update. *J Cardiothorac Vasc Anesth.* (2018) 32:2330–8. doi: 10.1053/j.jvca.2017.12.026

7. Hemmerling TM, Bluteau MC, Kazan R, Bracco D. Significant decrease of cerebral oxygen saturation during single-lung ventilation measured using absolute oximetry. *Br J Anaesth.* (2008) 101:870–5. doi: 10.1093/bja/aen275

8. Durkin C, Romano K, Egan S, Lohser J. Hypoxemia during one-lung ventilation: does it really matter? *Curr Anesthesiol Rep.* (2021) 1–7. doi: 10.1007/s40140-021-00470-5

9. Watts ME, Pocock R, Claudianos C. Brain energy and oxygen metabolism: emerging role in normal function and disease. *Front Mol Neurosci.* (2018) 11:216. doi: 10.3389/fnmol.2018.00216

10. Benni PB, Macleod D, Ikeda K, Lin HM. A validation method for near-infrared spectroscopy based tissue oximeters for cerebral and somatic tissue oxygen saturation measurements. *J Clin Monit Comput.* (2018) 32:269–84. doi: 10.1007/s10877-017-0015-1

11. Yu Y, Zhang K, Zhang L, Zong H, Meng L, Han R. Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults. *Cochrane Database Syst Rev.* (2018) 1:CD010947. doi: 10.1002/14651858.CD010947.pub2

12. Kazan R, Bracco D, Hemmerling TM. Reduced cerebral oxygen saturation measured by absolute cerebral oximetry during thoracic surgery correlates with postoperative complications. *Br J Anaesth.* (2009) 103:811–6. doi: 10.1093/bja/aep309

13. Tang L, Kazan R, Taddei R, Zaouter C, Cyr S, Hemmerling TM. Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. *Br J Anaesth.* (2012) 108:623–9. doi: 10.1093/bja/aer501

14. Li XM, Li F, Liu ZK, Shao MT. Investigation of one-lung ventilation postoperative cognitive dysfunction and regional cerebral oxygen saturation relations. *J Zhejiang Univ Sci B.* (2015) 16:1042–8. doi: 10.1631/jzus.B1500030

15. Murakawa K, Kitamura Y, Watanabe S, Hongo S, Shinomiya K, Sendo T. Clinical risk factors associated with postoperative delirium and evaluation of delirium management and assessment team in lung and esophageal cancer patients. *J. Pharm Health Care Sci.* (2015) 1. doi: 10.1186/s40780-014-0002-3

16. Lee H-S, Hayashi K, Motoishi M, Sawai S, Horimoto K, Hanaoka J. Postoperative delirium after lung resection for primary lung cancer: Risk factors, risk scoring system, and prognosis. *PLoS ONE.* (2019) 14. doi: 10.1371/journal.pone.0223917

17. Cui F, Zhao W, Mu DL, Zhao X, Li XY, Wang DX, et al. Association between cerebral desaturation and postoperative delirium in thoracotomy with one-lung ventilation: a prospective cohort study. *Anesth Analg.* (2021) 133:176–86. doi: 10.1213/ANE.0000000000005489

18. Chai XQ, Ma J, Xie YH, Wang D, Chen KZ. Flurbiprofen axetil increases arterial oxygen partial pressure by decreasing intrapulmonary shunt in patients undergoing one-lung ventilation. *J Anesth.* (2015) 29:881–6. doi: 10.1007/s00540-015-2060-6

19. 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. *Eur J Anaesthesiol.* (2007) 24:59–65. doi: 10.1017/S0265021506001025

20. Fischer GW, Lin HM, Krol M, Galati MF, Di Luozzo G, Griepp RB, et al. Noninvasive cerebral oxygenation may predict outcome in patients undergoing aortic arch surgery. *J Thorac Cardiovasc Surg.* (2011) 141:815–21. doi: 10.1016/j.jtcvs.2010.05.017

21. Rolfson Db, M.J., and Jhangri Gs, Rockwood K. (1999). Validity of the confusion assessment method in detecting postoperative delirium in the elderly. *Int Psychogeriatr* 11, 431-438. doi: 10.1017/S10416102990 06043

22. Sanders RD, Pandharipande PP, Davidson AJ, Ma D, Maze M. Anticipating and managing postoperative delirium and cognitive decline in adults. *BMJ.* (2011) 343:d4331. doi: 10.1136/bmj.d4331

23. Ma XD, Li BP, Wang DL, Yang WS. Postoperative benefits of dexmedetomidine combined with flurbiprofen axetil after thyroid surgery. *Exp Ther Med.* (2017) 14:2148–52. doi: 10.3892/etm.2017.4717

24. Wang X, Wang Y, Hu Y, Wang L, Zhao W, Wei L, et al. Effect of flurbiprofen axetil on postoperative delirium for elderly patients. *Brain Behav.* (2019) 9:e01290. doi: 10.1002/brb3.1290

25. Cunningham C, Skelly DT. Non-steroidal anti-inflammatory drugs and cognitive function: are prostaglandins at the heart of cognitive impairment in dementia and delirium? *J Neuroimmune Pharmacol.* (2012) 7:60–73. doi: 10.1007/s11481-011-9312-5

26. Subramaniyan S, Terrando N. Neuroinflammation and perioperative neurocognitive disorders. *Anesth Analg.* (2019) 128:781–8. doi: 10.1213/ANE.0000000000004053

27. Li XM, Shao MT, Wang JJ, Wang YL. Relationship between post-operative cognitive dysfunction and regional cerebral oxygen saturation and beta-amyloid protein. *J Zhejiang Univ Sci B.* (2014) 15:870–8. doi: 10.1631/jzus.B1400130

28. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth Analg.* (2007) 104:51–8. doi: 10.1213/01.ane.0000246814.29362.f4

29. Plachky J, Hofer S, Volkmann M, Martin E, Bardenheuer HJ, Weigand MA. Regional cerebral oxygen saturation is a sensitive marker of cerebral hypoperfusion during orthotopic liver transplantation. *Anesth Analg.* (2004) 99:344–9. doi: 10.1213/01.ANE.0000124032.31843.61

30. Brinkman R, Amadeo RJ, Funk DJ, Girling LG, Grocott HP, Mutch WA. Cerebral oxygen desaturation during one-lung ventilation: correlation with hemodynamic variables. *Can J Anaesth.* (2013) 60:660–6. doi: 10.1007/s12630-013-9954-2

31. Roberts ML, Lin HM, Tinuoye E, Cohen E, Flores RM, Fischer GW, et al. The association of cerebral desaturation during one-lung ventilation and postoperative recovery: a prospective observational cohort study. *J Cardiothorac Vasc Anesth.* (2021) 35:542–50. doi: 10.1053/j.jvca.2020.07.065

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EDITED BY
Diansan Su,
Shanghai Jiao Tong University, China

REVIEWED BY
Changwei Wei,
Capital Medical University, China
Han Lu,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Bao Lang
wfrmyy91@163.com

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Effects of different levels of controlled hypotension on regional cerebral oxygen saturation and postoperative cognitive function in patients undergoing total knee arthroplasty

Yajuan Zhao[1], Chuanbo Zang[2], Shengjie Ren[2], Jianbin Fu[3], Ning Liu[1], Ziyu Zhou[3] and Bao Lang[1]*

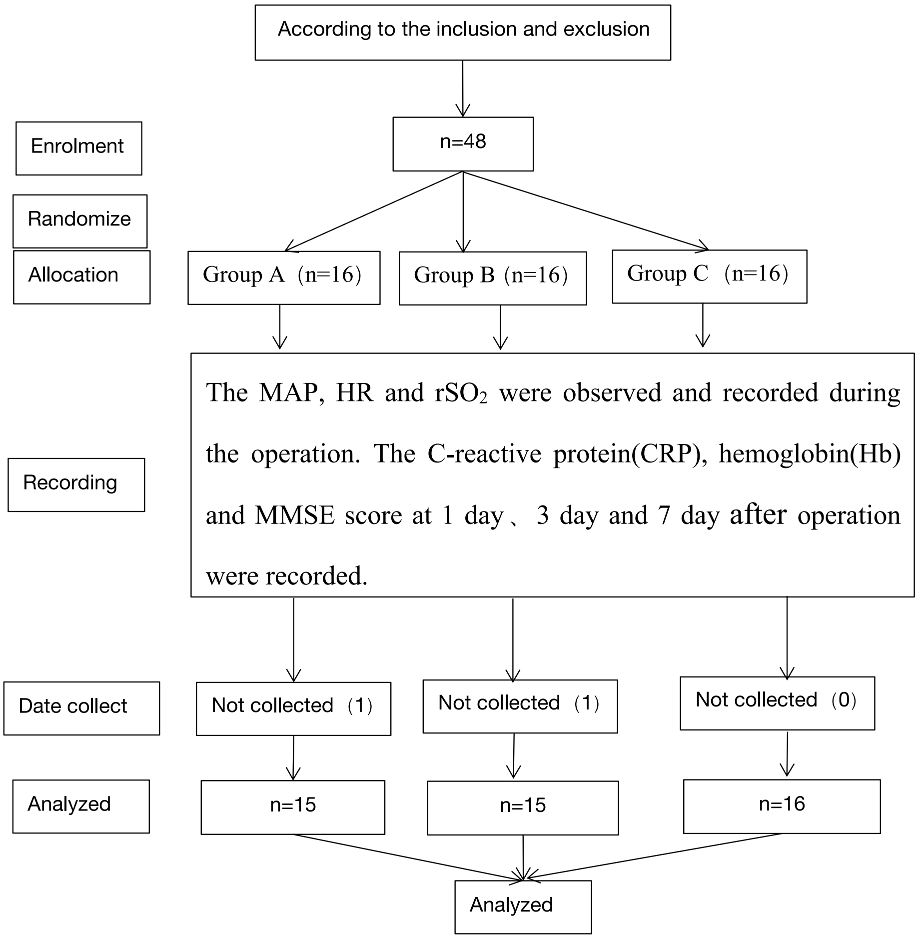
[1]Department of Anesthesiology, Weifang People's Hospital, Weifang, China, [2]School of Anesthesiology, Weifang Medical University, Weifang, China, [3]The 80th Group Army Hospital of the Chinese People's Liberation Army, Weifang, China

Background: Controlled hypotension technique was usually used to reduce intraoperative bleeding, and it could improve visualization of the surgical field during total knee arthroplasty (TKA). However, inappropriate controlled hypotension, through reducing cerebral blood flow or cerebral perfusion pressure, may cause postoperative cognitive dysfunction (POCD), so it is important to identify the appropriate level of controlled hypotension. Objective: To investigate the effects of different levels of controlled hypotension on regional cerebral oxygen saturation and postoperative cognitive function in patients undergoing TKA.

Methods: Patients meeting inclusion criteria were enrolled through preoperative visits and basic information was obtained. The patients were randomly divided into three groups: Group A, MAP was maintained at 90–100% of the baseline; Group B, MAP was maintained at 80–90% of the baseline; Group C, MAP was maintained at 70–80% of the baseline. The MAP, HR, and rSO_2 were observed and recorded during the operation. The C-reactive protein (CRP), hemoglobin (Hb) and MMSE score at 1, 3, and 7 days after operation were recorded. SPSS25.0 was used for data analysis.

Result: When the MAP had a decrease among the three groups, rSO_2 did not decrease significantly, and none of the patients experienced POCD which was measured by MMSE. And there was no correlation between the decline in rSO_2 and that in MAP.

Conclusion: No POCD was experienced in the three groups, and we recommend that the controlled hypotensive target indicated by MAP was



GRAPHICAL ABSTRACT
Study flowchat.

maintained at 70–80% of the baseline which not only decreases intraoperative bleeding and improve the quality of the surgical field, but also is still within safe levels.

KEYWORDS

controlled hypotension, cerebral oxygen saturation, postoperative cognitive function, aging people, TKA

Introduction

Total knee arthroplasty (TKA) is an effective method for the treatment of end-stage knee osteoarthritis. However, the large surgical wound and the amount of bleeding may seriously affect the prognosis. The traditional method is to use the tourniquet technique during surgery, and problems such as muscle and nerve injury caused by tourniquet are inevitable. Compared with tourniquet technique, controlled hypotension may have more advantages in TKA, which allows reduction of bleeding in the surgical field, minimization of blood loss, better visibility and therefore, it increases the surgeon's comfort, reduces the surgery time and prevents complications.

Controlled hypotension is defined as the reduction of systolic blood pressure (BP) to 80–90 mmHg, and that of MAP to 50–65 mmHg or 30% lower than the baseline level (1) while still providing adequate oxygen delivery to vital organs. However, extreme hypotension may cause.

Organ insufficiency and subsequent ischemic injury of vital organs, especially the brain (2), which has potential risk to cognitive function. Therefore, we set the 30% decrease from the baseline MAP as the minimum levels to investigate the effects of different levels of controlled hypotension on regional cerebral oxygen saturation and postoperative cognitive function in patients undergoing TKA.

Postoperative cognitive dysfunction (POCD) is a common complication induced by anesthesia or surgery, which affects the concentration, cognition and memory of patients. Maintaining sufficient cerebral perfusion and cerebral oxygen balance is the basic safety requirement of controlled hypotension. The purpose of this study was to investigate the effects of different levels of controlled hypotension on regional cerebral oxygen saturation and POCD in patients undergoing TKA and found out the suitable range of controlled hypotension for clinical reference.

Materials and methods

Setting and patients

This study protocol was approved by the Medical Institutional Ethics Committee of Wei Fang People Hospital and was registered in the China Clinical Trial Center (ChiCTR2200055120). The patients, aged 55–70 years old who were diagnosed with osteoarthritis and scheduled for TKA in general anesthesia at the Wei Fang People's Hospital From January 2022 to May 2022 were enrolled in this study. All patients had American Society of Anesthesiologists (ASA) grades I and II, and able to complete study questionnaires. All participants had to sign the informed consent form. Exclusion criteria: (1) preoperative mini-mental state examination (MMSE) score < 24 and unable to communicate normally, (2) hemoglobin (Hb) levels < 100 g/L, (3) cerebrovascular disease, (4) uncontrolled hypertension. (5) Have a neurological or psychiatric disorder.

Randomization and blinding

Patients meeting the criteria were enrolled through preoperative visits and informed consent was signed. The patients were randomly divided into three groups by anesthetist in the preoperative, using a list of numbers generated by the QuickCalcs. The group assignment numbers were sealed in an envelope, and opened once written informed consent was obtained. In group A: MAP was maintained at 90–100% of the baseline; in group B: MAP was maintained at 80–90% of the baseline; in group C: MAP was maintained at 70–80% of the baseline. All operations were performed by the same group of surgeons, and postoperative visits were conducted by the investigator, who was unaware of the grouping.

Anesthesia and postoperative treatment

All included patients were prepared for routing general anesthesia by inserting an intravenous line, and electrocardiogram, non-invasive blood pressure, pulse oximetry, and rSO_2 were monitored. All patients were administered 0.5μg/kg (within 10 min) of dexmedetomidine as a premedication, and 30 mL of 0.3% ropivacaine was used for ultrasound-guided femoral nerve block. Induction anesthesia was achieved with propofol (closed loop target controlled infusion under bispectral index (BIS) monitoring, initial target concentration: 3–4 μg/mL), remifentanil (3–4 μg/kg), sufentanil (0.2μg/kg), and rocuronium (40 mg). The laryngeal mask was inserted when the patient was unconscious and BIS was stable at 40–60. The lungs were ventilated with 60% oxygen and controlled with a tidal volume of 6–8 mL/kg, and the respiration rate was 12–14 beats per minute. Propofol (closed loop target controlled infusion under BIS monitoring (40–60))and remifentanil (2.0–3.5 ng/mL TCI) was used to maintain anesthesia. Respiratory parameters were adjusted to maintain a $PetCO_2$ value of 35–45 mmHg. Before surgery, target level of controlled hypotension was achieved by increasing the depth of anesthesia (remifentanil) or nitroglycerin. The norepinephrine (40μg or 0.1–0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) would be administered to raise the MAP after lowering it below the target value. The heart rate was maintained at 50–80 beats/min and atropine and esmolol were used to regulate heart rate. All patients in the three groups maintained the MAP $\geq$ 70% of the baseline, and MAP $\geq$ 55 mmHg. When $rSO_2 <$ 80% of the baseline, or the lowest rSO_2 value $<$ 50% of the baseline and lasted more than 10 s, the blood pressure was increased until rSO_2 returned to 80% of the baseline.

Data collection

Before operation, relevant data was collected including gender, BMI, Hb, CRP, MMSE score, etc. The MAP, HR and rSO_2 of baseline (T_0), admission (T_1), oxygen inhalation (T_2), anesthesia induction (T_3), 5 min after controlled hypotension (T_4), 10 min after controlled hypotension (T_5), 20 min after controlled hypotension (T_6), the end of operation (T_7) and 5 min after operation (T_8) were observed and recorded. Postoperative Hb, CRP after operation, MMSE score at 1, 3, and 7 days after operation and PACU residence time were recorded.

Statistical analysis

In this study, SPSS 25.0 software (developed by IBM Corp.) was used for all data processing. For continuous data, normally distributed data is expressed as mean ± standard

TABLE 1 Demographic and preoperative characteristics.

	Group A	Group B	Group C	*P*-value
Male, *n* (%)	11(73.3%)	11(68.7%)	11 (73.3%)	0.947
Female, *n* (%)	4(26.7%)	5(31.3%)	4(26.7%)	
Age (year)	60.87 ± 3.93	61.06 ± 3.71	62.60 ± 4.14	0.606
BMI (kg/m^2)	26.18 ± 2.40	27.20 ± 3.74	26.07 ± 2.59	0.514
ASAI, *n* (%)	2(13.3%)	2(12.5%)	3(20.0%)	0.819
II, *n* (%)	13(86.7%)	14(87.5%)	12(80.0%)	
Preoperative MMSE score	28.07 ± 1.34	28.19 ± 1.17	27.33 ± 1.11	0.119
Hemoglobin (g/L)	132.53 ± 12.16	128.70 ± 9.68	126.35 ± 8.91	0.264
CRP (mg/L)	3.50 (2.40, 5.60)	2.90 (1.53, 4.78)	2.40(1.50, 6.20)	0.672

Values are means ± SDs, numbers (%), or medians and ranges. BMI, body mass index; ASA, American Society of Anesthesiologists; CRP, C-reactive protein.

TABLE 2 Changes in rSO_2 at various time points among the three groups.

	T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	*P*	*F*
Group A	66.24 ± 3.37	66.87 ± 2.13	68.13 ± 2.21	68.06 ± 2.18	66.61 ± 2.32	66.04 ± 2.26	65.98 ± 2.61	66.27 ± 2.53	67.51 ± 4.12	0.156	1.521
Group B	66.99 ± 2.27	67.52 ± 1.98	68.31 ± 1.81	68.28 ± 2.18	66.77 ± 2.60	66.14 ± 2.40	65.61 ± 2.54	66.36 ± 2.91	67.67 ± 2.59	0.021	2.358
Group C	66.46 ± 2.99	66.88 ± 3.12	67.63 ± 2.97	67.18 ± 3.11	65.67 ± 3.49	64.90 ± 3.51	64.58 ± 3.32	65.90 ± 2.55	66.16 ± 3.54	0.028	2.246
p-value	0.764	0.710	0.724	0.453	0.517	0.372	0.379	0.882	0.431		
F	0.85	1.085	1.025	2.530	2.106	3.176	3.115	0.394	2.694		

deviation, while non-normally distributed data is expressed as median [range between quartiles (IQR)]. ANOVA was used for continuous data consistent with normal distribution and homogeneity of variance; otherwise, Kruskal-Wallis test was used. The categorical data were represented in frequency and proportion, and analyzed using the χ^2-test or Fisher Freeman-Halton test as appropriate. $P < 0.05$ was considered statistically significant.

Results

Forty- eight patients were initially enrolled in this study. One patient in group A was later excluded due to loss of data; one patient in group B was excluded due to the shift of brain oxygen sensor in his forehead resulting in abnormal rSO_2 reading during controlled hypotension, which was not effective after many adjustments and both patients recovered well after operation. Finally, forty-six patients were enrolled.

Baseline characteristic

No significant differences in the baseline characteristic data were observed between the three groups, such as sex, age, BMI, ASA classification (**Table 1**).

Primary outcome

Influence of controlled hypotension on rSO_2

As is shown in **Table 2**, there was no statistical difference in rSO_2 between groups at each time point, but there was significant statistical difference at each time point within the Group B and Group C (Group B: $P = 0.021$; Group C: $P = 0.028$). The change trend of rSO_2 at each time point is shown in **Figure 1**. Before T3, the tendency of rSO_2 in all group was upward, then it began to descend after controlled hypotension. The rSO_2 in Group C was lower than that in the other two groups between T2-T8, but there was no statistical difference. There are relatively clear downward trend of rSO_2 in the Group B and Group C, and the influence of blood pressure on rSO_2 was more obvious at T6.

We further analyzed the correlation between the percentage of hypotension amplitude in each group and the percentage of rSO_2 reduction at three time points in the controlled hypotension process (**Figure 2** and **Table 3**), but none of the differences were statistically significant ($p = 0.417$). It is not difficult to find that the possibility of rSO_2 decline in group C is relatively large.

Influence of controlled hypotension on cognitive function

The cognitive function on 1, 3, and 7 days after surgery was measured using MMSE. There was no statistically significant

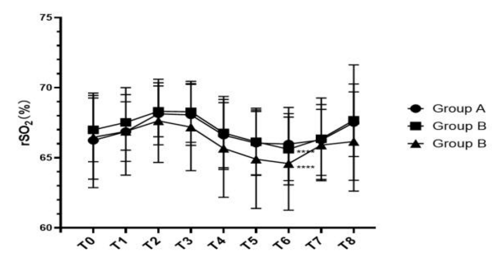


FIGURE 1
Line chart of rSO_2 changes at different time points.

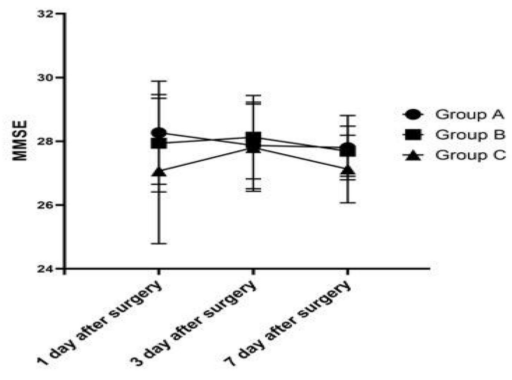


FIGURE 2
Comparison of postoperative MMSE scores among the three groups.

TABLE 3 The decreases in MAP and rSO_2 during controlled hypotension in all groups.

	Group A	Group B	Group C	*P*
△MAP	6.86 ± 3.78	16.60 ± 3.12	24.42 ± 5.37	<0.001
△rSO_2	−0.29 (−3.28, 3.19)	1.03(−3.21, 3.69)	0.61 (−0.70, 5.36)	0.417

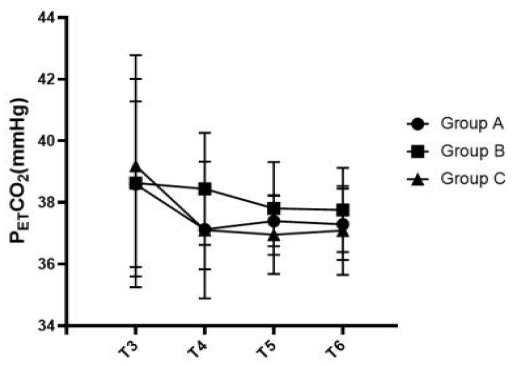


FIGURE 3
Comparison of $P_{KT}CO_2$ at various time points among the three groups.

difference (1 day after surgery: $P = 0.192$; 3 day after surgery: $P = 0.777$; 7 day after surgery: $P = 0.136$) between groups (Figure 2). The MMSE score of Group C was always lower than that of Group A and B after operation.

Secondary results

Intraoperative medication

Among all intraoperative drugs, only remifentanil and deoxyepinephrine showed significant statistical difference(remifentanil: $P < 0.001$, deoxyepinephrine: $P < 0.001$) (Table 4). However, the use of propofol, atropine and nitroglycerin among the three groups has no significant difference.

Figures 3–5 show that the $P_{ET}CO_2$, controlled hypotension duration and residence time of PACU were similar between these groups ($P > 0.05$). Figure 6 shows that Surgeons' satisfaction increased significantly in groups B and C ($P < 0.001$), and the magnitude of blood pressure reduction in Group A was hardly satisfactory to the doctor.

Bleeding and inflammation

Among the three groups, although there was no significant difference in the percentage decrease of hemoglobin level ($P = 0.935$), there was significant difference in postoperative CRP levels ($P < 0.001$) (Table 5). The results shown in Table 5 indicate the percentage reduction of hemoglobin in Group C was the least compared to the other two groups. The CRP index in Group A was significantly higher than that in the other two groups (Group A vs. group B, $P = 0.003$; Group A vs. group C, $P < 0.001$).

Discussion

A total of 46 participants were included in this study. We found that the short-term (rSO_2) or relatively long-term effects (MMSE score) of the magnitude of blood-pressure reduction in the three groups were limited, and there was some trend but no significant statistical difference. This difference may be made more pronounced by enlarging the sample size. Another finding is that the differences in primary outcomes among the three groups increased with the duration of hypotension.

Severe intraoperative and postoperative blood loss caused by TKA has always been a concern (3). Controlled hypotension technique and tourniquet are usually used to reduce intraoperative bleeding during TKA. Studies have shown that the use of tourniquet during operation will cause tourniquet-related ischemia-reperfusion injury (4). Some studies also found that the patients who experienced controlled hypotension but without tourniquet use during the operation had higher MOCA scores than those patients who used tourniquets (5). Therefore, we used controlled hypotension to reduce bleeding in this study.

