ORIGINAL ARTICLE

UDC: 616.348-006-089.5-089.168 : 575
DOI: https://doi.org/10.2298/VSP241009025B

APOE gene polymorphism as a potential predictor of postoperative cognitive dysfunction in colon cancer surgery under general anesthesia

Polimorfizam APOE gena kao potencijalni prediktor postoperativne kognitivne disfunkcije u operaciji raka debelog creva u opštoj anesteziji

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Abstract

Background/Aim. Postoperative cognitive dysfunction (POCD) occurs very often in operated patients. This increasingly frequent complication compromises the recovery of operated patients, impairs the quality of life of patients and their families, prolongs the length of hospital stay, and increases the cost of treatment. The aim of the study was to examine the association between the apolipoprotein E (APOE) ε4 allele and sociodemographic and clinical characteristics with the occurrence of POCD seven days and three months after colon cancer surgery (CCS) under general anesthesia (GA). **Methods.** A total of 113 patients aged 18 to 87 years who underwent CCS under GA in the period from 2021 to 2023 participated in the study. Preoperative preparation, anesthesia, and postoperative treatment were uniform and standardized for all patients. The assessment of cognitive status was conducted using the Mini Mental State Examination psychometric test on the day before surgery, on the seventh postoperative day, and three months after surgery. **Results.** Seven days after surgery, a statistically significant impairment of cognitive functions was found in patients with the APOE ε4 allele in their genotype ($p = 0.007$). Patients 65 years old or above were more likely to have POCD three months after surgery compared to younger patients (80.0% vs. 52.9%; $p = 0.003$). **Conclusion**. The presence of the APOE ε4 allele is a potential predictor of the occurrence of POCD seven days after surgery, and age is a significant sociodemographic factor for the occurrence of POCD three months after CCS is performed under GA.

Key words:
anesthesia, general; cognitive dysfunction; colonic neoplasms; prognosis; psychological tests.

Apstrakt

Uvod/Cilj. Postoperativni kognitivni poremećaj (*postoperative cognitive dysfunction* – POCD) se veoma često javlja kod operisanih bolesnika. Ta sve češća komplikacija negativno utiče na oporavak operisanih bolesnika, narušava kvalitet života kako bolesnika tako i njihovih porodica, produžava dužinu hospitalizacije i uvećava troškove lečenja. Cilj rada bio je da se ispita povezanost ε4 alela apolipoproteina E (APOE), sociodemografskih i kliničkih karakteristika sa pojavom POCD sedam dana i tri meseca posle operacije karcinoma debelog creva (KDC) u opštoj anesteziji (OA). **Metode.** U istraživanju je učestvovalo 113 bolesnika starosne dobi od 18 do 87 godina koji su bili podvrgnuti operaciji KDC u OA u periodu od 2021. do 2023. godine. Preoperativna priprema, anestezija i postoperativno lečenje bili su ujednačeni i standardizovani kod svih bolesnika. Procena kognitivnog statusa urađena je na osnovu psihometrijskog testa *Mini Mental State Examination* jedan dan pre operacije, sedmog postoperativnog dana i tri meseca posle operacije. **Rezultati**. Sedam dana posle operacije, utvrđen je statistički značajan poremećaj kognitivnih funkcija kod bolesnika koji su u svom genotipu imali ε4

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alel APOE ($p = 0,007$). Bolesnici od 65 godina i stariji češće su imali POCD tri meseca posle operacije u poređenju sa mlađim bolesnicima (80,0% vs. 52,9%; $p < 0,003$). **Zaključak**. Prisustvo ε4 alela APOE predstavlja potencijalni prediktor nastanka POCD sedam dana posle operacije, a godine starosti predstavljaju značajan sociodemografski faktor nastanka POCD tri meseca posle operacije KDC u OA.

Ključne reči:
anestezija, opšta; saznanje, disfunkcija; kolon, neoplazme; prognoza; psihološki testovi.

Introduction

Postoperative cognitive dysfunction (POCD) is one of the most significant neurological morbidities after surgery and anesthesia, which is a significant increase on a global scale. The estimated current prevalence of POCD in a short period, seven days after the surgery, is approximately 3–53% [1]. POCD is particularly associated with age and complex operations. As such, this problem has a great impact on the quality of life of the patient and family. At the same time, it causes high social and personal costs [1, 2]. POCD is defined using one or more standardized psychometric tests, such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Clock Drawing Test (CDT), as well as a range of other psychometric tests [3–7]. The MMSE is one of the most commonly used tests for examining cognitive state. It includes testing different domains of cognition, such as concentration, visual-spatial abstraction, attention, and memory [7].

The majority of studies focused on examining predisposing risk factors for the occurrence of POCD, including neurological disorders, surgical interventions, level of education, sex, age, types of anesthesia, and drugs used in anesthesia [2,8].