Controlled hypotension is defined as the reduction of systolic blood pressure (BP) to 80–90 mmHg, and that of MAP to 50–65 mmHg or 30% lower than the baseline level (1) while still providing adequate oxygen delivery to vital organs. A research has shown that lowering the MAP to 2/3 of the initial value does not cause any damage (6, 7). Therefore, we set the 30% decrease from the baseline MAP as the minimum levels to investigate the effects of different levels of controlled hypotension on regional cerebral oxygen saturation and postoperative cognitive function in patients undergoing TKA.

TABLE 4 Comparison of intraoperative medication among the three groups.

	Group A	Group B	Group C	*P*-value
Remifentanil (mL, 20 μg/mL)	11.65 ± 0.93[a]	12.63 ± 1.50[b]	14.48 ± 1.72[ba]	<0.001
Propofol (mL, 10 mg/mL)	37.40 ± 2.16	36.10 ± 5.60	37.93 ± 4.83	0.532
Deoxyepinephrine (μg)	100.00 (60.00, 140.00)[dc]	20.00 (0.00, 70.00)[c]	0.00 (0.00, 0.00)[d]	<0.001
Nitroglycerin (μg)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 20.00)	0.057
Atropine (mg)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.000

[a]Group A vs. group C, $P < 0.001$, [b]Group B vs. group C, $P = 0.003$, [c]Group A vs. group B, $P = 0.022$, [d]Group A vs. group C, $P < 0.001$.

However, one study had shown that extreme hypotension may cause organ insufficiency and subsequent ischemic injury of vital organs, especially the brain (2), which has potential risk to cognitive function.

The biggest risk of controlled hypotension is hypoxic brain damage caused by insufficient cerebral blood perfusion. rSO_2 mainly monitors the oxygenation at the level of bilateral frontal lobes, but it can roughly reflect the balance of oxygen supply and demand in the whole brain. In this study, we aimed to determine the relationship between the different degrees of controlled hypotension and postoperative cognitive function, Studies have shown that intraoperative hypotension is a risk factor for POCD (8–10). However, the conclusion was not reached in our study, we observed that a 20–30% decrease of baseline MAP allowed reduction of bleeding in the surgical field, minimization of blood loss, better visibility and therefore, it increases the surgeon's comfort, reduces the surgery time and prevents complications. An analytical research about risk factors of early cognitive dysfunction in Elderly Patients after Total Knee shown that the level of preoperative cognitive function, postoperative CRP level, and postoperative pain were independent risk factors for POCD (11). However, no significant differences in the baseline characteristic data were observed between the three groups, such as sex, age, BMI, SBP, DBP, Hb levels, CRP levels, and ASA physical status, even the baseline MMSE score.

In this study, we adjusted the depth of anesthesia by adjusting the dose of remifentanil. When the expected hypotension level was not reached, we combined nitroglycerin to reduce the blood pressure to the target value. Remifentanil (RFN), an ultrashort-acting opioid and μ receptor agonist, enables easy adjustment of the depth of anesthesia and reduction of the MAP and HR through cardiodepressive action (12, 13). Earlier studies also indicated the positive effect of propofol as an anesthetic in reducing MAP through its effect on precapillary arterioles (14). In this study, we used propofol under closed-loop systems under BIS anesthesia depth monitoring to eliminate the effect of propofol on POCD. In addition, the research of Picton P shown that CO_2 levels can influence CBF by regulating the dilation and constriction of cerebral vessels and alter rSO_2 levels (15), and this result is also consistent with some other studies, they also found the correlation analysis between $PetCO_2$ and rSO_2 (16, 17). Therefore, we kept the $P_{ET}CO_2$ in the three groups at a similar level.

Our results showed that MAP values decreased in all groups immediately after induction of anesthesia (T_3), but instead of decreasing with it, the value of rSO_2 rised, and this may be related to the inhalation of 100% oxygen. During controlled hypotension, we found that rSO_2 gradually decreased and reached the lowest at T_6 with the continuation of controlled hypotension, while the value was restored to the baseline level at T_7 and T_8. However, although the three groups had different degrees of controlled hypotension, there was no

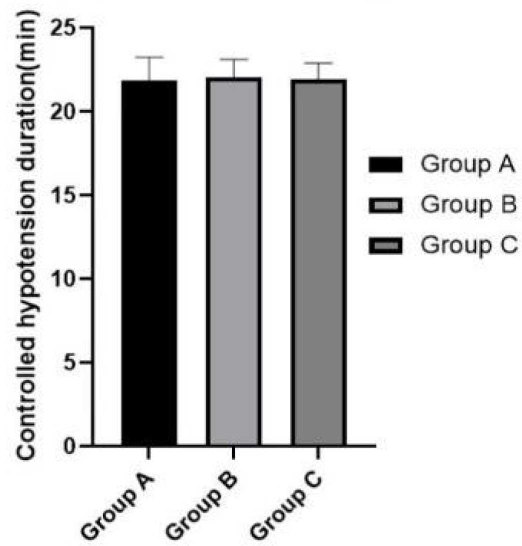


FIGURE 4
Comparison of controlled hypotension duration.

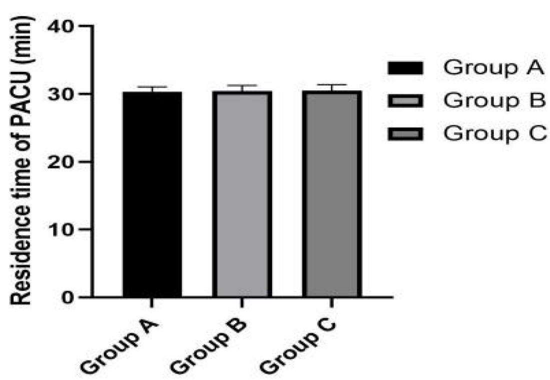


FIGURE 5
Residence time of PACU.

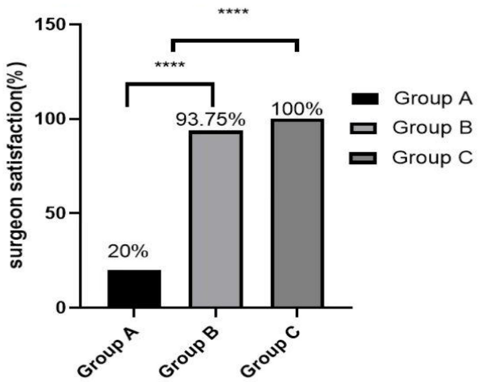


FIGURE 6
Surgeon satisfaction. ****Group A vs. Group B, $P < 0.001$ and Group A vs. Group C, $P < 0.001$.

statistical difference in rSO_2 at the same time among the three groups. Some studies found that MAP was moderately cross-correlated with current rSO_2 ($r = 0.728$) (9, 18), but our study is not consistent with it. From the analysis of our results, it can be seen that the decrease of rSO_2 has the same trend as the decrease of MAP during the controlled hypotension period, however, we didn't find the significant correlation between the decrease percentage of rSO_2 and MAP in the three groups. When the baseline MAP decreased by 20–30% (24.42 ± 5.37), the decrease in rSO_2 from the baseline was only 0.61 (−0.70, 5.36)% in Group C. At the same time, analysis of cognitive function on 1, 3, and 7 days after surgery showed that MMSE scores were lowest in the group with the maximum degree of controlled hypotension, although there was no statistically significant difference and none of the patients had obvious clinical manifestations of cognitive dysfunction. This may be related to the short duration of controlled hypotension and surgery in this study. Some studies also revealed that longer duration of surgery (OR1.82, 1.01∼3.16) were risk factors for POCD (19). A randomized trial shown that BIS decreases delayed neurocognitive recovery and postoperative neurocognitive disorder (20). And preoperative use of dexmedetomidine (OR0.70, 0.08∼0.94) and preemptive analgesia (OR0.75, 0.13–0.90) were the protective factors for POCD in elderly patients with laparoscopic surgery (12). In our study, the maximum degree of controlled hypotension is 30% of the baseline MAP, and the minimum value of MAP is above 60 mmHg. In brain physiology, cerebral pressure autoregulation, during MAP between 60 and 150 mmHg, maintains a relatively stable CBF. Since the reduction from baseline MAP did not proceed beyond the range of cerebral autoregulation, the grouping of this study is relatively reasonable, and both MAP and rSO_2 values were restored to baseline levels after the end of the operation. The results of a study showed that mean arterial pressure < 50 mmHg (1 mmHg = 0.133 kPa) was closely related to a decrease in cognitive function (21).

A Randomized Controlled Trial about the effect of deliberate hypotension on regional cerebral oxygen saturation during functional endoscopic sinus surgery shown that none of the patients experienced cerebral desaturation events (CDEs) when the baseline MAP was decreased by 30%, which result is also consistent with our study (9). In this study, monitoring of rSO_2 while controlled hypotension and timely intervention can reduce the occurrence of postoperative neurological disorders, and the criteria for cerebral ischemia are reduction of 10 index points in rSO_2 from a stable baseline, absolute value of rSO2 < 50%, 20–25% reduction in relative rSO_2 (22). Thus, rSO_2 was more than 20% lower than the baseline, the controlled hypotension was stopped in the event of further drop till rSO_2 was restored to acceptable levels.

The conclusion that the occurrence of cognitive dysfunction is affected by intraoperative blood loss including postoperative oozing in elderly patients has consistently been confirmed (8, 9). Studies have shown that the estimation of hemoglobin mass loss was found to be a more accurate method to estimate perioperative blood loss (23). In our study, percentage decrease of hemoglobin level is least in Group C, although no statistically significant differences were observed among the three groups. Moreover, Group C obtained the best surgical field and surgeon satisfaction. In addition, there was no statistical difference in PACU residence time among the three group. More severe controlled hypotension does not present a disadvantage in postoperative recovery.

A finding indicated that inflammation is significantly associated with the development of POCD. In molecular biology, microglia are important cells that maintain the balance of inflammation in the brain (24). The increased levels of peripheral inflammatory factors induced by surgical stimuli cause microglial activation (25), which produce cytokines and result in the production of a range of inflammatory factors in areas of the central nervous system (CNS). However, there are researches finding that the mechanism of POCD is related to

TABLE 5 Comparison of postoperative indicators among the three groups.

	Group A	Group B	Group C	*P*-value
Percentage decrease of hemoglobin level	0.15 ± 0.04	0.15 ± 0.04	0.14 ± 0.03	0.935
CRP (mg/L)	108.00 (89.00, 168.00)[ab]	73.45 (18.20, 82.60)[a]	32.50 (19.10, 58.10)[b]	<0.001

[a]Group A vs. group B, $P = 0.003$; [b]Group A vs. group C, $P < 0.001$.

inflammatory response (26, 27), CRP serves as a marker of non-specific acute-phase response in inflammation, infection, and tissue damage, related to the development of POCD. Several studies demonstrated that increased CRP levels were associated with POCD (23, 28–30). In our study, CRP in the group C was significantly lower than that in the other two groups, but none of the patients developed POCD.

This study has some limitations. First, the groups in this study were too small to achieve statistical significance when they were divided into subgroups, and we suggest that further studies should incorporate larger sample sizes. Second, we used MMSE as a measure for cognitive function, which is a very quick cognitive test, but is less suitable to detect the subtle cognitive impairment associated with POCD (31). Third, the patients we selected had an limit of age, partly because the study population was relatively young, and the average age was 62.51 ± 3.89 years. Therefore, the extrapolation of these results to elderly surgical patients must be cautious, because these elderly patients have become more sensitive to the development of POCD itself, even without hypotension. Finally, in this study, the lowest value of the controlled hypotension is only 30% of the basic value, we can try to further reduce the degree of the controlled hypotension to observe its relationship with rSO_2.

Conclusion

Our study found that the decrease of rSO_2 was related to the decrease level of MAP in TKA. Based on our findings, we recommend that the controlled hypotensive target indicated by MAP be reduced by 20–30%, which not only decreases intraoperative bleeding and improves the quality of the surgical field of vision, but also is still within safe levels.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Institutional Ethics Committee of Wei Fang People Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ: manuscript writing. CZ: collecting data. SR: statistical analysis. JF, NL, and ZZ: literature review. BL: design research plan. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Erdem AF, Kayabasoglu G, Tas Tuna A, Palabiyik O, Tomak Y, Beyaz SG. Effect of controlled hypotension on regional cerebral oxygen saturation during rhinoplasty: a prospective study. *J Clin Monit Comput.* (2016) 30:655–60. doi: 10.1007/s10877-015-9768-6

2. Rodrigo C. Induced hypotension during anesthesia with special reference to orthognathic surgery. *Anesth Prog.* (1995) 42:41–58.

3. Cundy WJ, Theodoulou A, Ling CM, Krishnan J, Wilson CJ. Blood loss in total knee arthroplasty. *J Knee Surg.* (2017) 30:452–9. doi: 10.1055/s-0036-1592147

4. Leurcharusmee P, Sawaddiruk P, Punjasawadwong Y, Chattipakorn N, Chattipakorn SC. The possible pathophysiological outcomes and mechanisms of tourniquet-induced ischemia-reperfusion injury during total knee arthroplasty. *Oxid Med Cell Longev.* (2018) 2018:8087598. doi: 10.1155/2018/8087598

5. Dong J, Min S, He KH, Peng LH, Cao J, Ran W. Effects of the nontourniquet combined with controlled hypotension technique on pain and long-term prognosis in elderly patients after total knee arthroplasty: a randomized controlled study. *J Anesth.* (2019) 33:587–93. doi: 10.1007/s00540-019-02671-z

6. Townes BD, Dikmen SS, Bledsoe SW, Hornbein TF, Martin DC, Janesheski JA. Neuropsychological changes in a young, healthy population after controlled hypotensive anesthesia. *Anesth Analg.* (1986) 65:955–9.

7. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. international study of post-operative cognitive dysfunction. *Lancet.* (1998) 351:857–61.

8. Zhang J, Liu G, Zhang F, Fang H, Zhang D, Liu S, et al. Analysis of postoperative cognitive dysfunction and influencing factors of dexmedetomidine anesthesia in elderly patients with colorectal cancer. *Oncol Lett.* (2019) 18:3058–64. doi: 10.3892/ol.2019.10611

9. Zhou H, Li F, Ye W, Wang M, Zhou X, Feng J, et al. Correlation between plasma CircRNA-089763 and postoperative cognitive dysfunction in elderly patients undergoing non-cardiac surgery. *Front Behav Neurosci.* (2020) 14:587715. doi: 10.3389/fnbeh.2020.587715

10. Maheshwari K, Ahuja S, Khanna AK, Mao G, Perez-Protto S, Farag E, et al. Association between perioperative hypotension and delirium in postoperative critically ill patients: a retrospective cohort analysis. *Anesth Analg.* (2020) 130:636–43. doi: 10.1213/ANE.0000000000004517

11. Ren S, Yuan F, Yuan S, Zang C, Zhang Y, Lang B. Early cognitive dysfunction in elderly patients after total knee arthroplasty: an analysis of risk factors and cognitive functional levels. *Biomed Res Int.* (2022) 2022:5372603. doi: 10.1155/2022/5372603

12. Coskun D, Celebi H, Karaca G, Karabiyik L. Remifentanil versus fentanyl compared in a target-controlled infusion of propofol anesthesia: quality of anesthesia and recovery profile. *J Anesth.* (2010) 24:373–9. doi: 10.1007/s00540-010-0898-1

13. Eberhart LH, Kussin A, Arndt C, Lange H, Folz BJ, Werner JA, et al. Effect of a balanced anaesthetic technique using desflurane and remifentanil on surgical conditions during microscopic and endoscopic sinus surgery. *Rhinology.* (2007) 45:72–8.

14. Goswami U, Babbar S, Tiwari S. Comparative evaluation of the effects of propofol and sevoflurane on cognitive function and memory in patients undergoing laparoscopic cholecystectomy: a randomised prospective study. *Indian J Anaesth.* (2015) 59:150–5. doi: 10.4103/0019-5049.153036

15. Picton P, Dering A, Alexander A, Neff M, Miller BS, Shanks A, et al. Influence of ventilation strategies and anesthetic techniques on regional cerebral oximetry in the beach chair position: a prospective interventional study with a randomized comparison of two anesthetics. *Anesthesiology.* (2015) 123:765–74. doi: 10.1097/ALN.0000000000000798

16. Zhang L, Yu Y, Xue J, Lei W, Huang Y, Li Y, et al. Effect of deliberate hypotension on regional cerebral oxygen saturation during functional endoscopic sinus surgery: a randomized controlled trial. *Front Surg.* (2021) 8:681471. doi: 10.3389/fsurg.2021.681471

17. Heller JA, DeMaria S Jr, Govindaraj S, Lin HM, Fischer GW, Evans A, et al. Cerebral oximetry monitoring during sinus endoscopy. *Laryngoscope.* (2015) 125:E127–31. doi: 10.1002/lary.25027

18. Farzanegan B, Eraghi MG, Abdollahi S, Ghorbani J, Khalili A, Moshari R, et al. Evaluation of cerebral oxygen saturation during hypotensive anesthesia in functional endoscopic sinus surgery. *J Anaesthesiol Clin Pharmacol.* (2018) 34:503–6. doi: 10.4103/joacp.JOACP_248_17

19. Fan Y, Liu X, Wu S, Liu Y. The risk factors for cognitive dysfunction in elderly patients after laparoscopic surgery: a retrospective analysis. *Medicine.* (2021) 100:e23977. doi: 10.1097/MD.0000000000023977

20. 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) 14:2081–91.

21. Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology.* (2007) 106:572–90. doi: 10.1097/00000542-200703000-00023

22. Nielsen HB. Systematic review of near-infrared spectroscopy determined cerebral oxygenation during non-cardiac surgery. *Front Physiol.* (2014) 5:93. doi: 10.3389/fphys.2014.00093

23. Jaramillo S, Montane-Muntane M, Gambus PL, Capitan D, Navarro-Ripoll R, Blasi A. Perioperative blood loss: estimation of blood volume loss or haemoglobin mass loss? *Blood Transfus.* (2020) 18:20–9. doi: 10.2450/2019.0204-19

24. Saxena S, Maze M. Impact on the brain of the inflammatory response to surgery. *Presse Med.* (2018) 47(4 Pt 2.):e73–81. doi: 10.1016/j.lpm.2018.03.011

25. Hoogland IC, Houbolt C, van Westerloo DJ, van Gool WA, van de Beek D. Systemic inflammation and microglial activation: systematic review of animal experiments. *J Neuroinflammation.* (2015) 12:114. doi: 10.1186/s12974-015-0332-6

26. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): a meta-analysis of observational studies. *PLoS One.* (2018) 13:e0195659. doi: 10.1371/journal.pone.0195659

27. Peng L, Xu L, Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis. *PLoS One.* (2013) 8:e79624. doi: 10.1371/journal.pone.0079624

28. Androsova G, Krause R, Winterer G, Schneider R. Biomarkers of postoperative delirium and cognitive dysfunction. *Front Aging Neurosci.* (2015) 7:112. doi: 10.3389/fnagi.2015.00112

29. Dillon ST, Vasunilashorn SM, Ngo L, Otu HH, Inouye SK, Jones RN, et al. Higher C-reactive protein levels predict postoperative delirium in older patients undergoing major elective surgery: a longitudinal nested case-control study. *Biol Psychiatry.* (2017) 81:145–53. doi: 10.1016/j.biopsych.2016.03.2098

30. Neerland BE, Hall RJ, Seljeflot I, Frihagen F, MacLullich AM, Raeder J, et al. Associations between delirium and preoperative cerebrospinal fluid c-reactive protein. interleukin-6, and interleukin-6 receptor in individuals with acute hip fracture. *J Am Geriatr Soc.* (2016) 64:1456–63. doi: 10.1111/jgs.14238

31. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res.* (2009) 43:411–31. doi: 10.1016/j.jpsychires.2008.04.014

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EDITED BY
Yasushi Satoh,
National Defense Medical College, Japan

REVIEWED BY
Shengxiang Liang,
Fujian University of Traditional Chinese Medicine, China
Xiaoyu Xia,
The Military General Hospital of Beijing PLA, China

*CORRESPONDENCE
Dezhi Kang
kdz99988@vip.sina.com
Dengliang Wang
wdlchina2003@yahoo.com.cn

†These authors have contributed equally to this work and share first authorship

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Altered hippocampal functional connectivity after the rupture of anterior communicating artery aneurysm

Fuxiang Chen[1,2,3†], Jiawei Cai[1,2,3†], Linsun Dai[1,2,3†], Yuanxiang Lin[1,2,3], Lianghong Yu[1,2,3], Zhangya Lin[1,2,3], Yaqing Kang[4], Ting Yu[1,2,3], Dengliang Wang[1,2,3]* and Dezhi Kang[1,2,3]*

[1]Department of Neurosurgery, Neurosurgery Research Institute, The First Affiliated Hospital, Fujian Medical University, Fuzhou, China, [2]Department of Neurosurgery, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou, China, [3]Fujian Provincial Institutes of Brain Disorders and Brain Sciences, First Affiliated Hospital, Fujian Medical University, Fuzhou, China, [4]Department of Radiology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China

Background and purpose: Aneurysmal subarachnoid hemorrhage (SAH) predisposes hippocampal injury, a major cause of follow-up cognitive impairment. Our previous study has revealed an abnormal resting-state brain network in patients after the rupture of anterior communicating artery (ACoA) aneurysm. However, the functional connectivity (FC) characteristics of the hippocampus and its relationship with cognitive performance in these patients remain unknown.

Methods: This study ultimately included 26 patients and 19 age- and sex-matched controls who completed quality control for resting-state functional magnetic resonance imaging (fMRI). The mean time series for each side of the hippocampus was extracted from individuals and then a seed-to-voxel analysis was performed. We compared the difference in FC strength between the two groups and subsequently analyzed the correlations between abnormal FC and their cognitive performance.

Results: The results of bilateral hippocampus-based FC analysis were largely consistent. Compared with the healthy controls, patients after the rupture of ACoA aneurysm exhibited significantly decreased FC between the hippocampus and other brain structures within the Papez circuit, including bilateral anterior and middle cingulate cortex (MCC), bilateral medial superior frontal gyrus, and left inferior temporal gyrus (ITG). Instead, increased FC between the hippocampus and bilateral insula was observed. Correlation analyses showed that more subjective memory complaints or lower total cognitive scores were associated with decreased connectivity in the hippocampus and several brain regions such as left anterior cingulate cortex (ACC) and frontotemporal cortex.

Conclusion: These results extend our previous findings and suggest that patients with ruptured ACoA aneurysm exist hypoconnectivity between the hippocampus and multiple brain regions within the Papez circuit. Deactivation of the Papez circuit may be a crucial neural mechanism related to cognitive deficits in patients after the rupture of ACoA aneurysm.

KEYWORDS

anterior communicating artery aneurysm, subarachnoid hemorrhage, hippocampus, cognitive impairment, functional connectivity, Papez circuit

Introduction

Subarachnoid hemorrhage (SAH) caused by the rupture of anterior communicating artery (ACoA) aneurysm is a devastating cerebrovascular event with high morbidity and mortality (Hong et al., 2012; Ito et al., 2015). Cognitive impairment reportedly occurs in approximately half of the surviving patients, of which memory loss is the most common complaint, preventing them from returning to their normal life (Beeckmans et al., 2020; Neifert et al., 2021). Therefore, there is an urgent clinical need for the treatment of cognitive dysfunction following the rupture of cerebral aneurysm. However, the neural mechanisms underlying cognitive deficits after the rupture of ACoA aneurysm remain unclear, resulting in limited treatment.

Numerous neuroimaging studies have been performed to explore cognitive deficits caused by neurological problems, including hemorrhagic cerebrovascular disease (Baldassarre et al., 2016; Siegel et al., 2016; Adhikari et al., 2017; Chung et al., 2021). There was compelling evidence that cognitive dysfunction is associated with an aberrant functional brain network (Maher et al., 2015; Mikell et al., 2015; Nelson et al., 2016). It is well established that resting-state functional magnetic resonance imaging (fMRI) reflects the spontaneous neural activity of the brain and is of great value for assessing brain network characteristics (Fox et al., 2014). Unexpectedly, few studies concentrated the effect of ruptured cerebral aneurysms on brain activity and intrinsic connectivity (Maher et al., 2015; Mikell et al., 2015; Su et al., 2018). A domestic study using resting-state fMRI revealed significant abnormal functional connectivity (FC) of medial temporal lobe and thalamus in the group of patients with SAH as compared to the healthy controls (Su et al., 2018). Furthermore, the decreased FC between several brain regions, such as left thalamus-left inferior parietal lobe and left inferior temporal gyrus (ITG)-bilateral inferior frontal gyrus, was significantly associated with their poor memory performance (Su et al., 2018). Another two resting-state fMRI studies focused primarily on post-SAH executive function impairment, in which disruption of frontal networks or frontoparietal connectivity in the patients' group was found (Maher et al., 2015; Mikell et al., 2015). These studies to a certain extent shed light on the functional brain network mechanisms of cognitive dysfunction after the rupture of cerebral aneurysm.

Notably, the location of ruptured aneurysms in the abovementioned three studies was not unique that would undoubtedly lead to different patterns of structural brain damage, and further had a non-negligible impact on the findings of functional brain network analysis. Take the example of ruptured anterior circulation aneurysms, damage to adjacent brain structures and the probability of vasospasm are both related to their locations. Therefore, we found that patients suffering from the rupture of ACoA aneurysm clinically tend to present more severe symptoms (Beeckmans et al., 2020; Neifert et al., 2021). In addition, hydrocephalus is a common sequela after aneurysmal SAH that usually leads to cognitive deficits. Similarly, epileptic seizure secondary to the rupture of cerebral aneurysm has also been reported to induce long-term cognitive function decline (Taufique et al., 2016). Hence, these confounding factors should be considered together to better understand the intrinsic network mechanisms of cognitive dysfunction after aneurysmal SAH and to accurately provide characteristic brain network markers for that trouble.

As the ACoA aneurysms locate in the anterior interhemispheric region, the medial prefrontal cortex (mPFC) is theoretically more susceptible to mechanical insult due to its close distance in anatomy when an aneurysm ruptures. The medial superior frontal gyrus (SFGmed) is a principal component of mPFC, which is involved in a variety of cognitive processes (Rolls et al., 2022). Therefore, we recently set the SFGmed as the region of interest (ROI) to perform a seed-based analysis and found significantly decreased resting-state FC of the SFGmed in patients with ruptured ACoA aneurysm. Notably, resting-state images of these patients were acquired after surgical clipping or endovascular coiling. Although the quality control of these imaging data was accomplished according to standard procedures, we should not completely ignore the effect of metal artifacts on fMRI data analysis (Khursheed et al., 2011). Furthermore, the SFGmed consists of presupplementary motor area and supplementary motor area, which play an important role in cognitive control and motor, respectively, indicating different roles of subregions (Zhang et al., 2012). Therefore, another brain region involvement of cognitive function, simultaneously distant from the aneurysm, and capable of functionally similar anatomical subregions may be more preferred.

The hippocampus is generally considered one of the brain regions most affected by aneurysmal SAH and is closely correlated with follow-up cognitive function decline, especially memory loss (Wostrack et al., 2014; Veldeman et al., 2017). Accumulating evidence from the SAH model of animal and neuroimaging studies has revealed that patients following the rupture of cerebral aneurysms present structural and functional changes in the hippocampus (Bendel et al., 2009; Sherchan et al., 2011; Wostrack et al., 2014), including structural atrophy, white matter degeneration, and hypoactivity (Wostrack et al., 2014; Cho and Jang, 2020). In our previous study, decreased FC between the hippocampus and the SFGmed was found in patients after the rupture of ACoA aneurysm, which was also extensively demonstrated in abundant studies concerning cognitive function. In addition, published studies have revealed that hippocampal activity was increased after running training or non-invasion brain stimulation (Huiskamp et al., 2020; Niu et al., 2022), suggesting an ability of neuroplasticity. In addition, neuromodulation targeting directly the hippocampus was considered a potential and promising alternative method to some non-acoustic brain stimulation modalities (Huang et al., 2022). Taken together, investigating the hippocampal resting-state FC in patients with a history of ACoA aneurysm rupture is reasonable and meaningful.

Therefore, this study is an extension of our previous study on functional brain network in patients after the rupture of ACoA aneurysm. The aim of this study is to explore the alterations of bilateral hippocampal connectivity in patients with ruptured ACoA aneurysm and their relationship with impaired cognitive function. We hypothesized the decline in hippocampal connectivity in patients with SAH due to ruptured ACoA aneurysm as compared to healthy controls, and abnormalities of some network features were related to their cognitive performance.

Materials and methods

Participants

We recruited patients with a history of ACoA aneurysm rupture for more than 6 months from the database of the First Affiliated Hospital of Fujian Medical University. Other inclusion criteria were age ranging from 35 to 70 years old and normal cognitive function before the SAH onset. Exclusion criteria were (1) neuropsychiatric diseases or previous stroke; (2) occurrence of epileptic seizure or delayed cerebral ischemia during hospitalization; and 3) hydrocephalus secondary to SAH. The original participants consisted of 27 (16 males, mean age 56.5 years, range 36–74) patients and 20 (11 males, mean age 53.3 years, range 49–68) age- and sex-matched healthy controls. All participants were right-handed. The local Ethics Committee approved this study, and all subjects gave their written informed consent.

MRI acquisition

All structural imaging and resting-state fMRI scanning were obtained by the same 3.0-T imaging scanner (Siemens Medical Solutions, Germany). T1-weighted structural images were acquired with the following parameters: repetition time (TR) = 2,300 ms, echo time (TE) = 3.09 ms, field of view (FOV) = 256 × 240 mm, flip angle = 9°, matrix = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm^3, 192 sagittal slices, thickness = 1 mm, and spaced = 0.5 mm. Earplugs and foam padding were used to minimize scanner noise and restrict head motion. When the resting-state fMRI acquisition starts, individuals were asked to stay awake and to think of nothing. Resting-state data were collected with the following parameters: TE = 30 ms, TR = 3,000 ms, flip angle = 90°, FOV = 240 × 240 mm, matrix = 80 × 80, voxel size = 3.0 × 3.0 × 3.4 mm^3, 50 slices with no gap, and thickness = 3.4 mm. A total of 205 time points was collected for individuals, and the fMRI data were acquired over 10 min. All participants were inspected by a radiologist to exclude morphological abnormalities.

Assessment of cognitive function

Cognitive function assessment was carried out after fMRI acquisition by two researchers who were blinded to this study. According to a previous report (Kim et al., 2021), the Subjective Memory Complaints Questionnaire (SMCQ) and the Montreal Cognitive Assessment (MoCA) were used to measure subjective memory problems and cognitive status, respectively.

Data preprocessing

Resting-state data preprocessing was performed by the Data Processing Assistant for Resting-State fMRI (DPARSF; http://restfmri.net/forum/DPARSF). The first 10 time points of fMRI data were discarded from the analysis in consideration of magnetization stabilization and the adaption of subjects to the scanning environment. Standard preprocessing steps were performed as previously reported, including the following: (1) slice timing (reference slice was the middle slice); (2) head motion correction; (3) spatially normalized to the Montreal Neurological Institute template (voxel size was resampled to 2 mm isotropic voxels); (4) smoothing with a Gaussian filter by 8 mm full width at half-maximum; (5) linear detrending; (6) bandpass temporal filtering (0.01–0.08 Hz); and (7) regressing

FIGURE 1
Regions of interest. The left hippocampus and right hippocampus labeling with color. L, left; R, right.

out nuisance covariates (Friston 24 head motion parameters, whiter matter signal, and cerebrospinal fluid signal).

Then, binary masks of the left hippocampus and the right hippocampus were chosen to set as seed regions (Figure 1). The Anatomical Automatic Labeling atlas was used to define the bilateral hippocampus. Seed-based analyses were performed. Mean time courses from all voxels within the unilateral hippocampus were extracted and used as reference time courses. The Pearson correlation coefficient was calculated between the mean time courses of each reference and voxel. Subsequently, Fisher's z transformation was applied to normalize the original correlation maps. The FC maps of the two regions were established and then analyzed in SPM12 using the analysis of variance model for calculating the difference between group-level functional maps. Brain regions were considered significant within a threshold of $p < 0.05$ after the false discovery rate was corrected for multiple comparisons and cluster size of >50.

Statistical analysis

Data were represented as the mean ± standard deviation and analyzed by using SPSS version 20.0. Independent sample *t*-test and chi-square test were used to evaluate differences in demographic and clinical characteristics. The Mann–Whitney *U*-test was used to analyze the nonparametric data. A two-tailed Pearson's correlation analysis was used to obtain the correlations between the FC strength values of the significant brain regions and the cognitive scores. The significance level was set to 0.05.

Results

Demographic and clinical characteristics of the subjects

All the participants underwent MRI scanning, while one subject in each group was excluded due to excessive head motion during fMRI scanning. Mean interval between aneurysm rupture and MRI acquirement was 23.9 months. The clinical and demographic features of the remaining subjects are shown in Table 1. There was no significant difference in age, sex, and education level.

Comparisons of the intrinsic connectivity between the two groups

The seed-to-voxel FC analyses showed similar changes in the brain network of bilateral hippocampus. Specifically, when the left hippocampus was defined as ROI, reduction in intrinsic connectivity was found in bilateral anterior cingulate cortex (ACC), bilateral middle cingulate cortex (MCC), bilateral SFGmed, and left ITG in the group of ruptured ACoA aneurysm as compared to the healthy controls. Conversely, significantly

TABLE 1 Clinical features of all the participants.

	Patients with ruptured ACoA aneurysm	Controls	*P* value
Age (year)	57.3 ± 9.8	53.3 ± 7.2	0.12
Gender (male/female)	15/11	10/9	0.77
Education (years)	9.1 ± 4.3	9.4 ± 4.1	0.623
Hunt-Hess on admission			
<3	23	-	
3	2	-	
>3	1	-	
Size of aneurysm			
≤5 mm	12	-	
5–10 mm	13	-	
>10 mm	1	-	
Aneurysm treatment			
Coiling	8	-	
Clipping	18	-	
MoCA	23.88 ± 5.37	29.42 ± 0.84	<0.01
SMCQ	4.16 ± 3.88	0.11 ± 0.32	<0.001

The values were represented as mean ± standard deviation. ACoA, anterior communicating artery; MoCA, Montreal Cognitive Assessment; SMCQ, Subjective Memory Complaints Questionnaire.

increased functional brain connectivity was observed between the left hippocampus and the bilateral insula (Figure 2 and Table 2). Similar to the results of the left hippocampus-based FC analysis, decreased cerebral intrinsic connectivity in bilateral ACC, bilateral MCC, bilateral SFGmed, and left ITG was also uncovered with a seed placed in the right hippocampus. In addition, we revealed FC strength decline in the right hippocampus-left fusiform gyrus, and the right hippocampus-left middle temporal gyrus. Compared with healthy controls, hippocampal hyperconnectivity with bilateral insula and left hippocampus was found in patients with ruptured ACoA aneurysm (Figure 3 and Table 3).

Correlations between FC strength and cognitive function in the patients' group

We then performed correlation analyses between hippocampal connectivity and cognitive or memory performance in patients suffering from the rupture of ACoA aneurysm. As shown in Figure 4, a connection between the left hippocampus and the left ACC was found to be positively correlated with the MoCA total score. In addition, we also discovered that the strength of intrinsic connectivity between the right hippocampus and multiple brain regions was negatively correlated with SMCQ scores, including left temporal pole, right ITG, left orbital part of inferior frontal gyrus (ORBinf), and right ORBinf ($r = -0.421$, $r = -0.443$, $r = -0.453$, and $r = -0.479$, respectively).

Discussion

To the best of our knowledge, this is the first study to explore the hippocampal connectivity with respect to patients with ruptured ACoA aneurysm. Consistent with our hypothesis, this study primarily uncovered significantly decreased FC in multiple brain regions, including bilateral ACC, bilateral MCC, bilateral SFGmed, and left ITG. Besides, the altered patterns of connectivity were largely overlapped in bilateral hippocampus. Conversely, the enhancement of connectivity strength between the hippocampus and the insula was found in the ACoA aneurysm group in comparison with healthy controls. Furthermore, hippocampal resting hypoconnectivity with several brain regions was significantly correlated with their memory loss.

Patients after the rupture of ACoA aneurysms are frequently reported to be associated with follow-up cognitive dysfunction, so the cognitive rehabilitation is necessary for them. Currently, functional brain network-directed neuromodulation has shown great promise in various cognitive disorders (Gimbel et al., 2021; Kolskår et al., 2021; Clancy et al., 2022). Several fMRI studies have shed light on this issue, and they revealed abnormalities of cognition-related networks in patients with aneurysmal SAH as compared to the control group. However, patients enrolled in these studies suffer from different locations of aneurysm that might cause diverse structural and functional brain damages. Meanwhile, some common factors contributing to cognitive declines such as hydrocephalus and epileptic seizure were also not ruled out. Therefore, to date, effective treatment options are

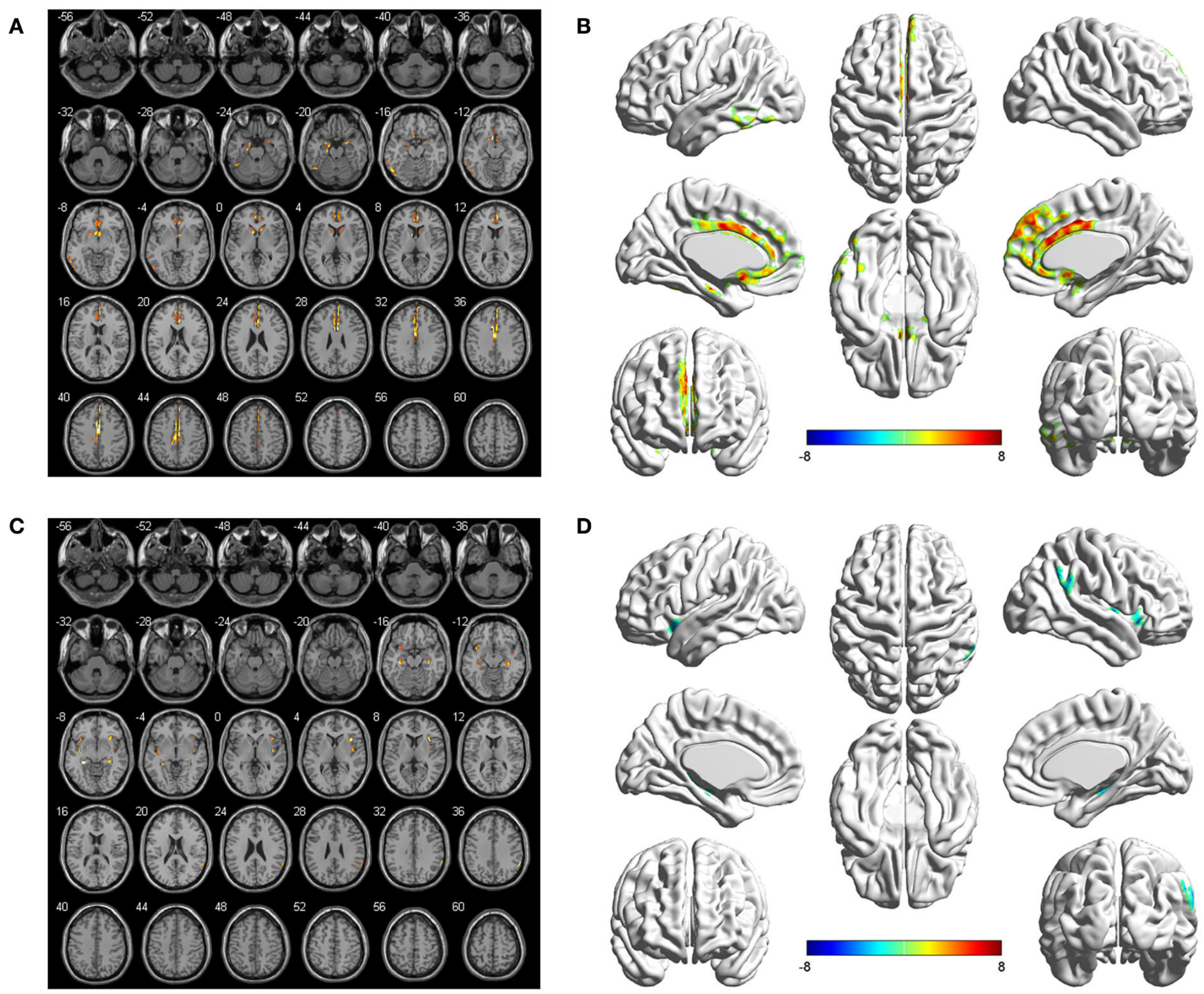

FIGURE 2
Differences in the left hippocampal connectivity between patients with ruptured ACoA aneurysm and healthy controls. Compared with the control group, brain regions labeling with color indicate decreased (upper panel) or increased functional connectivity (lower panel) in patients with ruptured ACoA aneurysm. Results were displayed in 2D **(A,C)** and 3D **(B,D)**, respectively. The displaying threshold was set to $p < 0.05$, false discovery rate corrected, and cluster size >50. Details of abnormal connectivity regions are shown in Table 2. ACoA, anterior communicating artery.

still lacking due to the deficiency of knowledge about neural mechanisms. These confounding factors were well controlled in our recent resting-state fMRI study, and we provided evidence of aberrant SFGmed-based functional networks in patients with ruptured ACoA aneurysm. In a previous study, subjective memory complaints were determined in 44.4% of all patients. Hippocampus is one of the most recognized core regions responsible for memory function, and it is particularly susceptible to aneurysmal SAH insult. In addition, we noticed artifacts caused by surgical materials that were adjacent to the SFGmed. Given that, we extended to investigate the alterations of hippocampal connectivity in these patients following the rupture of ACoA aneurysm.

Consistent with our previous findings, intrinsic connectivity between hippocampus and SFGmed, a subdivision of mPFC, was also decreased in patients after the rupture of ACoA aneurysm in comparison with healthy controls. These two brain structures are known to regulate a variety of cognitive processes. Structural injury or functional hypoactivation of them has been linked to cognitive impairment underlying various neurologic diseases (Robin et al., 2015). Evidence from the FC analyses has also suggested that hippocampus–mPFC interactions are important to cognitive maps (Das and Menon, 2021; Zheng et al., 2021). Therefore, it is plausible that the neural activity of SFGmed and hippocampus decreases in synchrony in patients with ruptured ACoA.

TABLE 2 Brain regions showing significant differences of the left hippocampus-based functional connectivity in patients with ruptured ACoA as compared to the healthy controls.

Brain region	Number of voxels	Peak MNI coordinates			Peak T value
		X	Y	Z	
Middle and anterior cingulate cortex	689	−8	12	36	9.30
Medial surperior frontal gyrus	205	4	64	10	7.33
Left inferior temporal gyrus	51	−58	−44	−18	6.90
Right insula	84	38	18	6	−9.51
Left insula	53	−38	8	−12	−5.37

ACoA, anterior communicating artery; MNI, Montreal Neurological Institute.

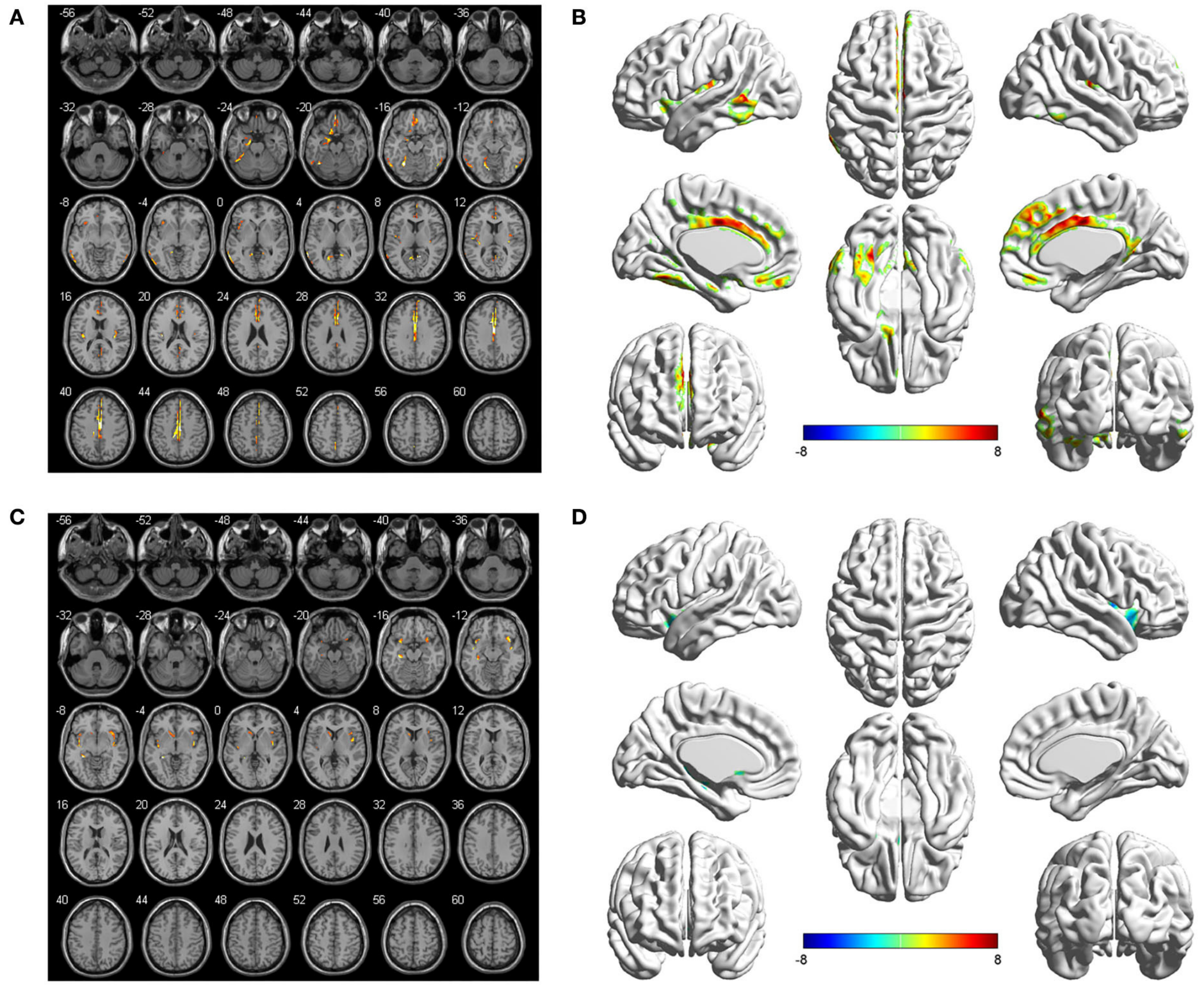

FIGURE 3
Differences in the right hippocampal connectivity between patients with ruptured ACoA aneurysm and healthy controls. Compared with the control group, brain regions labeling with color indicate decreased (upper panel) or increased functional connectivity (lower panel) in patients with ruptured ACoA aneurysm. Results were displayed in 2D **(A,C)** and 3D **(B,D)**, respectively. The displaying threshold was set to $p < 0.05$, false discovery rate corrected, and cluster size >50. Details of abnormal connectivity regions are shown in Table 2. ACoA, anterior communicating artery.

In this study, we found that the patients with aneurysmal SAH showed significantly lower FC with the bilateral ACC and MCC no matter which side of the hippocampus was set as a seed (Figures 2, 3). As we know, the cingulate gyrus and hippocampus are important components of the limbic system and the hippocampal pathway to ACC participating in the

TABLE 3 Brain regions showing significant differences of the right hippocampus-based functional connectivity in patients with ruptured ACoA as compared to the healthy controls.

Brain region	Number of voxels	Peak MNI coordinates			Peak T value
		X	Y	Z	
Left fusiform gyrus	96	−38	−58	−20	7.69
Left middle and inferior temporal gyrus	128	−64	−52	4	7.85
Middle and anterior cingulate cortex, medial surperior frontal gyrus	969	4	−16	46	11.11
Right insula	99	40	16	−12	−7.57
Left hippocampus	64	−32	−36	−8	−9.55
Left insula	93	−44	−2	−14	−7.10

ACoA, anterior communicating artery; MNI, Montreal Neurological Institute.

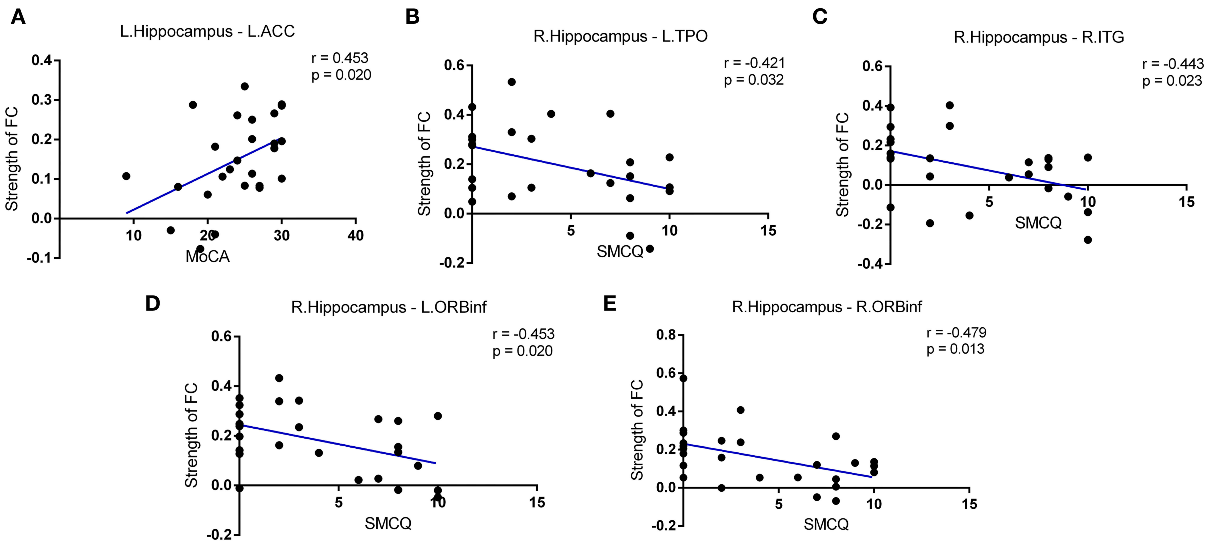

FIGURE 4
Correlations between intrinsic connectivity strength and cognitive function in patients after the rupture of ACoA aneurysm. **(A)** Positive correlation between MoCA scores and connection between left hippocampus-left ACC. Negative correlations between SMCQ scores and right hippocampus-left TPO **(B)**, right hippocampus-right ITG **(C)**, and right hippocampus-bilateral ORBinf **(D,E)** connectivity strength. ACoA, anterior communicating artery; MoCA, Montreal Cognitive Assessment; ACC, anterior cingulate cortex; SMCQ, Subjective Memory Complaints Questionnaire; ITG, inferior temporal gyrus; TPO, temporal pole; ORBinf, orbital part of inferior frontal gyrus.

formation of the Papez circuit in the human brain, which serves a principal function of memory retention and emotion control (Marchesi et al., 2022; Rolls et al., 2022). Evidence from animal studies suggests that hippocampal terminations innervated most of the excitatory neurons within ACC, suggesting strong excitatory effects on ACC neurons following hippocampal activity (Wang and Ikemoto, 2016; Wang et al., 2021). Predictably, if the hippocampus is compromised under pathological conditions, such as cerebral aneurysm rupture, the ACC is very likely to present hypoactivity. In agreement with this speculation, several diffusion tensor imaging studies of cerebral white matter changes in patients with SAH also provided robust structural evidence (Hong et al., 2012; Jang et al., 2014; Lee et al., 2020; Premat et al., 2021). For example, Jang et al. found injuries of the cingulum and fornix in patients after an ACoA aneurysm rupture, which were suggested to be associated with sustained memory impairment (Hong et al., 2012). In another research, the fractional anisotropy value and the volume of the mammillothalamic tract in the SAH group were significantly lower than that in the control subjects (Jang et al., 2014). Collectively, disruption of the Papez circuit in patients after the rupture of ACoA aneurysm may provide a crucial structural basis for hypoactivity between the hippocampus and cingulate gyrus.