Due to the global trend of increased life expectancy and the growing number of the elderly population, the need for operative treatment has also increased significantly, which eventually leads us to the understanding that POCD could become a problem of epidemiological proportions [8]. Over the last decade, an increasing number of studies have been done examining the role of genetic risk factors in the development of POCD [9].

Apolipoprotein E (APOE) alleles are perhaps the most significant genetic determinants that have been investigated and linked to the development of POCD [10]. The mentioned gene for human APOE is located on chromosome 19 and contains three polymorphic alleles: ε2, ε3, and ε4. There are three heterozygotes (ε2/ε3, ε2/ε4, and ε3/ε4) and three homozygotes (ε2/ε2, ε3/ε3, and ε4/ε4). The APOE ε4 allele, which plays a leading role in the deposition of amyloid plaque, is the most significant risk factor for the development of Alzheimer's disease and POCD [10, 11]. The expression and effects of the APOE ε4 genotype are the result of a complex interaction between genetic predispositions and external influences [12].

A larger number of studies dealt with the connection between surgical interventions and POCD, where it was observed that they were positively correlated [13]. A more recent meta-analysis showed a significant association between the APOE ε4 allele and POCD seven days and three months after various surgical interventions. When studies involving patients who underwent cardiovascular surgery were excluded from the analysis, no significant association between POCD and the APOE ε4 allele was observed [9].

Up to now, little has been known about the association of POCD in patients who underwent colon and gastric cancer surgery [8, 14, 15]. Some studies examined the association of POCD in patients who underwent brain cancer surgery [16]. However, in the available literature, there is no data on the association between POCD and the APOE ε4 allele in patients who underwent colon cancer (CC) surgery – CCS under general anesthesia (GA).

The aim of our study was to examine the association of the APOE ε4 allele and sociodemographic and clinical variables with the occurrence of POCD seven days and three months after the CCS under GA.

Methods

The study was conducted according to the valid permission of the Ethics Committee of the University Hospital of Foča, Bosnia and Herzegovina (No. 1-1051/2, from 13 July 2021). The entire study was conducted following the principles of the Declaration of Helsinki, by the law on medical research involving human subjects. The patients gave their written consent for the study. The study was conducted from January 2021 to August 2023.

Study population

This prospective observational study included patients undergoing open CCS under GA. A total of 113 patients of both sexes, aged 18 to 87 years, were recruited for this study.

The criteria for inclusion in this study were as follows: patients over 18 years of age diagnosed with CC based on pathohistological (PH) findings after colonoscopy and patients without cognitive impairment before surgery, whose cognitive status was checked based on the MMSE. The following were excluded from the study: patients who did not provide informed consent or were incapable of doing so; those with a history of central nervous system disease, such as dementia and other neurodegenerative diseases, cerebrovascular disease, and liver or kidney failure; patients with visual or sensory disorders; patients who have language difficulties or significant hearing impairment; patients who have used antipsychotic medication or drugs affecting cognitive functions; patients diagnosed with psychiatric diseases, delirium or drug, alcohol, or opioid abuse.

For each participant, sociodemographic data (age, sex, level of education, marital status), clinical data related to the

primary disease [PH findings, tumor location, type of surgery, duration of anesthesia, body mass index (BMI), and blood transfusions], and medical history [presence of comorbidities, such as diabetes mellitus (DM), anemia, and hypertension] were collected. Additionally, the results of hematological, biochemical, and genetic analyses, as well as information on operative and postoperative complications, were documented seven days after surgery.

All patients were subjected to the same preoperative, operative, and postoperative anesthetic procedures. Based on the diagnosis, the appropriate surgical procedure was performed under endotracheal GA.

Psychometric testing

Prior to inclusion in the study, all subjects were psychometrically tested on the seventh day and three months after surgery. MMSE was used to assess POCD. The test includes the assessment of six domains through eleven questions: time orientation (5 points), place orientation (5 points), registration (3 points), attention and calculation (5 points), memory (3 points), and language (9 points). MMSE scale ranges from 0 to 30 points; a score of 23 points or less was defined as cognitive disorder [3, 7].

APOE genotyping

Genomic DNA was isolated from 200 μL of whole blood using a commercial kit (GeneJET Genomic DNA Purification Kit, Thermo Fisher Scientific, Waltham, MA, USA). A polymerase chain reaction (PCR) was performed in a final volume of 25 μL containing 0.5 mM forward F: 5'- TAA GCT TGG CAC GGC TGT CCA AGG A -3' and the reverse R: 5'- ACA GAA TTG GCC CCG GCC TGG TAC AC -3' primers [17]. PCR amplification consisted of 30 cycles of 30 sec at 90 °C, 20 sec at 72 °C, and 20 sec at 72 °C. PCR products [244 base pairs (bp)] were confirmed by 1% agarose gel electrophoresis and digested using HhaI (Biolabs New England, Ipswich, MA, USA). The digested products were analyzed on a 4% agarose gel. The fragment lengths were as follows: for e2/e2 genotype 94 bp and 81 bp; for e2/e3 genotype 94 bp, 81 bp, and 66 bp; for e2/e4 genotype 94 bp, 81 bp, 66 bp, and 58 bp; for e3/e3 genotype 94 bp and 58 bp; for e3/e4 genotype 94 bp, 66 bp, and 58 bp; for e4/e4 genotypes 66 bp and 58 bp.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25 software. Numerical data are presented as means or medians with corresponding measures of variability (ranges and standard deviations). Categorical data are presented as absolute numbers with frequencies. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test normal distribution. The Chi-square test, McNemar test, Wilcoxon, and Mann-Whitney *U* test were used as statistical tests. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