Similar to the hippocampus, the main function of the insula is also related to intrinsic cognitive function. Consequently, low activity in the hippocampus and insula, and decreased connectivity between them, has been often linked to cognitive disorders. Conversely, the resting-state connectivity between each side of the hippocampus and bilateral insula was a significant increase in patients suffering from ruptured ACoA aneurysm in comparison with control subjects. Inconsistent findings of hypoconnectivity between the hippocampus and the insula in this study may be a compensatory mechanism for the abnormal Papez circuit caused by cognitive impairment. In addition, functional imaging studies have suggested that there exists abundant interinsular connectivity in the physiological state. This discovery partly explains the synchronized changes of the bilateral insular intrinsic connectivity.

There are several limitations in our study. First, extensive studies have provided evidence of differential connectivity patterns across the long axis of hippocampus, in which the anterior section of the hippocampus is associated with memory encoding and the posterior section of the hippocampus is associated with memory retrieval. In our study, although the left hippocampus and the right hippocampus have largely overlapped patterns of connectivity with other brain regions in patients with ACoA aneurysm in comparison with healthy controls, the anatomical and functional specialization of the hippocampus should be brought into focus. Second, memory loss is the main complaint of patients included in this study. Although we have used the SMCQ to assess the memory deficit and the MoCA scale to evaluate total cognitive function, scales for other cognitive domains preferably also need to be evaluated. Third, low connectivity of several brain regions within the Papez circuit was observed in patients after the rupture of ACoA aneurysm. However, undirected connection analysis exists inherent limitations. In the future, it is necessary to conduct further directed FC analysis that can better guide the neuromodulation treatment of cognitive impairment.

In summary, this study provides evidence of a decline in intrinsic connectivity between hippocampus and multiple brain regions in patients with a history of ruptured ACoA aneurysm. Most of the cortical hypoconnectivity is mainly located in the Papez circuit. Our findings implicate that decreased FC within the Papez circuit may be associated with cognitive impairment following the rupture of ACoA aneurysm, which we hope will contribute to future translational therapy options after aneurysmal SAH.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Local Ethics Committee of the First Affiliated Hospital of Fujian Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FC, DK, and DW conceived and designed the experiments. FC, LD, and JC drafted the manuscript and participated in data processing and statistical analysis. DK revised the manuscript. YK performed the MRI scanning. TY, LY, and YL assessed the cognitive function. FC, ZL, DK, TY, YK, YL, LY, DW, JC, and LD helped to collect data on patients and healthy controls. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Adhikari, M. H., Hacker, C. D., Siegel, J. S., Griffa, A., Hagmann, P., Deco, G., et al. (2017). Decreased integration and information capacity in stroke measured by whole brain models of resting state activity. *Brain*. 140, 1068–1085. doi: 10.1093/brain/awx021

Baldassarre, A., Ramsey, L., Rengachary, J., Zinn, K., Siegel, J. S., Metcalf, N. V., et al. (2016). Dissociated functional connectivity profiles for motor and attention deficits in acute right-hemisphere stroke. *Brain*. 139, 2024–2038. doi: 10.1093/brain/aww107

Beeckmans, K., Crunelle, C., Van den Bossche, J., Dierckx, E., Michiels, K., Vancoillie, P., et al. (2020). Cognitive outcome after surgical clipping versus endovascular coiling in patients with subarachnoid hemorrhage due to ruptured anterior communicating artery aneurysm. *Acta Neurol. Belg*. 120, 123–132. doi: 10.1007/s13760-019-01245-w

Bendel, P., Koivisto, T., Niskanen, E., Kononen, M., Aikia, M., Hanninen, T., et al. (2009). Brain atrophy and neuropsychological outcome after treatment of ruptured anterior cerebral artery aneurysms: a voxel-based morphometric study. *Neuroradiology*. 51, 711–722. doi: 10.1007/s00234-009-0552-5

Cho, M. K., and Jang, S. H. (2020). Diffusion tensor imaging studies on spontaneous subarachnoid hemorrhage-related brain injury: a mini-review. *Front. Neurol*. 11, 283. doi: 10.3389/fneur.2020.00283

Chung, D., Oka, F., Jin, G., Harriott, A., Kura, S., Aykan, S., et al. (2021). Subarachnoid hemorrhage leads to early and persistent functional connectivity and behavioral changes in mice. *J. Cereb. Blood Flow Metab*. 41, 975–985. doi: 10.1177/0271678X20940152

Clancy, K., Andrzejewski, J., You, Y., Rosenberg, J., Ding, M., and Li, W. (2022). Transcranial stimulation of alpha oscillations up-regulates the default mode network. *Proc. Natl. Acad. Sci. USA*. 119. doi: 10.1073/pnas.2110868119

Das, A., and Menon, V. (2021). Asymmetric frequency-specific feedforward and feedback information flow between hippocampus and prefrontal cortex during verbal memory encoding and recall. *J. Neurosci*. 41, 8427–8440. doi: 10.1523/JNEUROSCI.0802-21.2021

Fox, M. D., Buckner, R. L., Liu, H., Chakravarty, M. M., Lozano, A. M., and Pascual-Leone, A. (2014). Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. *Proc. Natl. Acad. Sci. USA*. 111, E4367–4375. doi: 10.1073/pnas.1405003111

Gimbel, S., Ettenhofer, M., Cordero, E., Roy, M., and Chan, L. (2021). Brain bases of recovery following cognitive rehabilitation for traumatic brain injury: a preliminary study. *Brain Imaging Behav*. 15, 410–420. doi: 10.1007/s11682-020-00269-8

Hong, J., Choi, B., Chang, C., Kim, S., Jung, Y., Byun, W., et al. (2012). Injuries of the cingulum and fornix after rupture of an anterior communicating artery aneurysm: a diffusion tensor tractography study. *Neurosurgery*. 70, 819–823. doi: 10.1227/NEU.0b013e3182367124

Huang, Y., Wen, P., Song, B., and Li, Y. (2022). Numerical investigation of the energy distribution of low-intensity transcranial focused ultrasound neuromodulation for hippocampus. *Ultrasonics*. 124, 106724. doi: 10.1016/j.ultras.2022.106724

Huiskamp, M., Moumdjian, L., van Asch, P., Popescu, V., Schoonheim, M., Steenwijk, M., et al. (2020). A pilot study of the effects of running training on visuospatial memory in ms: a stronger functional embedding of the hippocampus in the default-mode network? *Mult. Scler.*. 26, 1594–1598. doi: 10.1177/1352458519863644

Ito, H., Morishima, H., Onodera, H., Wakui, D., Uchida, M., Sase, T., et al. (2015). Acute phase endovascular intervention on a pseudoaneurysm formed due to rupture of an anterior communicating artery aneurysm. *J. Neurointerv. Surg*. 7, e9. doi: 10.1136/neurintsurg-2013-011006.rep

Jang, S. H., Choi, B. Y., Kim, S. H., Chang, C. H., Jung, Y. J., and Kwon, H. G. (2014). Injury of the mammillothalamic tract in patients with subarachnoid haemorrhage: a retrospective diffusion tensor imaging study. *BMJ Open*. 4, e005613. doi: 10.1136/bmjopen-2014-005613

Khursheed, F., Rohlffs, F., Suzuki, S., Kim, D. H., and Ellmore, T. M. (2011). Artifact quantification and tractography from 3t mri after placement of aneurysm clips in subarachnoid hemorrhage patients. *BMC Med. Imaging*. 11, 19. doi: 10.1186/1471-2342-11-19

Kim, J., Shin, E., Han, K., Park, S., Youn, J., Jin, G., et al. (2021). Efficacy of smart speaker-based metamemory training in older adults: Case-control cohort study. *J. Med. Internet Res*. 23, e20177. doi: 10.2196/20177

Kolskår, K., Richard, G., Alnaes, D., Dørum, E., Sanders, A., Ulrichsen, K., et al. (2021). Reliability, sensitivity, and predictive value of fmri during multiple object tracking as a marker of cognitive training gain in combination with tdcs in stroke survivors. *Hum. Brain Mapp*. 42, 1167–1181. doi: 10.1002/hbm.25284

Lee, S. J., Kim, M. S., and Jang, S. H. (2020). White matter abnormalities in spontaneous subarachnoid hemorrhage: a tract-based spatial statistics study. *Stroke*. 51, e246–e249. doi: 10.1161/STROKEAHA.120.029996

Maher, M., Churchill, N. W., de Oliveira Manoel, A. L., Graham, S. J., Macdonald, R. L., and Schweizer, T. A. (2015). Altered resting-state connectivity within executive networks after aneurysmal subarachnoid hemorrhage. *PLoS ONE*. 10, e0130483. doi: 10.1371/journal.pone.0130483

Marchesi, O., Bonacchi, R., Valsasina, P., Rocca, M., and Filippi, M. (2022). Resting state effective connectivity abnormalities of the papez circuit and cognitive performance in multiple sclerosis. *Mol. Psychiatry*. doi: 10.1038/s41380-022-01625-4. [Epub ahead of print].

Mikell, C. B., Banks, G. P., Frey, H. P., Youngerman, B. E., Nelp, T. B., Karas, P. J., et al. (2015). Frontal networks associated with command following after hemorrhagic stroke. *Stroke*. 46, 49–57. doi: 10.1161/STROKEAHA.114.007645

Neifert, S., Chapman, E., Martini, M., Shuman, W., Schupper, A., Oermann, E., et al. (2021). Aneurysmal subarachnoid hemorrhage: the last decade. *Transl. Stroke Res*. 12, 428–446. doi: 10.1007/s12975-020-00867-0

Nelson, S., Edlow, B. L., Wu, O., Rosenthal, E. S., Westover, M. B., and Rordorf, G. (2016). Default mode network perfusion in aneurysmal subarachnoid hemorrhage. *Neurocrit. Care*. 25, 237–242. doi: 10.1007/s12028-016-0244-z

Niu, X., Yu, K., and He, B. (2022). Transcranial focused ultrasound induces sustained synaptic plasticity in rat hippocampus. *Brain Stimul*. 15, 352–359. doi: 10.1016/j.brs.2022.01.015

Premat, K., Azuar, C., Galanaud, D., Jacquens, A., Dormont, D., Degos, V., et al. (2021). *Pathomechanisms behind cognitive disorders following ruptured anterior communicating* aneurysms: a diffusion tensor imaging study. *J. Neuroradiol*. 49, 187–92. doi: 10.1016/j.neurad.2021.09.005

Robin, J., Hirshhorn, M., Rosenbaum, R., Winocur, G., Moscovitch, M., and Grady, C. (2015). Functional connectivity of hippocampal and prefrontal networks during episodic and spatial memory based on real-world environments. *Hippocampus*. 25, 81–93. doi: 10.1002/hipo.22352

Rolls, E., Deco, G., Huang, C., and Feng, J. (2022). *The human orbitofrontal cortex, vmpfc, and anterior cingulate cortex effective connectome: Emotion*, memory, and action. *Cerebral Cortex*. doi: 10.1093/cercor/bhac070. [Epub ahead of print].

Sherchan, P., Lekic, T., Suzuki, H., Hasegawa, Y., Rolland, W., Duris, K., et al. (2011). Minocycline improves functional outcomes, memory deficits, and histopathology after endovascular perforation-induced subarachnoid hemorrhage in rats. *J. Neurotrauma*. 28, 2503–2512. doi: 10.1089/neu.2011.1864

Siegel, J. S., Ramsey, L. E., Snyder, A. Z., Metcalf, N. V., Chacko, R. V., Weinberger, K., et al. (2016). Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Proc. Nat. Acad. Sci*. 113, E4367–E4376. doi: 10.1073/pnas.1521083113

Su, J., E. T., Guo, Q., Lei, Y., and Gu, Y. (2018). Memory deficits after aneurysmal subarachnoid hemorrhage: a functional magnetic resonance imaging study. *World Neurosurg*. 111, e500–e506. doi: 10.1016/j.wneu.2017.12.102

Taufique, Z., May, T., Meyers, E., Falo, C., Mayer, S., Agarwal, S., et al. (2016). Predictors of poor quality of life 1 year after subarachnoid hemorrhage. *Neurosurgery*. 78, 256–264. doi: 10.1227/NEU.0000000000001042

Veldeman, M., Coburn, M., Rossaint, R., Clusmann, H., Nolte, K., Kremer, B., et al. (2017). Xenon reduces neuronal hippocampal damage and alters the pattern of microglial activation after experimental subarachnoid hemorrhage: a randomized controlled animal trial. *Front. Neurol*. 8, 511. doi: 10.3389/fneur.2017.00511

Wang, D., and Ikemoto, S. (2016). Coordinated interaction between hippocampal sharp-wave ripples and anterior cingulate unit activity. *J. Neurosci*. 36, 10663–10672. doi: 10.1523/JNEUROSCI.1042-16.2016

Wang, J., John, Y., and Barbas, H. (2021). Pathways for contextual memory: the primate hippocampal pathway to anterior cingulate cortex. *Cerebral cortex*. 31, 1807–1826. doi: 10.1093/cercor/bhaa333

Wostrack, M., Friedrich, B., Hammer, K., Harmening, K., Stankewitz, A., Ringel, F., et al. (2014). Hippocampal damage and affective disorders after treatment of cerebral aneurysms. *J. Neurol*. 261, 2128–2135. doi: 10.1007/s00415-014-7464-y

Zhang, S., Ide, J., and Li, C. (2012). Resting-state functional connectivity of the medial superior frontal cortex. *Cerebral Cortex*. 22, 99–111. doi: 10.1093/cercor/bhr088

Zheng, L., Gao, Z., McAvan, A., Isham, E., and Ekstrom, A. (2021). Partially overlapping spatial environments trigger reinstatement in hippocampus and schema representations in prefrontal cortex. *Nat. Commun*. 12, 6231. doi: 10.1038/s41467-021-26 560-w

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Postoperative delirium in geriatric patients with hip fractures

Yang Chen[1,2], Shuai Liang[1,2], Huiwen Wu[1,2], Shihao Deng[1,2], Fangyuan Wang[1,2], Ciren Lunzhu[3] and Jun Li[1,2]*

[1]Department of Orthopedics, The Second Hospital of Anhui Medical University, Hefei, China, [2]Institute of Orthopedics, Research Center for Translational Medicine, The Second Hospital of Anhui Medical University, Hefei, China, [3]Department of Orthopedics, Shannan City People's Hospital, Shannan, China

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EDITED BY
Yiying Zhang,
Massachusetts General Hospital and Harvard Medical School, United States

REVIEWED BY
Nikhil Tondehal,
Mount Sinai Beth Israel, United States
Li Cong,
Affiliated Hospital of Xuzhou Medical University, China

*CORRESPONDENCE
Jun Li
✉ efylijunpaper@163.com

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Postoperative delirium (POD) is a frequent complication in geriatric patients with hip fractures, which is linked to poorer functional recovery, longer hospital stays, and higher short-and long-term mortality. Patients with increased age, preoperative cognitive impairment, comorbidities, perioperative polypharmacy, and delayed surgery are more prone to develop POD after hip fracture surgery. In this narrative review, we outlined the latest findings on postoperative delirium in geriatric patients with hip fractures, focusing on its pathophysiology, diagnosis, prevention, and treatment. Perioperative risk prediction, avoidance of certain medications, and orthogeriatric comprehensive care are all examples of effective interventions. Choices of anesthesia technique may not be associated with a significant difference in the incidence of postoperative delirium in geriatric patients with hip fractures. There are few pharmaceutical measures available for POD treatment. Dexmedetomidine and multimodal analgesia may be effective for managing postoperative delirium, and adverse complications should be considered when using antipsychotics. In conclusion, perioperative risk intervention based on orthogeriatric comprehensive care is the most effective strategy for preventing postoperative delirium in geriatric patients with hip fractures.

KEYWORDS

postoperative delirium, geriatric patients, hip fractures, orthogeriatrics, prevention, treatment

Introduction

Osteoporotic hip fracture is an important public health concern, with a reported one-year mortality of 12.7% in geriatric patients (Aharonoff et al., 1997). It affects women more frequently than males (Brauer et al., 2009), most likely because post-menopausal women have a higher incidence of osteoporosis (Cummings and Melton, 2002). Hip fracture in geriatric patients is linked to poor functional prognosis and a high frequency of postoperative complications, such as postoperative delirium (POD), pneumonia, urinary tract infections, deep vein thrombosis, and bleeding (Fischer et al., 2021; Schrøder et al., 2022). A third of geriatric patients encounter one or more postoperative

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complications, and 7.2% of patients experience multiple complications (Merchant et al., 2005). It is reported that compared with senior patients without fractures, those with hip fractures had a higher rate of postoperative mental problems (Kuo et al., 2021).

Postoperative delirium (POD) is one of the most common complications in geriatric patients with hip fractures (Merchant et al., 2005). It is a postoperative cognitive disturbance defined by abrupt and variable impairment in attention and awareness, with reported incidences varying from 4.7 to 74% (Maldonado, 2017; Flikweert et al., 2018; Connolly et al., 2020). POD usually occurs between postoperative days 2–5 (Jin et al., 2020). When patients develop POD, it is usually the most distressing component of the perioperative experience, adding to their personal, medical, and financial burdens (Leslie et al., 2008). POD is associated with increased hospital length of stay (Hecht et al., 2019), poor rehabilitation outcomes, such as impaired functional and cognitive recovery, even the onset of new dementia (Low et al., 2021; Meyer et al., 2021; Pereira et al., 2021), worsened mobility (Ouellet et al., 2019), and a higher risk of both short-term and long-term mortality (Bai et al., 2020; Liu et al., 2021). Additionally, postoperative delirium is a strong indicator for nursing home admission (de Jong et al., 2019). In light of these poor consequences and the high prevalence of POD in geriatric patients with hip fractures, early identification of patients at risk as well as implementation of prophylactic measures to reduce the frequency of POD is extremely desirable (Smith et al., 2017). The underlying pathophysiology of postoperative delirium in geriatric patients with hip fractures is still unclear, most studies focus on the involvement of neuroinflammation, neurotransmitters, and metabolism abnormality. Currently, there are still few effective measures for POD treatment. The most effective approach to preventing POD is to minimize its risk factors, and several risk prediction tools have been developed for risk stratification in geriatric patients with hip fractures. Additionally, avoidance of perioperative benzodiazepine administration and comprehensive multidisciplinary care play a significant role in POD management.

This review aims to describe current research advances on postoperative delirium in geriatric patients with hip fractures and to provide effective and feasible strategies for the prevention and treatment of POD.

Epidemiology and risk factors

Despite that the prevalence of POD in the general surgical population is only 2–3%, it can occur in up to 50–70% of high-risk patient groups (Watne et al., 2016). In particular, hip fracture surgery is associated with up to 70–80% risk of postoperative delirium. There are several reasons for this: a hip fracture is frequently seen in elderly patients who are frail; perioperative pain is a major concern; and the surgery is typically performed in an emergency setting with little chance for preoperative optimization (Jin et al., 2020).

The perioperative risk factors for POD in geriatric patients with hip fractures can be predisposing and precipitating. As is shown in the literature (Smith et al., 2017; Swarbrick and Partridge, 2022; Wittmann et al., 2022), predisposing risk factors include increased age, sensorial deficits, prior cognitive impairment, multimorbidity, malnutrition, and frailty, as well as precipitating risk factors including surgical procedures, ventilation time, and intensive care stay. In addition, there are also several independent predictors for POD in geriatric patients with hip fractures (Koskderelioglu et al., 2017; Mosk et al., 2017; Smith et al., 2017; Yang et al., 2017; Wang et al., 2018; Chen et al., 2020; Tantardini et al., 2020; Xing et al., 2020; Zhou et al., 2021; Table 1).

Increased age is an independent risk factor associated with POD in geriatric patients with hip fractures. Patients older than 71.5 years of age with hip fractures have a more than threefold increased risk of developing postoperative delirium (Xing et al., 2020), and the hypoactive subtype is more likely to develop in people over the age of 80 (Stagno et al., 2004). This may be because the risk of endothelial dysfunction and atherosclerosis increases with age, putting elderly patients at increased risk of cerebral embolism (Rudolph et al., 2009). Additionally, the age-related loss of cholinergic reserve is also a significant contributor. Interestingly, males are more prone to develop delirium after hip fracture surgery (Yang et al., 2017; Haynes et al., 2021), despite women having a larger frequency of hip fractures (Edelstein et al., 2004).

TABLE 1 Risk factors and predictors for postoperative delirium in geriatric patients with hip fractures.

Preoperative risk factors and predictors	Advanced age (> 75 years or 71.5 years)
	Male
	ASA classification (> 2 level)
	Institutionalization
	Cognitive impairment or dementia
	Low mini-mental state examination score
	Multiple comorbidities (e.g., heart failure, diabetes, stoke, depression)
	Hyponatremia or hypernatremia
	Acetylcholine <7.75 mmol/l or choline acetyltransferase <30.15 pg./ml
	Low hemoglobin levels
	Low prognostic nutritional index level
Intraoperative risk factors and predictors	Total hip arthroplasty
	Intraoperative bleeding
	High amount of blood transfusion
Postoperative risk factors and predictors	Pneumonia or a urinary tract infection
	Pain
	Morphine usage
	Postoperative acute kidney injury

ASA, American Society of Anesthesiologists.

A 20–45% risk of postoperative delirium is linked to emergency surgery, which is 1.5–3 times higher than the risk for comparable elective surgery (Ansaloni et al., 2010; Chaiwat et al., 2019). Surgery type may have an influence on POD in geriatric patients with hip fractures. Patients who underwent total hip arthroplasty were more likely to develop POD (OR 2.21; 95% CI 1.16–4.22; Bruce et al., 2007; Yang et al., 2017). The location of the fracture (transcervical fracture, intertrochanteric fracture, and subtrochanteric fracture) seems has no association with the occurrence of POD, according to existing literature (Smith et al., 2017; Xing et al., 2020). Preoperative dementia is also an independent risk factor for POD in elderly patients with hip fractures. Moreover, postoperative delirium plays moderation and mediation effects between preoperative dementia and postoperative adverse events. The effects of preoperative dementia on mortality, readmission, and revision surgery were dramatically enhanced by postoperative delirium (Haynes et al., 2021). ASA physical status classes 2 and 3 and the number of medical comorbidities were significant variables in assessing the risk of POD. The modified Charlson's Comorbidity Index (CCI) is a commonly used tool for assessment of medical comorbidities (Charlson et al., 1987). It is reported that 94% of hip fracturs patients with POD were associated with at least a medical complication (Mullen and Mullen, 1992). Postoperative infection, such as urinary tract infection and pneumonia, can also increase the POD risk in hip fracture patient. It may cause significant delays in cognitive processing speed, especially when it comes to memory retrieval (Bucks et al., 2008). Additionally, the risk of developing POD is increased by impaired vision or hearing because the elderly person cannot properly perceive the stimuli in the hospital environment (Staus, 2011).

Pathophysiological changes

The pathophysiology of postoperative delirium in elderly patients with hip fractures has not been entirely explored yet, and widely accepted hypotheses focus on the involvement of neuroinflammation, neurotransmitters, and metabolic abnormality.

Neuroinflammation

One generally accepted pathophysiological explanation for postoperative delirium in elderly patients with hip fractures is neuroinflammation (Figure 1). Surgical injuries act on Toll-like receptors through damage-associated molecular patterns or pathogen-associated molecular patterns to initiate an intracellular inflammatory response, and inflammatory mediators such as TNF - α are released into the brain, causing aseptic inflammation in the CNS, resulting in POD (Alam et al., 2018). Previous studies have shown that trauma caused by fracture and surgery is associated with increased perioperative systemic inflammatory mediators (Cape et al., 2014; Neerland et al., 2016). These peripheral inflammatory mediators are transported to the brain *via* three primary pathways: (a) Peripheral inflammation causes the loss of structural and functional integrity of the blood–brain barrier. Thus, inflammatory factors can cross the blood–brain barrier and enter the brain through capillary epithelial cells (Yang et al., 2017); (b) There are transporters in the afferent nerves of the vagus, which can directly transport the peripheral inflammatory substances to the corresponding nerve nuclei; (c) The increased concentration of inflammatory factors in plasma makes it possible for the inflammatory mediators to diffuse to brain tissue through the concentration gradient. The accumulation of central inflammatory mediators leads to the disruption of the large-scale neural networks in the brain, such as suppression of hippocampal plasticity and neurogenesis (Ekdahl et al., 2003; Prieto et al., 2019), neurotoxicity, and neuronal apoptosis (Tian et al., 2018). These damages ultimately result in the occurrence and progress of POD.

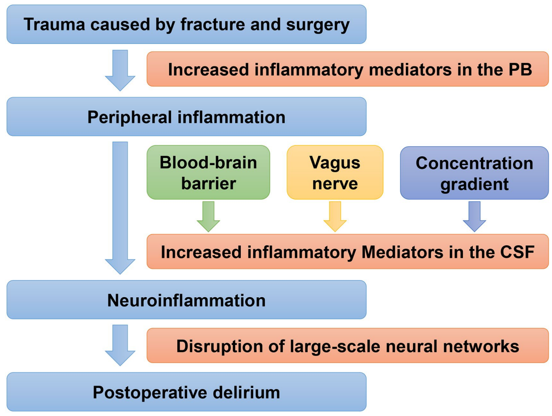

FIGURE 1
Neuroinflammation mechanism of postoperative delirium in geriatric patients with hip fractures. PB, peripheral blood; CSF, cerebrospinal fluid. Trauma caused by fracture and surgery is associated with increased systemic inflammatory mediators, which are transported from the periphery to the brain *via* three primary pathways, resulting in neuroinflammation, and finally lead to POD.

Neurotransmitters

The alteration in neurotransmitters is also a possible mechanism for the occurrence and development of POD, among which the most prominent is the deficiency or dysfunction of the cholinergic system (Adam et al., 2020). A prospective observational study demonstrated that the level of acetylcholine in the cerebral spinal fluid was significantly decreased in geriatric patients with postoperative cognitive dysfunction (Chen et al., 2020). Moreover, the cholinergic system interacts significantly with other neurotransmitter systems, and POD is also correlated with the malfunction of these other neurotransmitter systems. Particularly, acetylcholine deficiency is accompanied by an excess of dopamine, which is linked to critical postoperative delirium (Trzepacz, 2000). However, a randomized controlled trial of 261 patients found that postoperative administration of physostigmine did not affect the prevention of POD after liver resection (Spies et al., 2021), which may indicate the underlying mechanisms leading to neurotransmitter alterations still need to be explored to find effective drug targets.

Neurovascular changes

Postoperative delirium is more likely to occur in elderly patients with neurovascular changes. A review explored the association of neurodegenerative and neurovascular changes with the occurrence of POD (Kant et al., 2017), and it found that neurovascular changes, such as white-matter hyperintensities (Hatano et al., 2013; Root et al., 2013), preoperative old cerebral infarct (Otomo et al., 2013; Maekawa et al., 2014) and markers of white matter integrity (Shioiri et al., 2010; Cavallari et al., 2016), appear to be consistently associated with the occurrence of POD. Furthermore, these changes may even help to identify patients at increased risk of POD. Kyeong et al. (2018) developed a prediction model for estimating the probability of POD in geriatric patients with femoral neck fractures, with a correct classification rate of 86%. This model consists of three neural predisposing factors: the neuroticism score, the amplitude of low-frequency fluctuation in the dorsolateral prefrontal cortex, and the density of gray matter in the caudate or suprachiasmatic nucleus. It may accurately predict the likelihood of postoperative delirium by reflecting the fundamental pathophysiology.

Metabolic abnormality

Metabolic abnormality is shown to be associated with the occurrence and progression of POD. In a metabonomic study of geriatric hip fracture patients, it was discovered that, while glycolysis products were higher in POD patients after surgery, levels of ω3 and ω6 fatty acids were lower in those both before and after surgery, as well as intermediate levels of the tricarboxylic cycle and the branched-chain amino acid/aromatic amino acid ratio (Guo et al., 2019). These metabolic abnormalities most likely reduce the ability of the brain to provide neuroprotection and take part in neuroinflammatory responses. Another study applied untargeted metabolomics techniques to investigate the change of serum metabolites in POD patients undergoing cardiopulmonary bypass, and found that low serum lipid metabolic phosphatidylinositol was linked to an increased risk of POD in the geriatric patient, which may shed fresh light on the pathophysiology of POD (Huang et al., 2022).

Serum biomarkers and predictors

High clinical significance can result from the identification of predictive biomarkers that allow for early risk stratification of hip fracture patients who are vulnerable to POD. The incidence and severity of POD in hip fracture patients were associated with higher levels of white blood cells, neutrophil/lymphocyte ratio, neutrophil percentage, and lower levels of mean platelet volume and basophil percentage (Thisayakorn et al., 2021; Li et al., 2022), which further demonstrated that immune-inflammatory processes are involved in the pathophysiology of POD. Prognostic Nutritional Index (PNI) is a convenient and accurate way to quantify nutritional status, and it was calculated as $10 \times$ albumins (g/dl) $+ 0.005 \times$ total lymphocyte count (per mm^3; Onodera et al., 1984). It is reported that lower preoperative PNI value (cut-off value: 47.45, sensitivity: 86.0%, specificity: 51.9%, OR: 2.88, 95% CI: 1.25–6.64, $p = 0.012$) was associated with increased POD risk in geriatric patients with hip fractures, and it was a predictor for POD with an area under the curve of 0.686 (95% CI: 0.604–0.767, $p < 0.001$; Xing et al., 2020). The neuropeptide galanin is a neuromodulator ubiquitously present in the central and peripheral nervous systems as well as nonneural tissues, and its levels are abnormally high in depressive and dementia-like diseases (Counts et al., 2001; Alexandris et al., 2015). It is reported that the increased serum neuropeptide galanin level can predict postoperative cognitive dysfunction in geriatric patients with hip fractures ($p = 0.035$). However, the association between serum neuropeptide galanin level and POD in geriatric patients with hip fractures has not been investigated yet.

Diagnosis

In the current, the diagnosis of postoperative delirium in geriatric patients with hip fractures mainly relies on clinical characteristics. Patients with POD frequently exhibit either hyperactive or hypoactive types, or a mixed type, which alternates between these motor subtypes (Vlisides and Avidan, 2019). The hypoactive type is more prevalent in elderly people, frequently goes undiagnosed, and is linked to higher rates of other postoperative complications and mortality (Oh et al., 2017). Additionally, in the clinical setting, the workload of clinicians is so high that it is difficult to detect POD in time, so the underdiagnosis rate of delirium remains high. Studies found a delirium underdiagnosis rate of 60% in elderly patients with cancer and an even higher rate of 84.6% in elderly patients in the emergency setting (de la Cruz et al., 2015; Boucher et al., 2019).

Diagnosis criteria

Delirium has been defined as a disturbance in attention and consciousness based on the following standards in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013; European Delirium Association, American Delirium Society, 2014): (A) Disturbance in attention (i.e., reduced ability to focus, sustain, or shift attention) and awareness (reduced orientation to the environment); (B) The disturbance develops over a short period (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day; (C) An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception); (D) The disturbances in Criteria A and C are not better explained by a pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as a coma; (E) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Diagnosis instrument

Prompt diagnosis of delirium in geriatric patients with hip fractures is the first key step in its appropriate treatment, and the diagnosis approaches in these patients must be convenient and easy to operate. The widely used instrument for POD diagnosis in the clinical setting is the confusion assessment method (CAM) developed in 1990, which is a bedside structured interview with the patient (Inouye et al., 1990). It concentrates on the most notable clinical characteristics of delirium: (1) acute change in mental status with a fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. To make the diagnosis of delirium, (1) and (2) must be present, and the patient must have signs of either (3) or (4). Additionally, in the intensive care unit (ICU) setting, POD is often diagnosed using CAM-ICU, a 2-min version of CAM that is convenient to use and highly accurate (Ely et al., 2001; Heo et al., 2011).

The Mini-mental state examination (MMSE) is also a wildly used instrument for the diagnosis of POD. It is intended to assess abilities related to orientation, memory, attention, object identification, compliance with verbal and written instructions, free writing of sentences, and copying complicated polygons (Folstein et al., 1975). The Organic brain syndrome (OBS) scale mainly assesses two dimensions: disorientation and confusion. A disorientation subscale based on an interview describes the patient's capacity for time, place, and self-identity orientation; a confusion subscale based on the researcher's or the nursing staff's observations that assess a variety of cognitive, perceptual, emotional, and personality alterations, as well as physical and practical impairments, and variations in the clinical condition (Berggren et al., 1987).

There is a study that compared 11 instruments for delirium assessment, and it found that the CAM is the best bedside delirium assessment tool, which takes 5 min to administer, while the MMSE (score < 24) is the least useful for identifying a patient with delirium (Wong et al., 2010). Furthermore, Marcantonio et al. (2014) have developed a 3-min diagnostic interview based on the CAM, called 3D-CAM, which assesses 4 CAM features with cognitive tests, patients question, and interviewer observation. It was demonstrated to have good sensitivity [95% (84, 99%)] and specificity [94% (90, 97%)] in comparison to a reference standard, and was shown to be effective in POD diagnosis in geriatric patients with hip fractures (Neuman et al., 2021).

Severity assessment

Increasing evidence indicates that delirium, as well as its severity, is associated with worse outcomes (de Miguel et al., 2018; Sieber et al., 2018). It is vital to measure delirium severity to assess prognosis and to monitor treatment response. The most frequently used instruments to rate the severity of POD include the Confusion Assessment Method-Severity (CAM-S; Inouye et al., 2014), the Delirium Rating Scale-Revised-98 (DRS-R-98; de Rooij et al., 2006), and the Memorial Delirium Assessment Scale (MDAS) (Breitbart et al., 1997). The same fundamental concept of delirium severity is measured by each of these delirium instruments, with a high degree of correlation (Gross et al., 2018).

However, postoperative delirium is characterized by acute onset and recurrent fluctuations. It is difficult for the bedside assessment instruments such as the CAM-S to dynamically grasp the recurrent fluctuations, and the accuracy of these scales in assessing POD depends on the training level of assessors. Furthermore, it is demonstrated that the electrocardiogram (ECG) slowing, such as a composite of generalized theta or delta slowing (OR 10.3, 95% CI, and 5.3–20.1), is associated with delirium severity and poor clinical outcomes (Kimchi et al., 2019). Recently, an automated physiologic process that quantifies the presence and severity of delirium directly has been reported, called the Electroencephalographic Confusion Assessment Method Severity Score (E-CAM-S; van Sleuwen et al., 2022). It is based on a learning-to-rank machine learning model of forehead electroencephalography signals, with a level of performance comparable to conventional interview-based clinical assessment. Tesh et al. (2022) developed the Visual EEG Confusion Assessment Method Severity (VE-CAM-S) for the diagnosis of delirium severity, which was strongly associated with clinically important outcomes. Those ECG-based assessment methods may help close the delirium diagnostic gap and develop more effective delirium treatments and prevention strategies.

Prevention and treatment

Hitherto, there is still no effective strategy to treat POD in geriatric patients with hip fractures, and studies on the management of postoperative delirium mainly concentrate on its precautions. According to a 2020 meta-analysis, 91% of trials about POD focused on prevention and only 9% on its treatment (Pieri et al., 2020). The prevention and treatment measures of POD in geriatric patients with hip fractures can be divided into non-pharmacological and pharmacological interventions.

Non-pharmacological interventions

Risk prediction and reduction

Early identification of hip fracture patients with POD risk and adoption of effective intervention are important to prevent the occurrence and development of POD. The risk factors and predictors of POD in geriatric patients with hip fractures are listed in Table 1. Clinicians should be vigilant for POD in patients who present with these features during the perioperative period. In recent years, a variety of risk prediction models have been developed to predict POD risk in geriatric patients with hip fractures (Kim et al., 2020; Oberai et al., 2021; Shen et al., 2022; Table 2), which enable delirium risk stratification for hip fracture patients and facilitate the development of strategies for POD. Adapted from the AWOL (Age, WORLD backward, Orientation, illness severity) delirium prediction tool for medical inpatients Douglas et al. (2013), Whitlock et al. (2020) developed a perioperative delirium risk stratification tool called AWOL-S (Age, WORLD backward, Orientation, illness severity, Surgery-specific risk) for elective surgical patients. The AWOL-S tool shows a moderate level of accuracy for delirium prediction in patients undergoing elective surgery, with 75% sensitivity and 59% specificity. According to its procedure-specific delirium risk score, hip fracture surgery belongs to the high-risk level, which needs continuing delirium prevention interventions after discharge from anesthesia care. Bishara et al. (2022) developed a delirium risk prediction model based on machine learning, which demonstrated excellent calibration compared with models developed with traditional logistic regression. It is not limited by time and space and can be repeated and standardized to assess patients. However, the incidence of POD in this study (5.3%) was lower than commonly reported POD rates, which may be owing to the inclusion of a younger population and all procedures, even those considered to have a low risk of delirium, such as gynecologic, urologic and plastics. Future studies could validate the sensitivity and specificity of this model specifically in elderly patients with hip fractures.

Orthogeriatric comprehensive care

Orthogeriatric comprehensive care is a multidisciplinary methodology of systematic assessment and optimization for elderly patients following orthopedic surgery, which plays a significant role in the progress of geriatric patients with hip fractures (Li et al., 2021). The orthogeriatric comprehensive care team usually includes orthopedic surgeons, geriatricians, physiotherapists, occupational therapists, and nurses. The primary responsibility of the team includes the identification of risk factors, optimization of nutrition and bowel function, as well as management of comorbidities, complications, pain, and fluid imbalances for geriatric patients with hip fractures (Figure 2). A 2020 meta-analysis showed that comprehensive interventions, such as education, awareness, and multidisciplinary collaboration around POD prevention and management, significantly reduced the prevalence of POD (Igwe et al., 2020).

A substantially reduced incidence of POD in patients with hip fractures was shown to be associated with proactive geriatrics consultation and orthogeriatric co-management during the perioperative period (Marcantonio et al., 2001; Pollmann et al., 2021). In a meta-analysis of 1840 elderly patients with hip fractures (Wang et al., 2017), the incidence of POD in the comprehensive geriatric care group was significantly reduced compared to the routine orthopedic care group (OR 0.71; 95% CI, 0.57–0.89; $p = 0.003$). It also revealed that comprehensive geriatric care may accelerate cognitive function recovery after hip fracture surgery. However, these findings should be interpreted cautiously in light of the limitations of this study. For example, the instruments used to diagnose patients with POD are inconsistent, with variable sensitivity and specificity, and the influencing factors such as staff member experience, anesthetic method, and inclusion/exclusion criteria would differ between studies.

Additionally, Enomoto et al. (2021) created a clinical program called the Delirium Team Approach, which included educational sessions, reviews of preprinted doctor orders, and routine delirium screening. They found that implementation of this program could shorten postoperative hospital stays and reduce the incidence of POD in elderly patients after cardiovascular surgery. Furthermore, more multicenter RCTs with excellent methodology are required to gather proof of the effect of comprehensive orthogeriatric care on POD prevention in geriatric patients with hip fractures.

Choice of anesthetic technique

The choice of regional anesthesia or general anesthesia was thought to have an impact on the occurrence of POD previously (Ravi et al., 2019). However, recent results of several multicenter large-scale randomized controlled trials showed that regional anesthesia (spinal, subarachnoid, or both techniques combined with no sedation) did not significantly reduce the risk of POD in geriatric patients with hip fractures compared to general anesthesia (Neuman et al., 2021; Li et al., 2022). These findings indicated that the decision of which anesthetic to use during hip fracture surgery may depend more on patient desire than on predicted variations in clinical results. Additionally, in a randomized controlled trial of 94 geriatric patients with hip fractures (Gu et al., 2021), ultrasound-guided multiple nerve block was shown to be a safe and more effective anesthetic technique than general anesthesia, with reduced intravenous opioid consumption and POD incidence. However, the POD incidence in this study was the secondary outcome, and it was assessed by the delirium index, which is not widely used in clinical practice.

When it comes to general anesthesia, there are contradictory views on the effects of intravenous and inhalation anesthesia on POD. Several studies suggested that inhalation anesthesia, such as sevoflurane anesthesia, may increase the risk of POD by inducing or exacerbating neuroinflammation (Zhang et al., 2013; Saller et al., 2022). On the contrary, a randomized controlled trial of 209 geriatric patients following total hip or knee replacements found

TABLE 2 Risk prediction models for postoperative delirium in geriatric patients with hip fractures.

Source	Variables	OR (95% CI)	Scores	AUC (95% CI)
Kim et al. (2020)	Preoperative delirium	8.32 (6.78–10.21)	8	Derivation cohorts: 0.77 (0.76–0.78); Validation cohorts: 0.77 (0.75–0.79)
	Preoperative dementia	2.38 (2.05–2.76)	3	
	Age			
	70–79 year	1.60 (1.20–2.12)	2	
	80–89 year	2.09 (1.59–2.74)	2	
	≥90 year	2.43 (1.82–3.23)	3	
	Medical co-management	1.43 (1.13–1.81)	1	
	ASA physical status III - V	1.40 (1.14–1.73)	1	
	Functional dependence	1.37 (1.17–1.61)	1	
	Smoking	1.36 (1.07–1.72)	1	
	SIRS/sepsis/septic shock	1.34 (1.09–1.65)	1	
	Preoperative use of mobility aid	1.32 (1.14–1.52)	1	
Oberai et al. (2021)	Age > 80 year	1.6 (1.4–1.9)	5	Derivation cohorts: 0.742; Validation cohorts: 0.746
	Male gender	1.3 (1.1–1.5)	2	
	Mobilization opportunity	1.9 (1.4–2.6)	6	
	Surgery delay	1.7 (1.2–2.5)	6	
	Cognition not assessed	1.5 (1.3–1.9)	4	
	Cognition impaired	1.7 (1.3–2.1)	5	
	Prior impaired cognition or known dementia	3.90 (3.2–4.7)	14	
Shen et al. (2022)	Preoperative delirium	4.21 (3.25–9.14)	4	Derivation cohorts: 0.848 (0.72–0.90); Validation cohorts: 0.833 (0.68–0.89)
	CVA with the modified Rankin scale			
	≥4	3.17 (1.16–5.06)	3	
	2–3	2.25 (1.26–4.29)	2	
	Diabetes with random glucose level			
	> 13 mmol/l	2.43 (1.32–2.99)	2	
	8–13 mmol/l	1.36 (1.15–1.67)	1	
	CCI score			
	≥9	2.32 (1.69–4.83)	2	
	6–8	1.29 (1.03–2.52)	1	
	Age			
	≥80 year	1.87 (1.25–2.50)	2	
	70–79 year	1.11 (1.07–2.19)	1	
	Application of Benzodiazepines in surgery	1.44 (1.24–3.17)	1	
	Surgical delay ≥ 2 days	1.15 (1.13–1.28)	1	
	Creatine ≥ 90 µmol/l	1.09 (1.02–1.13)	1	
	Active smoker	1.05 (1.04–1.94)	1	

OR, odds ratio; CI, confidence interval; AUC, area under the curve; ASA, American Society of Anaesthesiologists; SIRS, systemic inflammatory response syndrome; CVA, cerebrovascular accident; CCI, Carlson comorbidity index.

that sevoflurane was superior to propofol in the reduction of POD duration ($p = 0.049$; Mei et al., 2020). However, a growing body of studies has revealed that neither the incidence nor the severity of POD changed significantly between intravenous and inhalation anesthesia (Royse et al., 2011; Lurati Buse et al., 2012; Miller et al., 2018; Jin et al., 2020). Future studies still need to further explore the effects of different anesthesia techniques on the incidence and severity of POD in geriatric patients with hip fractures.

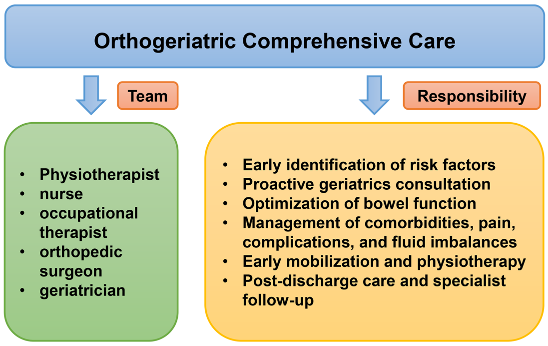

FIGURE 2
Orthogeriatric comprehensive care in geriatric patients with hip fractures for management of postoperative complication.

Pharmacological interventions

Pharmacologic strategies for the prevention and management of POD in geriatric patients with hip fractures have been studied for many years, while effective candidate drugs with strong evidence have not been found yet (Pluta et al., 2020). Drugs such as steroids (Swarbrick and Partridge, 2022), melatonin (Campbell et al., 2019), and vitamin D (Hung et al., 2022) have all been reported to be associated with POD, but all lack strong evidence. In the current, most studies focus on three medications: dexmedetomidine, antipsychotics, and analgesics.

Dexmedetomidine

It is reported that dexmedetomidine is an effective medication in the prevention of POD in hospitalized geriatric patients (León-Salas et al., 2020), but current studies mainly focus on the effect of dexmedetomidine on POD in geriatric patients after cardiovascular surgery. Dexmedetomidine was shown to be the most promising agent able to prevent the occurrence of POD in patients after cardiac surgeries, according to a 2020 meta-analysis of 56 RCTs that examined 38 interventions (Pieri et al., 2020). Two randomized controlled trials compared the effect of dexmedetomidine to midazolam and clonidine respectively, and both found that dexmedetomidine was more effective in the prevention of POD in patients who underwent stomatological or cardiovascular surgeries (Shokri and Ali, 2020; Wang et al., 2020). However, in a 2022 meta-analysis of 30 RCTs comprising 4,090 patients (Patel et al., 2022), perioperative dexmedetomidine administration failed to reduce the incidence of delirium in patients after cardiac surgeries. The possible explanation is that this meta-analysis included an increased number of trials, many of which have been published relatively recently and have not shown a beneficial relationship between dexmedetomidine and POD, and this study excluded trials at high risk of bias.

Whether dexmedetomidine is the most effective candidate for POD still needs further study. Additionally, adverse events such as bradycardia should be considered (Zeng et al., 2019). Future studies should focus on the effects of dexmedetomidine on POD in elderly patients with hip fractures to find effective and feasible dosing methods.

Analgesics

Acute pain in patients who underwent noncardiac surgery strongly mediates the relationship between preoperative cognitive impairment and postoperative delirium (Ma et al., 2022), therefore, adequate analgesia plays an essential role in the rehabilitation of geriatric hip fracture patients (Mears and Kates, 2015). Commonly used perioperative analgesic drugs include nonsteroidal anti-inflammatory drugs and opioids, narcotic and non-narcotic, respectively. Acetaminophen is an efficacious medication for analgesia in geriatric patients with hip fractures (Tsang et al., 2013; Bollinger et al., 2015). There is a retrospective study of 123 geriatric hip fracture patients (Connolly et al., 2020), which showed that intravenous acetaminophen had reduced the incidence of POD from 32.8 to 15.4% (p =0.024). In a 2021 network meta-analysis (Lee et al., 2021), the combination of propofol and acetaminophen was the most successful pharmaceutical strategy with a minimal incidence of POD.

Although opioid administration can itself be a risk factor for POD (Duprey et al., 2021), pain is probably a stronger POD trigger in geriatric patients with hip fractures (Morrison et al., 2003). Two RCTs compared morphine and oxycodone to sufentanil respectively, and they found that both low-dose morphine intrathecal analgesia and oxycodone patient-controlled intravenous analgesia are superior to sufentanil patient-controlled intravenous analgesia in the prevention of POD in geriatric patients with hip fractures (Gan et al., 2020; Xu et al., 2022). Therefore, multimodal analgesia is recommended for the management of POD in geriatric patients with hip fractures.

Antipsychotics

Antipsychotics are dopamine D_2 receptor antagonists, with varying degrees of affinity to muscarinic, serotonergic, and α_2 adrenergic receptors (Farah, 2005). They can be divided into first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). FGAs are also known as typical antipsychotics and relate to increased risks of psychomotor complications; SGAs are also called atypical antipsychotics and are linked to higher chances of cardiovascular and metabolic complications (Jin et al., 2020). The effect of antipsychotics on POD in geriatric patients with hip fractures is still doubtful, owing to minimal evidence and variable complications of them (Pluta et al., 2020).

Haloperidol, a typical antipsychotic, was studied in multiple trials with inconsistent results (Igwe et al., 2020; Li et al., 2021; Tillemans et al., 2021). According to a meta-analysis of patients admitted to an ICU, haloperidol prophylaxis could lower the incidence of POD compared to the placebo (RR 0.63; $p=0.004$; Lin et al., 2020). However, two massive prospective RCTs that compared haloperidol to ketamine or ziprasidone respectively, indicated that none of the three medications could shorten the frequency and duration of postoperative cognitive dysfunction and POD in patients with a critical illness (Girard et al., 2018; Hollinger et al., 2021). Some studies supported the efficacy of SGAs such as aripiprazole, risperidone, and olanzapine in the treatment of POD; nevertheless, the quality of the evidence is poor because of the heterogeneity and bias of the research (Tachi et al., 2021; Sugawara et al., 2022). Moreover, the safety of antipsychotics is more concerning than their efficacy. Boncyk et al. (2021) conducted a trial comparing haloperidol, olanzapine, and quetiapine in the management of delirious patients in the ICU. They reported that all three antipsychotics were associated with noticeably fewer days spent alive and out of the hospital, and similar results were also reported previously (Maust et al., 2015; Agar et al., 2017; Ralph and Espinet, 2018).

In conclusion, antipsychotics are mainly used in the management of POD in critically ill patients in the ICU, and future studies could focus on the effect of antipsychotics on POD in elderly patients with hip fractures.

Medication avoidance

Perioperative administration of certain medications has been considered an important risk factor for POD in geriatric patients with hip fractures, including antihistamines and scopolamine (Alagiakrishnan and Wiens, 2004; By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019). The most investigated perioperative medications with POD risk are benzodiazepines, antidepressants, and gabapentinoids.

Benzodiazepine receptor agonists (BZDRAs) are commonly used sedatives during the perioperative period, which can lower the consumption of intraoperative anesthetics (Nakagawa et al., 2000). However, numerous studies have demonstrated that perioperative usage of BZDRAs is linked to a higher risk of POD in geriatric patients with hip fractures (Poeran et al., 2020; Hernandez et al., 2021; Duprey et al., 2022; Lertkovit et al., 2022). The concrete mechanisms of benzodiazepine-induced POD vary based on the subtype of BZDRAs: Diazepam may affect the chloride plasticity mediated by Na^+-K^+-2Cl-cotransporter isoform 1 and result in the gamma-aminobutyric acid α receptor malfunction (Matsumoto et al., 2021); midazolam can alter the expression and activity of acetyl-and butyryl-cholinesterase genes (Rump et al., 2022), and both contribute to benzodiazepine - induced POD. Additionally, a retrospective cohort study of 250 patients who were scheduled for surgery under general anesthesia investigated the relationship between the time course of BZDRAs use and the incidence of POD. It was discovered that the prevalence of POD was highest in the patients who stopped taking BZDRAs after surgery, which indicated that abrupt discontinuation of BZDRAs should be avoided during the perioperative period (Omichi et al., 2021).

Antidepressant administration during the perioperative period is also associated with a high incidence of POD in geriatric patients with hip fractures. In a matched case–control study of geriatric patients after hip or knee surgeries (Kassie et al., 2022), exposures to selective serotonin reuptake inhibitors (SSRIs) such as sertraline, citalopram, escitalopram, and fluvoxamine before surgery in cases were considerably greater than those in controls, which indicated that reduced preoperative use of SSRIs may prevent the occurrence of POD. Additionally, gabapentin and gabapentin combined with midazolam have also been found to be associated with a considerably increased risk of POD, according to several massive observatory studies in patients following major noncardiac surgeries (Athanassoglou et al., 2022; Duprey et al., 2022; Park et al., 2022). However, whether gabapentin can increase the incidence of POD in geriatric patients with hip fractures still needs further study.

Conclusion

Postoperative delirium in geriatric patients with hip fractures is significantly related to high short - and long-term mortality as well as poor functional and cognitive recovery. The concrete mechanism of POD is still elusive, and early identification of patients with POD risks is imperative. In the current, prevention interventions such as risk prediction and orthogeriatric comprehensive care are the most effective measures for POD management. Dexmedetomidine prophylaxis and multimode analgesia may be effective for reducing the prevalence and severity of POD in geriatric patients with hip fractures, which needs more large-scale multicentral RCTs to investigate their safety and efficacy.

Author contributions

YC and JL conceived the idea of this review. YC drafted the manuscript and created the figures. SL, HW, SD, FW, and CL performed the literature search and reviewed the content of this manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Adam, E. H., Haas, V., Lindau, S., Zacharowski, K., and Scheller, B. (2020). Cholinesterase alterations in delirium after cardiosurgery: a German monocentric prospective study. *BMJ Open* 10:e031212. doi: 10.1136/bmjopen-2019-031212

Agar, M. R., Lawlor, P. G., Quinn, S., Draper, B., Caplan, G. A., Rowett, D., et al. (2017). Efficacy of Oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. *JAMA Intern. Med.* 177, 34–42. doi: 10.1001/jamainternmed.2016.7491

Aharonoff, G. B., Koval, K. J., Skovron, M. L., and Zuckerman, J. D. (1997). Hip fractures in the elderly: predictors of one year mortality. *J. Orthop. Trauma* 11, 162–165. doi: 10.1097/00005131-199704000-00004

Alagiakrishnan, K., and Wiens, C. A. (2004). An approach to drug induced delirium in the elderly. *Postgrad. Med. J.* 80, 388–393. doi: 10.1136/pgmj.2003.017236

Alam, A., Hana, Z., Jin, Z., Suen, K. C., and Ma, D. (2018). Surgery, neuroinflammation and cognitive impairment. *EBioMedicine* 37, 547–556. doi: 10.1016/j.ebiom.2018.10.021

Alexandris, A., Liu, A. K., Chang, R. C., Pearce, R. K., and Gentleman, S. M. (2015). Differential expression of galanin in the cholinergic basal forebrain of patients with Lewy body disorders. *Acta Neuropathol. Commun.* 3:77. doi: 10.1186/s40478-015-0249-4

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorder: DSM-5.* Arlington, VA: American Psychiatric Publishing.

Ansaloni, L., Catena, F., Chattat, R., Fortuna, D., Franceschi, C., Mascitti, P., et al. (2010). Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br. J. Surg.* 97, 273–280. doi: 10.1002/bjs.6843

Athanassoglou, V., Cozowicz, C., Zhong, H., Illescas, A., Poeran, J., Liu, J., et al. (2022). Association of perioperative midazolam use and complications: a population-based analysis. *Reg. Anesth. Pain Med.* 47, 228–233. doi: 10.1136/rapm-2021-102989

Bai, J., Liang, Y., Zhang, P., Liang, X., He, J., Wang, J., et al. (2020). Association between postoperative delirium and mortality in elderly patients undergoing hip fractures surgery: a meta-analysis. *Osteoporos. Int.* 31, 317–326. doi: 10.1007/s00198-019-05172-7

Berggren, D., Gustafson, Y., Eriksson, B., Bucht, G., Hansson, L. I., Reiz, S., et al. (1987). Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. *Anesth. Analg.* 66, 497–504.

Bishara, A., Chiu, C., Whitlock, E. L., Douglas, V. C., Lee, S., Butte, A. J., et al. (2022). Postoperative delirium prediction using machine learning models and preoperative electronic health record data. *BMC Anesthesiol.* 22:8. doi: 10.1186/s12871-021-01543-y

Bollinger, A. J., Butler, P. D., Nies, M. S., Sietsema, D. L., Jones, C. B., and Endres, T. J. (2015). Is scheduled intravenous acetaminophen effective in the pain management protocol of geriatric hip fractures? *Geriatr. Orthop. Surg. Rehabil.* 6, 202–208. doi: 10.1177/2151458515588560

Boncyk, C. S., Farrin, E., Stollings, J. L., Rumbaugh, K., Wilson, J. E., Marshall, M., et al. (2021). Pharmacologic Management of Intensive Care Unit Delirium: clinical prescribing practices and outcomes in more than 8500 patient encounters. *Anesth. Analg.* 133, 713–722. doi: 10.1213/ane.0000000000005365

Boucher, V., Lamontagne, M. E., Nadeau, A., Carmichael, P. H., Yadav, K., Voyer, P., et al. (2019). Unrecognized incident delirium in older emergency department patients. *J. Emerg. Med.* 57, 535–542. doi: 10.1016/j.jemermed.2019.05.024

Brauer, C. A., Coca-Perraillon, M., Cutler, D. M., and Rosen, A. B. (2009). Incidence and mortality of hip fractures in the United States. *JAMA* 302, 1573–1579. doi: 10.1001/jama.2009.1462

Breitbart, W., Rosenfeld, B., Roth, A., Smith, M. J., Cohen, K., and Passik, S. (1997). The memorial delirium assessment scale. *J. Pain Symptom Manag.* 13, 128–137. doi: 10.1016/s0885-3924(96)00316-8

Bruce, A. J., Ritchie, C. W., Blizard, R., Lai, R., and Raven, P. (2007). The incidence of delirium associated with orthopedic surgery: a meta-analytic review. *Int. Psychogeriatr.* 19, 197–214. doi: 10.1017/s104161020600425x

Bucks, R. S., Gidron, Y., Harris, P., Teeling, J., Wesnes, K. A., and Perry, V. H. (2008). Selective effects of upper respiratory tract infection on cognition, mood and emotion processing: a prospective study. *Brain Behav. Immun.* 22, 399–407. doi: 10.1016/j.bbi.2007.09.005

By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel (2019). American Geriatrics Society 2019 updated AGS beers criteria® for potentially inappropriate medication use in older adults. *J. Am. Geriatr. Soc.* 67, 674–694. doi: 10.1111/jgs.15767

Campbell, A. M., Axon, D. R., Martin, J. R., Slack, M. K., Mollon, L., and Lee, J. K. (2019). Melatonin for the prevention of postoperative delirium in older adults: a systematic review and meta-analysis. *BMC Geriatr.* 19:272. doi: 10.1186/s12877-019-1297-6

Cape, E., Hall, R. J., van Munster, B. C., de Vries, A., Howie, S. E., Pearson, A., et al. (2014). Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture. *J. Psychosom. Res.* 77, 219–225. doi: 10.1016/j.jpsychores.2014.06.014

Cavallari, M., Dai, W., Guttmann, C. R., Meier, D. S., Ngo, L. H., Hshieh, T. T., et al. (2016). Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. *Brain J. Neurol.* 139, 1282–1294. doi: 10.1093/brain/aww010

Chaiwat, O., Chanidnuan, M., Pancharoen, W., Vijitmala, K., Danpornprasert, P., Toadithep, P., et al. (2019). Postoperative delirium in critically ill surgical patients: incidence, risk factors, and predictive scores. *BMC Anesthesiol.* 19:39. doi: 10.1186/s12871-019-0694-x

Charlson, M. E., Pompei, P., Ales, K. L., and Mac Kenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 40, 373–383. doi: 10.1016/0021-9681(87)90171-8

Chen, L., Zhang, S., Tian, W., Huang, L., Jiang, X., Chen, X., et al. (2020). Cerebral spinal fluid cholinergic biomarkers predict postoperative cognitive dysfunction in aged patients – a prospective, observational, single center study. *J. Clin. Anesth.* 62:109743. doi: 10.1016/j.jclinane.2020.109743

Connolly, K. P., Kleinman, R. S., Stevenson, K. L., Neuman, M. D., and Mehta, S. N. (2020). Delirium reduced with intravenous acetaminophen in geriatric hip fracture patients. *J. Am. Acad. Orthop. Surg.* 28, 325–331. doi: 10.5435/jaaos-d-17-00925

Counts, S. E., Perez, S. E., Kahl, U., Bartfai, T., Bowser, R. P., Deecher, D. C., et al. (2001). Galanin: neurobiologic mechanisms and therapeutic potential for Alzheimer's disease. *CNS Drug Rev.* 7, 445–470. doi: 10.1111/j.1527-3458.2001.tb00210.x

Cummings, S. R., and Melton, L. J. (2002). Epidemiology and outcomes of osteoporotic fractures. *Lancet* 359, 1761–1767. doi: 10.1016/S0140-6736(02)08657-9

de Jong, L., van Rijckevorsel, V., Raats, J. W., Klem, T., Kuijper, T. M., and Roukema, G. R. (2019). Delirium after hip hemiarthroplasty for proximal femoral fractures in elderly patients: risk factors and clinical outcomes. *Clin. Interv. Aging* 14, 427–435. doi: 10.2147/cia.S189760

de la Cruz, M., Fan, J., Yennu, S., Tanco, K., Shin, S., Wu, J., et al. (2015). The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. *Support. Care Cancer* 23, 2427–2433. doi: 10.1007/s00520-015-2610-3

de Miguel, A. M., Roca Chacon, O., Martinez-Alonso, M., Serrano Godoy, M., Mas Atance, J., and Garcia, G. R. (2018). Hip fracture in the elderly patient: prognostic factors for mortality and functional recovery at one year. *Rev. Esp. Geriatr. Gerontol.* 53, 247–254. doi: 10.1016/j.regg.2018.04.447

de Rooij, S. E., van Munster, B. C., Korevaar, J. C., Casteelen, G., Schuurmans, M. J., van der Mast, R. C., et al. (2006). Delirium subtype identification and the validation of the delirium rating scale--Revised-98 (Dutch version) in hospitalized elderly patients. *Int. J. Geriatr. Psychiatry* 21, 876–882. doi: 10.1002/gps.1577

Douglas, V. C., Hessler, C. S., Dhaliwal, G., Betjemann, J. P., Fukuda, K. A., Alameddine, L. R., et al. (2013). The AWOL tool: derivation and validation of a delirium prediction rule. *J. Hosp. Med.* 8, 493–499. doi: 10.1002/jhm.2062

Duprey, M. S., Devlin, J. W., Griffith, J. L., Travison, T. G., Briesacher, B. A., Jones, R., et al. (2022). Association between perioperative medication use and postoperative delirium and cognition in older adults undergoing elective noncardiac surgery. *Anesth. Analg.* 134, 1154–1163. doi: 10.1213/ane.0000000000005959

Duprey, M. S., Dijkstra-Kersten, S. M. A., Zaal, I. J., Briesacher, B. A., Saczynski, J. S., Griffith, J. L., et al. (2021). Opioid use increases the risk of delirium in critically ill adults independently of pain. *Am. J. Respir. Crit. Care Med.* 204, 566–572. doi: 10.1164/rccm.202010-3794OC

Edelstein, D. M., Aharonoff, G. B., Karp, A., Capla, E. L., Zuckerman, J. D., and Koval, K. J. (2004). Effect of postoperative delirium on outcome after hip fracture. *Clin. Orthop. Relat. Res.* 422, 195–200. doi: 10.1097/01.blo.0000128649.59959.0c

Ekdahl, C. T., Claasen, J. H., Bonde, S., Kokaia, Z., and Lindvall, O. (2003). Inflammation is detrimental for neurogenesis in adult brain. *Proc. Natl. Acad. Sci. U. S. A.* 100, 13632–13637. doi: 10.1073/pnas.2234031100

Ely, E. W., Margolin, R., Francis, J., May, L., Truman, B., Dittus, R., et al. (2001). Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit. Care Med.* 29, 1370–1379. doi: 10.1097/00003246-200107000-00012

Enomoto, K., Kosaka, S., Kimura, T., Matsubara, M., Kitada, Y., Mieno, M., et al. (2021). Prevention of postoperative delirium after cardiovascular surgery: a team-based approach. *J. Thorac. Cardiovasc. Surg.* S0022-5223(21)01126-0. doi: 10.1016/j.jtcvs.2021.07.027 [Epub ahead of print].

European Delirium Association, American Delirium Society (2014). The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. *BMC Med.* 12:141. doi: 10.1186/s12916-014-0141-2

Farah, A. (2005). Atypicality of atypical antipsychotics. *Prim. Care Companion J. Clin. Psychiatry* 7, 268–274. doi: 10.4088/pcc.v07n0602

Fischer, H., Maleitzke, T., Eder, C., Ahmad, S., Stöckle, U., and Braun, K. F. (2021). Management of proximal femur fractures in the elderly: current concepts and treatment options. *Eur. J. Med. Res.* 26:86. doi: 10.1186/s40001-021-00556-0

Flikweert, E. R., Wendt, K. W., Diercks, R. L., Izaks, G. J., Landsheer, D., Stevens, M., et al. (2018). Complications after hip fracture surgery: are they preventable? *Eur. J. Trauma Emerg. Surg.* 44, 573–580. doi: 10.1007/s00068-017-0826-2

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Gan, J., Tu, Q., Miao, S., Lei, T., Cui, X., Yan, J., et al. (2020). Effects of oxycodone applied for patient-controlled analgesia on postoperative cognitive function in elderly patients undergoing total hip arthroplasty: a randomized controlled clinical trial. *Aging Clin. Exp. Res.* 32, 329–337. doi: 10.1007/s40520-019-01202-w

Girard, T. D., Exline, M. C., Carson, S. S., Hough, C. L., Rock, P., Gong, M. N., et al. (2018). Haloperidol and ziprasidone for treatment of delirium in critical illness. *N. Engl. J. Med.* 379, 2506–2516. doi: 10.1056/NEJMoa1808217

Gross, A. L., Tommet, D., D'Aquila, M., Schmitt, E., Marcantonio, E. R., Helfand, B., et al. (2018). Harmonization of delirium severity instruments: a comparison of the DRS-R-98, MDAS, and CAM-S using item response theory. *BMC Med. Res. Methodol.* 18:92. doi: 10.1186/s12874-018-0552-4

Gu, J., Wang, E., Dai, S., Dong, R., Xu, F., Shen, Z., et al. (2021). Ultrasound-guided multiple nerve blocks: a safe and effective anesthetic modality in geriatric hip fracture patients. *Clin. J. Pain* 37, 881–886. doi: 10.1097/ajp.0000000000000988

Guo, Y., Li, Y., Zhang, Y., Fang, S., Xu, X., Zhao, A., et al. (2019). Post-operative delirium associated with metabolic alterations following hemi-arthroplasty in older patients. *Age Ageing* 49, 88–95. doi: 10.1093/ageing/afz132

Hatano, Y., Narumoto, J., Shibata, K., Matsuoka, T., Taniguchi, S., Hata, Y., et al. (2013). White-matter hyperintensities predict delirium after cardiac surgery. *Am. J. Geriatr. Psychiatry* 21, 938–945. doi: 10.1016/j.jagp.2013.01.061

Haynes, M. S., Alder, K. D., Toombs, C., Amakiri, I. C., Rubin, L. E., and Grauer, J. N. (2021). Predictors and sequelae of postoperative delirium in a geriatric patient population with hip fracture. *J. Am. Acad. Orthop. Surg. Glob. Res. Rev.* 5:e20.00221. doi: 10.5435/JAAOSGlobal-D-20-00221

Hecht, G., Slee, C. A., Goodell, P. B., Taylor, S. L., and Wolinsky, P. R. (2019). Predictive modeling for geriatric hip fracture patients: early surgery and delirium have the largest influence on length of stay. *J. Am. Acad. Orthop. Surg.* 27, e293–e300. doi: 10.5435/jaaos-d-17-00447

Heo, E. Y., Lee, B. J., Hahm, B. J., Song, E. H., Lee, H. A., Yoo, C. G., et al. (2011). Translation and validation of the Korean confusion assessment method for the intensive care unit. *BMC Psychiatry* 11:94. doi: 10.1186/1471-244x-11-94

Hernandez, N. M., Cunningham, D. J., Hinton, Z. W., Wu, C. J., and Seyler, T. M. (2021). Are patients taking benzodiazepines at increased risk for complications following primary Total knee arthroplasty? *J. Arthroplast.* 36, 1611–1616. doi: 10.1016/j.arth.2020.12.004

Hollinger, A., Rüst, C. A., Riegger, H., Gysi, B., Tran, F., Brügger, J., et al. (2021). Ketamine vs. haloperidol for prevention of cognitive dysfunction and postoperative delirium: a phase IV multicentre randomised placebo-controlled double-blind clinical trial. *J. Clin. Anesth.* 68:110099. doi: 10.1016/j.jclinane.2020.110099

Huang, H., Han, J., Li, Y., Yang, Y., Shen, J., Fu, Q., et al. (2022). Early serum metabolism profile of post-operative delirium in elderly patients following cardiac surgery with cardiopulmonary bypass. *Front. Aging Neurosci.* 14:857902. doi: 10.3389/fnagi.2022.857902

Hung, K. C., Wang, L. K., Lin, Y. T., Yu, C. H., Chang, C. Y., Sun, C. K., et al. (2022). Association of preoperative vitamin D deficiency with the risk of postoperative delirium and cognitive dysfunction: a meta-analysis. *J. Clin. Anesth.* 79:110681. doi: 10.1016/j.jclinane.2022.110681

Igwe, E. O., Nealon, J., Mohammed, M., Hickey, B., Chou, K. R., Chen, K. H., et al. (2020). Multi-disciplinary and pharmacological interventions to reduce post-operative delirium in elderly patients: a systematic review and meta-analysis. *J. Clin. Anesth.* 67:110004. doi: 10.1016/j.jclinane.2020.110004

Inouye, S. K., Kosar, C. M., Tommet, D., Schmitt, E. M., Puelle, M. R., Saczynski, J. S., et al. (2014). The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. *Ann. Intern. Med.* 160, 526–533. doi: 10.7326/m13-1927

Inouye, S. K., van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P., and Horwitz, R. I. (1990). Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann. Intern. Med.* 113, 941–948. doi: 10.7326/0003-4819-113-12-941

Jin, Z., Hu, J., and Ma, D. (2020). Postoperative delirium: perioperative assessment, risk reduction, and management. *Br. J. Anaesth.* 125, 492–504. doi: 10.1016/j.bja.2020.06.063

Kant, I. M. J., de Bresser, J., van Montfort, S. J. T., Slooter, A. J. C., and Hendrikse, J. (2017). MRI markers of neurodegenerative and neurovascular changes in relation to postoperative delirium and postoperative cognitive decline. *Am. J. Geriatr. Psychiatry* 25, 1048–1061. doi: 10.1016/j.jagp.2017.06.016

Kassie, G. M., Roughead, E. E., Nguyen, T. A., Pratt, N. L., and Kalisch Ellett, L. M. (2022). The risk of preoperative central nervous system-acting medications on delirium following hip or knee surgery: a matched case-control study. *Drug Saf.* 45, 75–82. doi: 10.1007/s40264-021-01136-1

Kim, E. M., Li, G., and Kim, M. (2020). Development of a risk score to predict postoperative delirium in patients with hip fracture. *Anesth. Analg.* 130, 79–86. doi: 10.1213/ane.0000000000004386

Kimchi, E. Y., Neelagiri, A., Whitt, W., Sagi, A. R., Ryan, S. L., Gadbois, G., et al. (2019). Clinical EEG slowing correlates with delirium severity and predicts poor clinical outcomes. *Neurology* 93, e1260–e1271. doi: 10.1212/WNL.0000000000008164

Koskderelioglu, A., Onder, O., Gucuyener, M., Altay, T., Kayali, C., and Gedizlioglu, M. (2017). Screening for postoperative delirium in patients with acute hip fracture: assessment of predictive factors. *Geriatr Gerontol Int* 17, 919–924. doi: 10.1111/ggi.12806

Kuo, L. Y., Hsu, P. T., Wu, W. T., Lee, R. P., Wang, J. H., Chen, H. W., et al. (2021). The incidence of mental disorder increases after hip fracture in older people: a nationwide cohort study. *BMC Geriatr.* 21:249. doi: 10.1186/s12877-021-02195-w

Kyeong, S., Shin, J. E., Yang, K. H., Lee, W. S., Chung, T. S., and Kim, J. J. (2018). Neural predisposing factors of postoperative delirium in elderly patients with femoral neck fracture. *Sci. Rep.* 8:7602. doi: 10.1038/s41598-018-26030-2

Lee, J. M., Cho, Y. J., Ahn, E. J., Choi, G. J., and Kang, H. (2021). Pharmacological strategies to prevent postoperative delirium: a systematic review and network meta-analysis. *Anesth. Pain Med. (Seoul)* 16, 28–48. doi: 10.17085/apm.20079

León-Salas, B., Trujillo-Martín, M. M., Del Castillo, L. P. M., García, J. G., Pérez-Ros, P., Ruiz, F. R., et al. (2020). Pharmacologic interventions for prevention of delirium in hospitalized older people: a meta-analysis. *Arch. Gerontol. Geriatr.* 90:104171. doi: 10.1016/j.archger.2020.104171

Lertkovit, S., Siriussawakul, A., Suraarunsumrit, P., Lertpipopmetha, W., Manomaiwong, N., Wivatdechakul, W., et al. (2022). Polypharmacy in older adults undergoing major surgery: prevalence, association with postoperative cognitive dysfunction and potential associated anesthetic agents. *Front. Med.* 9:811954. doi: 10.3389/fmed.2022.811954

Leslie, D. L., Marcantonio, E. R., Zhang, Y., Leo-Summers, L., and Inouye, S. K. (2008). One-year health care costs associated with delirium in the elderly population. *Arch. Intern. Med.* 168, 27–32. doi: 10.1001/archinternmed.2007.4

Li, T., Li, J., Yuan, L., Wu, J., Jiang, C., Daniels, J., et al. (2022). Effect of regional vs general anesthesia on incidence of postoperative delirium in older patients undergoing hip fracture surgery: the RAGA randomized trial. *JAMA* 327, 50–58. doi: 10.1001/jama.2021.22647

Li, X., Wang, G., He, Y., Wang, Z., and Zhang, M. (2022). White-cell derived inflammatory biomarkers in prediction of postoperative delirium in elderly patients undergoing surgery for lower limb fracture under non-general Anaesthesia. *Clin. Interv. Aging* 17, 383–392. doi: 10.2147/CIA.S346954

Li, X., Wang, Y., Liu, J., Xiong, Y., Chen, S., Han, J., et al. (2021). Effects of perioperative interventions for preventing postoperative delirium: a protocol for systematic review and meta-analysis of randomized controlled trials. *Medicine* 100:e26662. doi: 10.1097/md.0000000000026662

Lin, P., Zhang, J., Shi, F., and Liang, Z. A. (2020). Can haloperidol prophylaxis reduce the incidence of delirium in critically ill patients in intensive care units? A systematic review and meta-analysis. *Heart Lung* 49, 265–272. doi: 10.1016/j.hrtlng.2020.01.010

Liu, K., Sheng, J., Zhang, H., Liu, L., Tang, Y., Zhu, Z., et al. (2021). Risk factors for mortality after Uncemented bipolar hemiarthroplasty for geriatric displaced femoral neck fracture. *Orthopedics* 44, e570–e576. doi: 10.3928/01477447-20210618-19

Low, S., Wee, E., and Dorevitch, M. (2021). Impact of place of residence, frailty and other factors on rehabilitation outcomes post hip fracture. *Age Ageing* 50, 423–430. doi: 10.1093/ageing/afaa131

Lurati Buse, G. A., Schumacher, P., Seeberger, E., Studer, W., Schuman, R. M., Fassl, J., et al. (2012). Randomized comparison of sevoflurane versus propofol to reduce perioperative myocardial ischemia in patients undergoing noncardiac surgery. *Circulation* 126, 2696–2704. doi: 10.1161/circulationaha.112.126144

Ma, J. H., Liu, Y. F., Hong, H., Li, C. J., Cui, F., Mu, D. L., et al. (2022). Effect of acute pain on the association between preoperative cognitive impairment and postoperative delirium: a secondary analysis of three trials. *Br. J. Anaesth.* S0007-0912(22)00356-7. doi: 10.1016/j.bja.2022.06.033 [Epub ahead of print].

Maekawa, K., Baba, T., Otomo, S., Morishita, S., and Tamura, N. (2014). Low pre-existing gray matter volume in the medial temporal lobe and white matter lesions are associated with postoperative cognitive dysfunction after cardiac surgery. *PLoS One* 9:e87375. doi: 10.1371/journal.pone.0087375

Maldonado, J. R. (2017). Acute brain failure: pathophysiology, diagnosis, management, and sequelae of delirium. *Crit. Care Clin.* 33, 461–519. doi: 10.1016/j.ccc.2017.03.013

Marcantonio, E. R., Flacker, J. M., Wright, R. J., and Resnick, N. M. (2001). Reducing delirium after hip fracture: a randomized trial. *J. Am. Geriatr. Soc.* 49, 516–522. doi: 10.1046/j.1532-5415.2001.49108.x

Marcantonio, E. R., Ngo, L. H., O'Connor, M., Jones, R. N., Crane, P. K., Metzger, E. D., et al. (2014). 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann. Intern. Med.* 161, 554–561. doi: 10.7326/M14-0865

Matsumoto, D., Ushio, S., Wada, Y., Noda, Y., Esumi, S., Izushi, Y., et al. (2021). Bumetanide prevents diazepam-modified anxiety-like behavior in lipopolysaccharide-treated mice. *Eur. J. Pharmacol.* 904:174195. doi: 10.1016/j.ejphar.2021.174195

Maust, D. T., Kim, H. M., Seyfried, L. S., Chiang, C., Kavanagh, J., Schneider, L. S., et al. (2015). Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiat.* 72, 438–445. doi: 10.1001/jamapsychiatry.2014.3018

Mears, S. C., and Kates, S. L. (2015). A guide to improving the Care of Patients with fragility fractures, edition 2. *Geriatr. Orthop. Surg. Rehabil.* 6, 58–120. doi: 10.1177/2151458515572697

Mei, X., Zheng, H. L., Li, C., Ma, X., Zheng, H., Marcantonio, E., et al. (2020). The effects of Propofol and sevoflurane on postoperative delirium in older patients: a randomized clinical trial study. *J. Alzheimers Dis.* 76, 1627–1636. doi: 10.3233/jad-200322

Merchant, R. A., Lui, K. L., Ismail, N. H., Wong, H. P., and Sitoh, Y. Y. (2005). The relationship between postoperative complications and outcomes after hip fracture surgery. *Ann. Acad. Med. Singap.* 34, 163–168.

Meyer, M., Gotz, J., Parik, L., Renkawitz, T., Grifka, J., Maderbacher, G., et al. (2021). Postoperative delirium is a risk factor for complications and poor outcome after total hip and knee arthroplasty. *Acta Orthop.* 92, 695–700. doi: 10.1080/17453674.2021.1980676

Miller, D., Lewis, S. R., Pritchard, M. W., Schofield-Robinson, O. J., Shelton, C. L., Alderson, P., et al. (2018). Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. *Cochrane Database Syst. Rev.* 8:Cd012317. doi: 10.1002/14651858.CD012317.pub2

Morrison, R. S., Magaziner, J., Gilbert, M., Koval, K. J., McLaughlin, M. A., Orosz, G., et al. (2003). Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J. Gerontol. A Biol. Sci. Med. Sci.* 58, 76–81. doi: 10.1093/gerona/58.1.m76

Mosk, C. A., Mus, M., Vroemen, J. P., van der Ploeg, T., Vos, D. I., Elmans, L. H., et al. (2017). Dementia and delirium, the outcomes in elderly hip fracture patients. *Clin. Interv. Aging* 12, 421–430. doi: 10.2147/cia.S115945

Mullen, J. O., and Mullen, N. L. (1992). Hip fracture mortality. A prospective, multifactorial study to predict and minimize death risk. *Clin. Orthop. Relat. Res.* 280, 214–222.

Nakagawa, M., Mammoto, T., Hazama, A., Kita, T., Akamatsu, T., Kambara, N., et al. (2000). Midazolam premedication reduces propofol requirements for sedation during regional anesthesia. *Can. J. Anesth.* 47, 47–49. doi: 10.1007/BF03020731

Neerland, B. E., Hall, R. J., Seljeflot, I., Frihagen, F., Mac Lullich, A. M., Raeder, J., et al. (2016). Associations between delirium and preoperative cerebrospinal fluid C-reactive protein, Interleukin-6, and Interleukin-6 receptor in individuals with acute hip fracture. *J. Am. Geriatr. Soc.* 64, 1456–1463. doi: 10.1111/jgs.14238

Neuman, M. D., Feng, R., Carson, J. L., Gaskins, L. J., Dillane, D., Sessler, D. I., et al. (2021). Spinal anesthesia or general anesthesia for hip surgery in older adults. *N. Engl. J. Med.* 385, 2025–2035. doi: 10.1056/NEJMoa2113514

Oberai, T., Oosterhoff, J. H. F., Woodman, R., Doornberg, J. N., Kerkhoffs, G., and Jaarsma, R. (2021). Development of a postoperative delirium risk scoring tool using data from the Australian and New Zealand hip fracture registry: an analysis of 6672 patients 2017-2018. *Arch. Gerontol. Geriatr.* 94:104368. doi: 10.1016/j.archger.2021.104368

Oh, E. S., Fong, T. G., Hshieh, T. T., and Inouye, S. K. (2017). Delirium in older persons: advances in diagnosis and treatment. *JAMA* 318, 1161–1174. doi: 10.1001/jama.2017.12067

Omichi, C., Ayani, N., Oya, N., Matsumoto, Y., Tanaka, M., Morimoto, T., et al. (2021). Association between discontinuation of benzodiazepine receptor agonists and post-operative delirium among inpatients with liaison intervention: a retrospective cohort study. *Compr. Psychiatry* 104:152216. doi: 10.1016/j.comppsych.2020.152216

Onodera, T., Goseki, N., and Kosaki, G. (1984). Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi* 85, 1001–1005.

Otomo, S., Maekawa, K., Goto, T., Baba, T., and Yoshitake, A. (2013). Pre-existing cerebral infarcts as a risk factor for delirium after coronary artery bypass graft surgery. *Interact. Cardiovasc. Thorac. Surg.* 17, 799–804. doi: 10.1093/icvts/ivt304

Ouellet, J. A., Ouellet, G. M., Romegialli, A. M., Hirsch, M., Berardi, L., Ramsey, C. M., et al. (2019). Functional outcomes after hip fracture in independent community-dwelling patients. *J. Am. Geriatr. Soc.* 67, 1386–1392. doi: 10.1111/jgs.15870

Park, C. M., Inouye, S. K., Marcantonio, E. R., Metzger, E., Bateman, B. T., Lie, J. J., et al. (2022). Perioperative gabapentin use and in-hospital adverse clinical events among older adults after major surgery. *JAMA Intern. Med.* 182, 1117–1127. doi: 10.1001/jamainternmed.2022.3680

Patel, M., Onwochei, D. N., and Desai, N. (2022). Influence of perioperative dexmedetomidine on the incidence of postoperative delirium in adult patients undergoing cardiac surgery. *Br. J. Anaesth.* 129, 67–83. doi: 10.1016/j.bja.2021.11.041

Pereira, J. V., Aung Thein, M. Z., Nitchingham, A., and Caplan, G. A. (2021). Delirium in older adults is associated with development of new dementia: a systematic review and meta-analysis. *Int. J. Geriatr. Psychiatry* 36, 993–1003. doi: 10.1002/gps.5508

Pieri, M., De Simone, A., Rose, S., De Domenico, P., Lembo, R., Denaro, G., et al. (2020). Trials focusing on prevention and treatment of delirium after cardiac surgery: a systematic review of randomized evidence. *J. Cardiothorac. Vasc. Anesth.* 34, 1641–1654. doi: 10.1053/j.jvca.2019.09.028

Pluta, M. P., Dziech, M., Czempik, P. F., Szczepańska, A. J., and Krzych, Ł. J. (2020). Antipsychotic drugs in prevention of postoperative delirium-what is known in 2020? *Int. J. Environ. Res. Public Health* 17:6069. doi: 10.3390/ijerph17176069

Poeran, J., Cozowicz, C., Zubizarreta, N., Weinstein, S. M., Deiner, S. G., Leipzig, R. M., et al. (2020). Modifiable factors associated with postoperative delirium after hip fracture repair: An age-stratified retrospective cohort study. *Eur. J. Anaesthesiol.* 37, 649–658. doi: 10.1097/eja.0000000000001197

Pollmann, C. T., Mellingsæter, M. R., Neerland, B. E., Straume-Næsheim, T., Årøen, A., and Watne, L. O. (2021). Orthogeriatric co-management reduces incidence of delirium in hip fracture patients. *Osteopos Int.* 32, 2225–2233. doi: 10.1007/s00198-021-05974-8

Prieto, G. A., Tong, L., Smith, E. D., and Cotman, C. W. (2019). TNFα and IL-1β but not IL-18 suppresses hippocampal long-term potentiation directly at the synapse. *Neurochem. Res.* 44, 49–60. doi: 10.1007/s11064-018-2517-8

Ralph, S. J., and Espinet, A. J. (2018). Increased all-cause mortality by antipsychotic drugs: updated review and meta-analysis in dementia and general mental health care. *J Alzheimers Dis. Rep.* 2, 1–26. doi: 10.3233/adr-170042

Ravi, B., Pincus, D., Choi, S., Jenkinson, R., Wasserstein, D. N., and Redelmeier, D. A. (2019). Association of Duration of surgery with postoperative delirium among patients receiving hip fracture repair. *JAMA Netw. Open* 2:e190111. doi: 10.1001/jamanetworkopen.2019.0111

Root, J. C., Pryor, K. O., Downey, R., Alici, Y., Davis, M. L., Holodny, A., et al. (2013). Association of pre-operative brain pathology with post-operative delirium in a cohort of non-small cell lung cancer patients undergoing surgical resection. *Psycho-Oncology* 22, 2087–2094. doi: 10.1002/pon.3262

Royse, C. F., Andrews, D. T., Newman, S. N., Stygall, J., Williams, Z., Pang, J., et al. (2011). The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery. *Anaesthesia* 66, 455–464. doi: 10.1111/j.1365-2044.2011.06704.x

Rudolph, J. L., Jones, R. N., Levkoff, S. E., Rockett, C., Inouye, S. K., Sellke, F. W., et al. (2009). Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation* 119, 229–236. doi: 10.1161/circulationaha.108.795260

Rump, K., Holtkamp, C., Bergmann, L., Nowak, H., Unterberg, M., Orlowski, J., et al. (2022). Midazolam impacts acetyl-and butyrylcholinesterase genes: An epigenetic explanation for postoperative delirium? *PLoS One* 17:e0271119. doi: 10.1371/journal.pone.0271119

Saller, T., Hubig, L., Seibold, H., Schroeder, Z., Wang, B., Groene, P., et al. (2022). Association between post-operative delirium and use of volatile anesthetics in the elderly: a real-world big data approach. *J. Clin. Anesth.* 83:110957. doi: 10.1016/j.jclinane.2022.110957

Schrøder, C. K., Hjelholt, T. J., Møller, H., Madsen, M., Pedersen, A. B., and Kristensen, P. K. (2022). Comorbidity and quality of in-hospital care for hip fracture patients. *J. Am. Med. Dir. Assoc.* 23, 671–677.e4. doi: 10.1016/j.jamda.2022.01.078

Shen, J., An, Y., Jiang, B., and Zhang, P. (2022). Derivation and validation of a prediction score for postoperative delirium in geriatric patients undergoing hip fracture surgery or hip arthroplasty. *Front. Surg.* 9:919886. doi: 10.3389/fsurg.2022.919886

Shioiri, A., Kurumaji, A., Takeuchi, T., Matsuda, H., Arai, H., and Nishikawa, T. (2010). White matter abnormalities as a risk factor for postoperative delirium revealed by diffusion tensor imaging. *Am. J. Geriatr. Psychiatry* 18, 743–753. doi: 10.1097/JGP.0b013e3181d145c5

Shokri, H., and Ali, I. (2020). A randomized control trial comparing prophylactic dexmedetomidine versus clonidine on rates and duration of delirium in older adult patients undergoing coronary artery bypass grafting. *J. Clin. Anesth.* 61:109622. doi: 10.1016/j.jclinane.2019.09.016

Sieber, F. E., Neufeld, K. J., Gottschalk, A., Bigelow, G. E., Oh, E. S., Rosenberg, P. B., et al. (2018). Effect of depth of sedation in older patients undergoing hip fracture repair on postoperative delirium: the STRIDE randomized clinical trial. *JAMA Surg.* 153, 987–995. doi: 10.1001/jamasurg.2018.2602

Smith, T. O., Cooper, A., Peryer, G., Griffiths, R., Fox, C., and Cross, J. (2017). Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis. *Int. J. Geriatr. Psychiatry* 32, 386–396. doi: 10.1002/gps.4655

Spies, C. D., Knaak, C., Mertens, M., Brockhaus, W. R., Shadenok, A., Wiebach, J., et al. (2021). Physostigmine for prevention of postoperative delirium and long-term cognitive dysfunction in liver surgery: a double-blinded randomised controlled trial. *Eur. J. Anaesthesiol.* 38, 943–956. doi: 10.1097/eja.0000000000001456

Stagno, D., Gibson, C., and Breitbart, W. (2004). The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. *Palliat. Support. Care* 2, 171–179. doi: 10.1017/s1478951504040234

Staus, R. (2011). Delirium in the older adult orthopaedic patient: predisposing, precipitating, and organic factors. *Orthop. Nurs.* 30, 231–238; quiz 239–240. doi: 10.1097/NOR.0b013e3182247c79

Sugawara, H., Koyama, A., Maruyama, T., Koda, Y., Fukunaga, H., Ishikawa, T., et al. (2022). Prospective clinical intervention study of aripiprazole and risperidone in the management of postoperative delirium in elderly patients after cardiovascular surgery. *Psychiatry Clin. Neurosci.* 76, 531–533. doi: 10.1111/pcn.13446

Swarbrick, C. J., and Partridge, J. S. L. (2022). Evidence-based strategies to reduce the incidence of postoperative delirium: a narrative review. *Anaesthesia* 77, 92–101. doi: 10.1111/anae.15607

Tachi, K., Fukuda, T., and Tanaka, M. (2021). Olanzapine attenuates postoperative cognitive dysfunction in adult rats. *Heliyon* 7:e06218. doi: 10.1016/j.heliyon.2021.e06218

Tantardini, V., Roca, F., Bahri, O., Compere, V., Dujardin, F., and Chassagne, P. (2020). Intraoperative hypotension and delirium in patients with hip fracture. *Geriatr. Psychol. Neuropsychiatr. Vieill.* 18, 25–33. doi: 10.1684/pnv.2019.0824

Tesh, R. A., Sun, H., Jing, J., Westmeijer, M., Neelagiri, A., Rajan, S., et al. (2022). VE-CAM-S: visual EEG-based grading of delirium severity and associations with clinical outcomes. *Crit. Care Explor.* 4:e0611. doi: 10.1097/cce.0000000000000611

Thisayakorn, P., Tangwongchai, S., Tantavisut, S., Thipakorn, Y., Sukhanonsawat, S., Wongwarawipat, T., et al. (2021). Immune, blood cell, and blood gas biomarkers of delirium in elderly individuals with hip fracture surgery. *Dement. Geriatr. Cogn. Disord.* 50, 161–169. doi: 10.1159/000517510

Tian, Y., Chen, K. Y., Liu, L. D., Dong, Y. X., Zhao, P., and Guo, S. B. (2018). Sevoflurane exacerbates cognitive impairment induced by Aβ (1-40) in rats through initiating neurotoxicity, Neuroinflammation, and neuronal apoptosis in rat hippocampus. *Mediat. Inflamm.* 2018:3802324. doi: 10.1155/2018/3802324

Tillemans, M. P. H., Butterhoff-Terlingen, M. H., Stuffken, R., Vreeswijk, R., Egberts, T. C. G., and Kalisvaart, K. J. (2021). The effect of the anticholinergic burden on duration and severity of delirium in older hip-surgery patients with and without haloperidol prophylaxis: a post hoc analysis. *Brain Behav.* 11:e2404. doi: 10.1002/brb3.2404

Trzepacz, P. T. (2000). Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Semin. Clin. Neuropsychiatry* 5, 132–148. doi: 10.153/SCNP00500132

Tsang, K. S., Page, J., and Mackenney, P. (2013). Can intravenous paracetamol reduce opioid use in preoperative hip fracture patients? *Orthopedics* 36, 20–24. doi: 10.3928/01477447-20130122-53

van Sleuwen, M., Sun, H., Eckhardt, C., Neelagiri, A., Tesh, R. A., Westmeijer, M., et al. (2022). Physiological assessment of delirium severity: the electroencephalographic confusion assessment method severity score (E-CAM-S). *Crit. Care Med.* 50, e11–e19. doi: 10.1097/ccm.0000000000005224

Vlisides, P., and Avidan, M. (2019). Recent advances in preventing and managing postoperative delirium. *F1000Res*:8. doi: 10.12688/f1000research.16780.1

Wang, C. G., Qin, Y. F., Wan, X., Song, L. C., Li, Z. J., and Li, H. (2018). Incidence and risk factors of postoperative delirium in the elderly patients with hip fracture. *J. Orthop. Surg. Res.* 13:186. doi: 10.1186/s13018-018-0897-8

Wang, Y., Tang, J., Zhou, F., Yang, L., and Wu, J. (2017). Comprehensive geriatric care reduces acute perioperative delirium in elderly patients with hip fractures: a meta-analysis. *Medicine* 96:e7361. doi: 10.1097/md.0000000000007361

Wang, L., Zhang, T., Huang, L., and Peng, W. (2020). Comparison between Dexmedetomidine and midazolam for sedation in patients with intubation after Oral and maxillofacial surgery. *Biomed Res. Int.* 2020, 7082597–7082596. doi: 10.1155/2020/7082597

Watne, L. O., Idland, A. V., Fekkes, D., Raeder, J., Frihagen, F., Ranhoff, A. H., et al. (2016). Increased CSF levels of aromatic amino acids in hip fracture patients with delirium suggests higher monoaminergic activity. *BMC Geriatr.* 16:149. doi: 10.1186/s12877-016-0324-0

Whitlock, E. L., Braehler, M. R., Kaplan, J. A., Finlayson, E., Rogers, S. E., Douglas, V., et al. (2020). Derivation, validation, sustained performance, and clinical impact of an electronic medical record-based perioperative delirium risk stratification tool. *Anesth. Analg.* 131, 1901–1910. doi: 10.1213/ane.0000000000005085

Wittmann, M., Kirfel, A., Jossen, D., Mayr, A., and Menzenbach, J. (2022). The impact of perioperative and predisposing risk factors on the development of postoperative delirium and a possible gender difference. *Geriatrics (Basel, Switzerland)* 7:65. doi: 10.3390/geriatrics7030065

Wong, C. L., Holroyd-Leduc, J., Simel, D. L., and Straus, S. E. (2010). Does this patient have delirium?: value of bedside instruments. *JAMA* 304, 779–786. doi: 10.1001/jama.2010.1182

Xing, H., Xiang, D., Li, Y., Ji, X., and Xie, G. (2020). Preoperative prognostic nutritional index predicts postoperative delirium in elderly patients after hip fracture surgery. *Psychogeriatrics* 20, 487–494. doi: 10.1111/psyg.12511

Xu, Z., Tang, Z., Yao, J., Liang, D., Jin, F., Liu, Y., et al. (2022). Comparison of low-dose morphine intrathecal analgesia and sufentanil PCIA in elderly patients with hip fracture undergoing single spinal anesthesia - a randomized clinical trial. *BMC Anesthesiol.* 22:124. doi: 10.1186/s12871-022-01677-7

Yang, S., Gu, C., Mandeville, E. T., Dong, Y., Esposito, E., Zhang, Y., et al. (2017). Anesthesia and surgery impair blood-brain barrier and cognitive function in mice. *Front. Immunol.* 8:902. doi: 10.3389/fimmu.2017.00902

Yang, Y., Zhao, X., Dong, T., Yang, Z., Zhang, Q., and Zhang, Y. (2017). Risk factors for postoperative delirium following hip fracture repair in elderly patients: a systematic review and meta-analysis. *Aging Clin. Exp. Res.* 29, 115–126. doi: 10.1007/s40520-016-0541-6

Zeng, H., Li, Z., He, J., and Fu, W. (2019). Dexmedetomidine for the prevention of postoperative delirium in elderly patients undergoing noncardiac surgery: a meta-analysis of randomized controlled trials. *PLoS One* 14:e0218088. doi: 10.1371/journal.pone.0218088

Zhang, L., Zhang, J., Yang, L., Dong, Y., Zhang, Y., and Xie, Z. (2013). Isoflurane and sevoflurane increase interleukin-6 levels through the nuclear factor-kappa B pathway in neuroglioma cells. *Br. J. Anaesth.* 110, i82–i91. doi: 10.1093/bja/aet115

Zhou, Q., Zhou, X., Zhang, Y., Hou, M., Tian, X., Yang, H., et al. (2021). Predictors of postoperative delirium in elderly patients following total hip and knee arthroplasty: a systematic review and meta-analysis. *BMC Musculoskelet. Disord.* 22:945. doi: 10.1186/s12891-021-04825-1

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EDITED BY
Chun Yang,
Nanjing Medical University, China

REVIEWED BY
Paolo Fabbietti,
National Institute of Science and Health for Aging (IRCCS), Italy
Li Cong,
Affiliated Hospital of Xuzhou Medical University, China
Nikhil Tondehal,
Mount Sinai Beth Israel, United States

*CORRESPONDENCE
François Labaste
✉ labaste.f@chu-toulouse.fr

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Postoperative delirium is a risk factor of institutionalization after hip fracture: an observational cohort study

François Labaste[1,2]*, François Delort[1], Fabrice Ferré[1], Fanny Bounes[1], Nicolas Reina[3], Philippe Valet[2], Cédric Dray[2] and Vincent Minville[1,2]

[1]Anesthesiology and Intensive Care Department CHU Toulouse, Toulouse, France, [2]Institut RESTORE UMR 1301-Inserm 5070-CNRS EFS Univ. P. Sabatier, Toulouse, France, [3]Orthopedic Surgery Department, CHU Toulouse, Toulouse, France

Introduction: Hip fracture is a common clinical problem in geriatric patients often associated with poor postoperative outcomes. Postoperative delirium (POD) and postoperative neurocognitive disorders (NCDs) are particularly frequent. The consequences of these disorders on postoperative recovery and autonomy are not fully described. The aim of this study was to determine the role of POD and NCDs on the need for institutionalization at 3 months after hip fracture surgery.

Method: A population-based prospective cohort study was conducted on hip fracture patients between March 2016 and March 2018. The baseline interview, which included a Mini-Mental State Examination (MMSE), was conducted in the hospital after admission for hip fracture. NCDs were appreciated by MMSE scoring evolution (difference between preoperative MMSE and MMSE at day 5 >2 points). POD was evaluated using the Confusion Assessment Method. The primary endpoint was the rate of new institutionalization at 3 months. We used a multivariate analysis to assess the risk of new institutionalization.

Results: A total of 63 patients were included. Thirteen patients (20.6%) were newly institutionalized at 3 months. Two factors were significantly associated with the risk of postoperative institutionalization at 3 months: POD (OR = 5.23; 95% CI 1.1–27.04; $p = 0.04$) and IADL evolution (OR = 1.8; 95% CI 1.23–2.74; $p = 0.003$).

Conclusion: Only POD but not NCDs was associated with the risk of dependency and institutionalization after hip fracture surgery. The prevention of POD appears to be essential for improving patient outcomes and optimizing the potential for returning home.

KEYWORDS
orthopedic surgery, hip fracture, delirium, dependence, institutionalization

Introduction

Hip fracture is a common clinical problem in geriatric patients often associated with an increased mortality rate and reduced functions (1). Excess mortality following hip fracture is high (1, 2). However, unfavorable outcomes go beyond mortality. Indeed, older individuals sustaining a hip fracture suffer from long-lasting limitations in mobility, activities of daily living, self-care, participation, and quality of life (1). Hip fracture-related cognitive changes, in one form or another, are a frequent postoperative complication (3–5). Postoperative delirium (POD) and neurocognitive disorders (NCDs) are also known to increase mortality, morbidity, and the risk of rehospitalization, especially in elderly patients (6–9). In survival patients, POD and NCDs lead to a loss of independence and a decline in activities of daily living (10, 11).

Therefore, previously independent living older people have a high risk of new admission to a nursing home during the subsequent months. Between 10 and 20% of hip fracture patients are institutionalized following fracture and surgery (1). Age, gender, physical function, social support, and health perception all have been found to be significantly related to outcome following a hip fracture (1, 6, 12). Prefracture cognitive impairment places patients at greater risk for institutionalization (13, 14). However, few data are available to describe the role of postoperative cognitive changes on the risk of long-term care placement need in these surgical patients (6, 15, 16). Moreover, the frailest elderly patients with preoperative dementia or mild cognitive impairment were not always excluded (16–18). To the best of our knowledge, no study has examined POD and postoperative NCDs together to determine the relative importance of each one in a no frailty and no dementia population.

The aim of this study was to assess possible associations between the occurrence of new institutionalization at 3 months and cognitive changes, POD, or postoperative NCDs in non-frail elderly patients operated for hip fracture.

Materials and methods

Study design and ethical considerations

The current study is a subgroup analysis of a prospective monocentric trial (APOCOGNIT, ClinicalTrial.gov NCT02574234). Patients were enrolled in the orthopedic service of the University Hospital of Toulouse (Toulouse, France), where an average of 800 hip fracture patients attend every year. The inclusion was performed from March 2016 to March 2018.

APOCOGNIT was approved by the Clinical Research Ethics Committee of the University Hospital of Toulouse in January 2016, with a decision number of 14 7313 02.

Written informed consent was obtained from all patients who agreed to participate in the APOCOGNIT study.

Participants

For the current study, among APOCOGNIT, all patients who completed the follow-up at 3 months and who lived at home before the fracture were included. Eligible patients were 75 years old or older and diagnosed during regular working hours with a hip fracture that required surgery. Exclusion criteria were patients with a history of dementia or mild cognitive disorders, patients with a preoperative MMSE (Mini-mental State Evaluation) score of <20 (which ranges from 0 to 30), patients with preoperative diagnosis of delirium and sepsis, patients refusing consent, and patients who did not understand the protocol.

Anesthesia procedure

All patients were operated within 24 h after admission to the hospital. If the operation was delayed more than 24 h, the patients were excluded from this study. All patients with spinal anesthesia (SA) were enrolled. If necessary, general anesthesia was performed for a second time (failure of SA).

Data collection

Preoperative assessment

Patients underwent a standardized interview conducted by an anesthesiologist. Demographic characteristics, behavioral factors, physical function, and coexisting conditions were assessed. In addition, by reviewing the patient's anesthesia records, the American Society of Anesthesiologists Classification was obtained. The Charlson comorbidity index, a weighted sum of 17 medical conditions, was also calculated (19).

Preoperative cognitive functions were measured using the MMSE. This scale was chosen because it is easy to use, as previously described (20). Functional capacities were assessed using the instrumental activities of daily living (IADL), which ranged from 0 (complete dependence) to 8 (complete independence).

Postoperative assessments

Postoperative cognitive assessment began on the next day after surgery and continued until discharge. Patients underwent daily assessment for delirium, which was determined according to the Confusion Assessment Method (CAM) diagnostic algorithm (21). The algorithm consists of four clinical criteria: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. To define a patient as having POD, both the first and the second criteria have to be present, as well as either the third or the fourth criteria (3, 21). The Confusion Assessment Method (CAM) was used in the French language and validated among the French elderly population (22).

At day 5 or at discharge if that happened before, a new MMSE scoring was performed.

As previously described (3, 20), postoperative NCDs were appreciated using the MMSE scoring evolution (difference between preoperative MMSE and MMSE at day 5 or at discharge).

After discharge, patients or their families were interviewed (via phone conversation) at 3 months to assess the IADL scale and to assess whether patients are newly institutionalized. Institutionalization was the primary outcome of the study and was defined as new admission to nursing home care within 3 months after hospital admission.

Statistical analysis

APOCOGNIT was an exploratory study designed to investigate the postoperative inflammatory profile of patients in relation to the occurrence of postoperative delirium. For the APOCOGNIT project, the number of subjects included was 105, with the aim

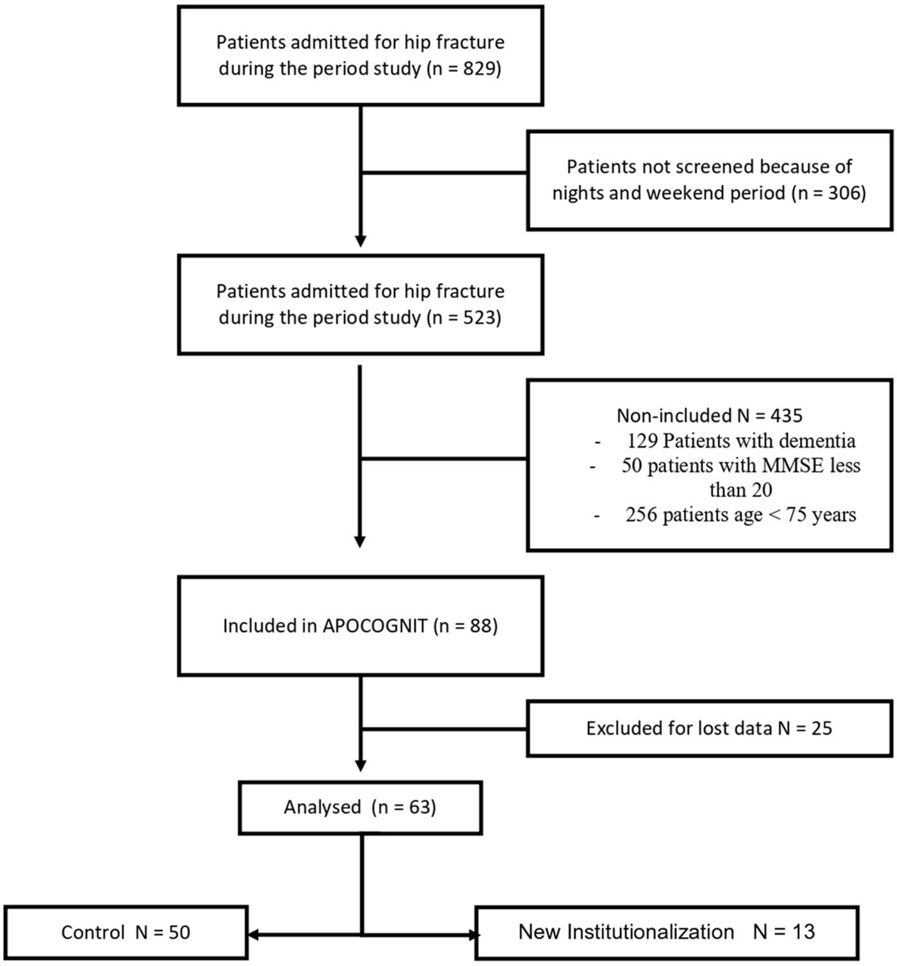

FIGURE 1
Flowchart diagram of the study.

of including at least 40 patients with postoperative delirium. We investigated the data of the subgroup of patients with 3-month follow-up.

For descriptive statistics, the results were expressed as median and 95% CI. The study population was then divided into two groups based on the occurrence of institutionalization at 3 months after hip fracture. After verification of the absence of normality of quantitative data (Anderson–Darling test), patient characteristics were compared using non-parametric tests (Mann–Whitney U-test for continuous variables and chi-square exact test for categorical variables).

The association between different covariates and dependent variables (institutionalization) was calculated using a multivariate analysis, setting an initial threshold at a p-value of < 05. After the exclusion of collinear covariates, stepwise regression (backward elimination) was applied, starting with all the variables initially chosen and then progressively removing non-significant ones.

We used XLSTAT® version 2019 1.1 statistical software (Addinsoft 2020). A p-value of < 0.05 was considered to be statistically significant.

Results

Among the 88 patients included in APOCOGNIT, 63 patients were included in this study (Figure 1). Seventeen patients were excluded because postoperative cognitive trajectory was not completed and another eight patients were excluded because they were institutionalized before surgery.

Demographic and clinical characteristics of patients are shown in Table 1. The median age of patients was 88 years (IQR 82.5–91), and the majority were women (80.9%). Fourteen patients (22.2%) had a POD, and a decrease in MMSE was observed with a median of 1 (IQR−1–3). The median of length of hospitalization was 9 days (IQR 7–12). Three months after surgery, patients presented a decline in activities of daily living, with a median loss of IADL at 2 (IQR 1–3).

Thirteen patients (20.6%) were newly institutionalized 3 months after hip fracture and surgery. The characteristics of patients and the univariate analysis are presented in Table 2.

There was no association between age ($p = 0.93$), sex ($p = 0.7$), preoperative IADL ($p = 0.99$), or Charlson comorbidity index

TABLE 1 Demographic and characteristics of patients undergoing hip fracture surgery, $N = 63$.

	Total $N = 63$
Age (years)	88.0 (82.5; 91.0)
Sex, women	80.9 (51)
Weight (kg)	62.0 (54.0; 70.0)
IBMI (kg/m^2)	23.0 (20,5; 25.0)
Preoperative MMSE	25.0 (23.0; 27.0)
Preoperative IADL	6.0 (4.5; 8.0)
Atrial fibrillation	36.5 (23)
Stroke	19.0 (12)
Diabetes	11.1 (7)
Chronic renal failure (MDRD < 60 ml/min/1.73 m^2)	38.0 (19)
High blood pressure	49.2 (31)
Ischemic cardiomyopathy	12.7 (7)
Tumor	15.8 (10)
Hypothyroidism	14.2 (9)
Surgery	58.7 (37)
Chronic cardiac failure	6.3 (4)
Surgery duration, min	90.0 (60.0; 120.0)
General anesthesia	19.0 (12)
ASA score > 2	44.4 (28)
Charlson score	5.0 (4.5; 6.5)
Delirium	22.2 (14)
MMSE at D5 or discharge	24.0 (22.0; 26.0)
MMSE evolution (D5–D1)	1.0 (−1; 3)
Length of hospitalization (days)	9.0 (7; 12)
3 months IADL	3.0 (1; 5)
IADL evolution (3 month–D1)	2.0 (1; 4)

The result is expressed as % (n) or median (Q3; Q1).
BMI, body mass index; MMSE, Mini-mental State Evaluation; IADL, instrumental activities of daily living; MDRD, Modification of Diet in Renal Disease.

(p= 0.74) and institutionalization. The evolution of MMSE during hospitalization was not different between the two groups ($p = 0.74$).

In multivariate analysis, the best model included POD, preoperative MMSE, and IADL evolution. Cognitive functions evaluated using MMSE at day 5 or at discharge appeared to be not significantly linked to the risk of institutionalization and were not included in our model.

Two factors were significantly associated with the risk of postoperative institutionalization at 3 months: POD (OR = 5.23; 95% CI 1.1–27.04; $p = 0.04$) and IADL evolution (OR = 1.8; 95% CI 1.23–2.74; $p = 0.003$).

Preoperative cognitive functions were not found to be significantly lower in patients with institutionalization at 3 months (OR = 0.78; 95% CI 0.6–1.02; $p = 0.07$). The results are shown in Table 3.

Discussion

The rate of new institutionalization was 20.6% at 3 months after a hip fracture. Delirium was found to be a risk factor of institutionalization in the multivariate analysis. Both preoperative and postoperative cognitive functions were not associated with the risk to be admitted in a nursing home. Moreover, the decline in activities of daily living was more important in patients who needed institutionalization.

These findings corroborate and extend those of previous investigations of the natural history of hip fracture and its impact on functional recovery (1, 12, 17). Placing the results in the context of earlier studies, the sample was comparable with others in rates of new nursing home placement, and the rates of new institutionalization are between 12 and 27% (23–25).

Moreover, previous studies provided clear evidence that patients recovering from hip fracture experience ongoing limitations in mobility and basic activities of daily living (1). In the present cohort, all patients presented a decline in activities of daily living at 3 months, and not surprisingly, IADL appeared as a predictive factor of the risk of institutionalization.

The current study reported that among patients with postoperative cognitive impairment, only patients who had POD would have a higher institutionalization rate. It has been found that patients who developed POD had poorer recovery within months after the surgery compared with those who did not develop it (26–28). Our study suggests that POD exerts an independent negative influence on functional recovery after hip fracture leading to an increase in poor postoperative outcomes and the need to be admitted to a nursing home. These results were already reported in a meta-analysis including medical and surgical patients, with or without memory impairment before hospitalization (6). Here, we choose to include only emergency surgical patients without preoperative cognitive impairment.

Neither the preoperative cognitive functions nor their evolution during hospitalization appeared to be linked to the risk of institutionalization. Postoperative NCDs and POD were found to be linked in a previous study (15, 20). POD significantly increased the risk of postoperative NCDs, especially in the 1st months. This relationship did not hold in longer term follow-up (29).

Several important clinical findings emerge from our study and have implications for surgeons, anesthetists, geriatricians, and other professionals involved in the care of hip fracture patients. Although early admission to a dedicated orthogeriatric unit seems not to be effective in reducing delirium (30), interdisciplinary orthogeriatric management improve long-term outcome of hip fracture patients (31, 32). In-hospital assessment of delirium seems to be important for identifying patients who are at higher risk of poor outcome after hip fracture surgery. Identification of POD in hip fracture patients can target those in need of more intensive or specialized rehabilitation. Because of their expertise in identifying and treating this condition, the finding provides additional support for geriatrician co-management of these patients

TABLE 2 New institutionalization at 3 month after hip fracture surgery, $N = 63$.

	Control	New institutionalization	p
	$N = 50$	$N = 13$	
Age (years)	88.0 (82.2; 91)	88.0 (85; 91)	0.939
Sex, women	80.0 (40.0)	84.6 (11.0)	0.700
Weight (kg)	63.0 (55.0; 70.0)	54.0 (50.0; 68.0)	0.199
IMC (kg/m^2)	23.5 (21.0; 25.0)	23.0 (20.0; 27.0)	0.772
Preoperative MMSE	25.0 (23.0; 27.5)	23.0 (21.0; 25.0)	0.040*
Preoperative IADL	6.0 (4.2; 8.0)	6.0 (5.0; 8.0)	0.985
Atrial fibrillation	34.0 (17)	46.2 (6)	0.422
Stroke	22.0 (11)	7.7 (1)	0.205
Diabetes	11.1 (7)	7.7 (1)	0.647
Chronic renal failure (MDRD < 60 ml/min/1.73 m^2)	38.0 (19)	30.8 (4)	0.626
High blood pressure	50.0 (25)	46.2 (6)	0.805
Ischemic cardiomyopathy	10.0 (5)	23.1 (3)	0.236
Tumor	14.0 (7)	23.1 (7)	0.442
Hypothyroidism	14 (7)	15.4 (2)	0.900
Surgery	56.0 (28)	69.2 (9)	0.382
Chronic cardiac failure	6.3 (4)	0 (0)	0.166
Surgery duration, min	90.0 (60.0; 120.0)	80.0 (60.0; 120.0)	0.772
General anesthesia	20.0 (10)	15.4 (2)	0.700
ASA score > 2	44.0 (20)	46.2 (6)	0.889
Charlson score	5.0 (4.2;7.0)	5.0 (5.0; 6.0)	0.741
Delirium	16 (8)	46.1 (6)	0.028*
MMSE at D5 or discharge	24.0 (22.0; 26)	22.0 (20.0; 25.0)	0.038*
MMSE evolution (D5–D1)	1 (-1.0; 3.0)	2.0 (−1.0; 3.0)	0.744
Length of hospitalization (days)	8.5 (7.0; 12.0)	9.0 (7.0; 10.0)	0.811
3 months IADL	3.0 (1.0; 5.0)	1.0 (0.0; 2.0)	0.009*
IADL evolution (3 month–D1)	2.0 (1.0; 3.0)	5.0 (3.0; 6.0)	0.002*

The result is expressed as % (n) or median (Q3; Q1)—$N = 63$.
BMI, body mass index; MMSE, Mini-mental State Evaluation; IADL, instrumental activities of daily living; MDRD, Modification of Diet in Renal Disease.
*Data included on multivariate analysis.

TABLE 3 Multivariate analysis.

	OR	IC 95%	p
Preoperative MMSE	0.79	0.59 – 1.07	0.127
Delirium	5.23	1.01 – 27.04	0.048
IADL evolution (3 month–D1)	1.80	1.23 – 2.74	0.003

MMSE, Mini-mental State Evaluation; IADL, Instrumental activities of daily living.
Hosmer–Lemeshow test = 0.92.
AUC of model = 0.87.

(31). A multidisciplinary care bundle, which is shown to reduce the incidence of delirium, has to be set up (33).

Thus, early identification and prevention strategies of POD appear crucial not only to achieve POD prevention but also to improve postoperative outcome and reduce institutionalization. In future, studies on POD treatment and prevention should take these objectives into account.

The current study has several limitations. First, the sample size was small. We were limited in our recruitment because we choose to involve aged patients without dementia, with a high preoperative MMSE. Thus, we selected cooperative patients with a good level of understanding. Second, cognitive evaluation was performed with MMSE, which is not actually recommended (3). The MMSE may lack the necessary sensitivity to identify mild cognitive impairment; thus, it is possible that more sensitive measures would have shown a higher incidence of postoperative NCD. However, MMSE was successfully used previously to study the postoperative cognitive trajectory (20). Finally, the first cognitive evaluation was performed a few hours after fracture. Patients with an acute fracture might find it difficult to concentrate on cognitive tasks because of pain or stress, which would bias toward over-diagnosing cognitive impairment with a preoperative MMSE < 20/30. This has led us to exclude more patients than expected.

Conclusion

In our study, POD and IADL evolution were linked to the risk of institutionalization. POD is a serious and common syndrome in hip fracture patients, and it may markedly affect the outcome and long-term prognosis. Interventions aimed at early identification, prevention, and treatment of this condition seem more necessary than ever. Further research is needed to identify the actual mechanisms by which delirium may contribute to poor outcomes and whether the prevention or reduction of delirium can improve outcomes after hip fracture.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University Hospital of Toulouse. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Dyer SM, Crotty M, Fairhall N, Magaziner J, Beaupre LA, Cameron ID, et al. A critical review of the long-term disability outcomes following hip fracture. *BMC Geriatr.* (2016) 16:158. doi: 10.1186/s12877-016-0332-0

2. Katsoulis M, Benetou V, Karapetyan T, Feskanich D, Grodstein F, Pettersson-Kymmer U, et al. Excess mortality after hip fracture in elderly persons from Europe and the USA: the CHANCES project. *J Intern Med.* (2017) 281:300–10. doi: 10.1111/joim.12586

3. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Anesthesiology.* (2018) 129:872–9. doi: 10.1097/ALN.0000000000002334

4. Patel V, Champaneria R, Dretzke J, Yeung J. Effect of regional versus general anaesthesia on postoperative delirium in elderly patients undergoing surgery for hip fracture: a systematic review. *Br Med J Open.* (2018) 8:e020757. doi: 10.1136/bmjopen-2017-020757

5. Yang Y, Zhao X, Dong T, Yang Z, Zhang Q, Zhang Y. Risk factors for postoperative delirium following hip fracture repair in elderly patients: a systematic review and meta-analysis. *Aging Clin Exp Res.* (2017) 29:115–26. doi: 10.1007/s40520-016-0541-6

6. Witlox J, Eurelings LSM, de Jonghe JFM, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *J Am Med Assoc.* (2010) 304:443–51. doi: 10.1001/jama.2010.1013

7. Hamilton GM, Wheeler K, Di Michele J, Lalu MM, McIsaac DI. A systematic review and meta-analysis examining the impact of incident postoperative delirium on mortality. *Anesthesiology.* (2017) 127:78–88. doi: 10.1097/ALN.0000000000001660

8. Kat MG, Vreeswijk R, de Jonghe JFM, van der Ploeg T, van Gool WA, Eikelenboom P, et al. Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years. *Dement Geriatr Cogn Disord.* (2008) 26:1–8. doi: 10.1159/000140611

9. Wiley Online Library. *Predictors of Rehospitalization Among Older Adults: Results of the CRIME Study—Sganga-—2017—Geriatrics and Gerontology International.* (2023). Available online at: https://onlinelibrary.wiley.com/doi/full/10.1111/ggi.12938 (accessed July 4, 2023).

10. Shi Z, Mei X, Li C, Chen Y, Zheng H, Wu Y, et al. Postoperative delirium is associated with long-term decline in activities of daily living. *Anesthesiology.* (2019) 131:492–500. doi: 10.1097/ALN.0000000000002849

11. Gearhart SL, Do EM, Owodunni O, Gabre-Kidan AA, Magnuson T. Loss of independence in older patients after operation for colorectal cancer. *J Am Coll Surg.* (2020) 230:573–82. doi: 10.1016/j.jamcollsurg.2019.12.021

12. Cree M, Soskolne CL, Belseck E, Hornig J, McElhaney JE, Brant R, et al. Mortality and institutionalization following hip fracture. *J Am Geriatr Soc.* (2000) 48:283–8. doi: 10.1111/j.1532-5415.2000.tb02647.x

13. Steiner JF, Kramer AM, Eilertsen TB, Kowalsky JC. Development and validation of a clinical prediction rule for prolonged nursing home residence after hip fracture. *J Am Geriatr Soc.* (1997) 45:1510–4. doi: 10.1111/j.1532-5415.1997.tb03204.x

14. Schaller F, Sidelnikov E, Theiler R, Egli A, Staehelin HB, Dick W, et al. Mild to moderate cognitive impairment is a major risk factor for mortality and nursing home admission in the first year after hip fracture. *Bone.* (2012) 51:347–52. doi: 10.1016/j.bone.2012.06.004

15. Bickel H, Gradinger R, Kochs E, Förstl H. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement Geriatr Cogn Disord.* (2008) 26:26–31. doi: 10.1159/000140804

16. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. *Dement Geriatr Cogn Disord.* (2005) 19:158–63. doi: 10.1159/000082888

17. Givens JL, Sanft TB, Marcantonio ER. Functional recovery after hip fracture: the combined effects of depressive symptoms, cognitive impairment, and delirium. *J Am Geriatr Soc.* (2008) 56:1075–9. doi: 10.1111/j.1532-5415.2008.01711.x

18. Mosk CA, Mus M, Vroemen JP, van der Ploeg T, Vos DI, Elmans LH, et al. Dementia and delirium, the outcomes in elderly hip fracture patients. *Clin Interv Aging.* (2017) 12:421–30. doi: 10.2147/CIA.S115945

19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* (1987) 40:373–83. doi: 10.1016/0021-9681(87)90171-8

20. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med.* (2012) 367:30–9. doi: 10.1056/NEJMoa1112923

21. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium? Value of bedside instruments. *J Am Med Assoc.* (2010) 304:779–86. doi: 10.1001/jama.2010.1182

22. Laplante J, Cole M, McCusker J, Singh S, Ouimet MA. Confusion assessment method. Validation of a French-language version. *Perspect Infirm Rev Off Ordre Infirm Infirm Quebec*. (2005) 3:12–4.

23. Rapp K, Rothenbacher D, Magaziner J, Becker C, Benzinger P, König H-H, et al. Risk of nursing home admission after femoral fracture compared with stroke, myocardial infarction, and pneumonia. *J Am Med Dir Assoc*. (2015) 16:715.e7–12. doi: 10.1016/j.jamda.2015.05.013

24. Katz PR. An international perspective on long term care: focus on nursing homes. *J Am Med Dir Assoc*. (2011) 12:487-492.e1. doi: 10.1016/j.jamda.2011.01.017

25. Autier P, Haentjens P, Bentin J, Baillon JM, Grivegnée AR, Closon MC, et al. Costs induced by hip fractures: a prospective controlled study in Belgium. Belgian Hip Fracture Study Group. *Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA*. (2000) 11:373–80. doi: 10.1007/s001980070102

26. Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc.* (2000) 48:618–24. doi: 10.1111/j.1532-5415.2000.tb04718.x

27. Marcantonio E, Ta T, Duthie E, Resnick NM. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. *J Am Geriatr Soc.* (2002) 50:850–7. doi: 10.1046/j.1532-5415.2002.50210.x

28. Rudolph JL, Inouye SK, Jones RN, Yang FM, Fong TG, Levkoff SE, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc.* (2010) 58:643–9. doi: 10.1111/j.1532-5415.2010.02762.x

29. Daiello LA, Racine AM, Gou RY, Marcantonio ER, Xie Z, Kunze LJ, et al. Postoperative delirium and postoperative cognitive dysfunction: overlap and divergence. *Anesthesiology.* (2019) 131:477–91. doi: 10.1097/ALN.0000000000002729

30. Watne LO, Torbergsen AC, Conroy S, Engedal K, Frihagen F, Hjorthaug GA, et al. The effect of a pre- and postoperative orthogeriatric service on cognitive function in patients with hip fracture: randomized controlled trial (Oslo Orthogeriatric Trial). *BMC Med.* (2014) 12:63. doi: 10.1186/1741-7015-12-63

31. Boddaert J, Cohen-Bittan J, Khiami F, Manach YL, Raux M, Beinis J-Y, et al. Postoperative admission to a dedicated geriatric unit decreases mortality in elderly patients with hip fracture. *PLoS ONE.* (2014) 9:e83795. doi: 10.1371/journal.pone.0083795

32. Neuerburg C, Förch S, Gleich J, Böcker W, Gosch M, Kammerlander C, et al. Improved outcome in hip fracture patients in the aging population following co-managed care compared to conventional surgical treatment: a retrospective, dual-center cohort study. *BMC Geriatr*. (2019) 19:330. doi: 10.1186/s12877-019-1289-6

33. Chuan A, Zhao L, Tillekeratne N, Alani S, Middleton PM, Harris IA, et al. The effect of a multidisciplinary care bundle on the incidence of delirium after hip fracture surgery: a quality improvement study. *Anaesthesia.* (2020) 75:63–71. doi: 10.1111/anae.14840

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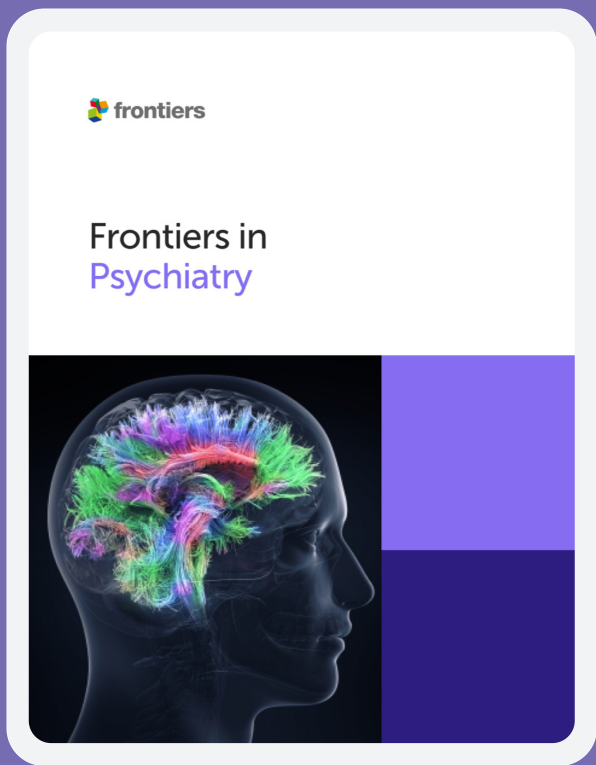

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