The sociodemographic and clinical characteristics of the patients are given in Table 1. A total of 113 patients participated in this study, and 51 (45.1%) were women. The average age was 66.62 ± 11.28 years. Of 113 patients, 74 (65.5%) were highly educated, and 110 (97.3%) were married. The average BMI was 26.24 ± 3.71 kg/m². The following comorbidities were present: 23 (20.4%) had DM, and 63 (55.8%) had hypertension. The most frequently diagnosed malignancy was sigmoid CC, identified in 42 (37.2%) patients, while the least common was descending CC, observed in 8 (7.1%) patients. Each patient received an average of 439.82 ± 193.10 mL of blood during the operation and an average of 200.44 ± 189.08 mL after the operation.

Table 1

Sociodemographic and clinical characteristics of 113 patients who underwent colon cancer surgery

Variables	Values
Age (years)	66.62 ± 11.28
Sex	
male	62 (54.9)
female	51 (45.1)
Level of education (years)	
≤ high school	74 (65.5)
> high school	39 (34.5)
Marital status	
married	110 (97.3)
single	3 (2.7)
BMI (kg/m²)	26.24 ± 3.71
Diabetes mellitus	
yes	23 (20.4)
no	90 (79.6)
Hypertension, n (%)	
yes	63 (55.8)
no	50 (44.2)
Duration of surgery (hrs)	4.43 ± 0.87
Total treatment time (days)	13.47 ± 1.52
Postoperative treatment time (days)	10.55 ± 1.41
Diagnosis	
ascending colon cancer	24 (21.2)
transvers colon cancer	17 (15.0)
descending colon cancer	8 (7.1)
sigmoid colon cancer	42 (37.2)
rectal cancer	22 (19.5)
Amount of blood during surgery (mL)	439.82 ± 193.10
Amount of blood after surgery (mL)	200.44 ± 189.08
Amount of blood all day (mL)	640.27 ± 281.01
APOE genotypes	
ε2/ε4	27 (23.9)
ε3/ε4	67 (59.3)
ε2/ε2	1 (0.9)
ε3/ε3	14 (12.4)
ε4/ε4	0 (0)
ε2/ε3	0 (0)
Not detected*	4 (3.5)

BMI – body mass index; APOE – apolipoprotein E.
Values are given as numbers (percentages) or mean ± standard deviation.
***could not be analyzed.**

The average duration of anesthesia was 4.43 ± 0.87 hrs, and the average length of hospital stay was 13.47 ± 1.52 days. At least one APOE ε4 allele was found in 94 (83.2%) patients. The most common allele combination was ε3/ε4, observed in 67 (59.3%) subjects, while no subjects carried the APOE ε2/ε3 or APOE ε4/ε4 allele combination.

Based on the MMSE, 105 (92.9%) patients had POCD seven days postoperatively, while POCD was found in 45 (39.8%) patients three months after surgery (Table 2).

Among patients with POCD seven days after surgery, 88 (89.8%) had at least one APOE ε4 allele, while this allele was present in 6 (54.5%) patients without POCD. This difference was statistically significant ($p = 0.007$). However, this difference was not observed three months postoperatively, where 36 (81.8%) patients with POCD and 58 (89.2%) patients without POCD carried at least one APOE ε4 allele ($p = 0.270$). Three months postoperatively, the incidence of POCD was significantly related only to older patients. About 36 (80.0%) patients aged 65 years and older exhibited POCD ($p = 0.003$). Other examined risk factors for the occurrence of POCD, such as level of education, BMI, duration of anesthesia, length of hospitalization, pain, and amount of prescribed blood during and after surgery, did not show statistical significance seven days or three months after surgery. Furthermore, no significant difference was found in hematological and biochemical parameters between patients with and without POCD seven days after the surgical intervention (Table 3).

Table 2

The incidence of POCD in patients seven days and three months after CCS according to the MMSE score

Time after surgery	MMSE score (points)	
	patients with POCD (0–23)	patients without POCD (24–30)
7 days	105 (92.9)	8 (7.1)
3 months	45 (39.8)	68 (60.2)

CCS – colon cancer surgery; MMSE – Mini Mental State Examination; POCD – postoperative cognitive dysfunction.
Values are given as numbers (percentages).

Table 3

Sociodemographic, clinical, and genetic characteristics of patients with and without POCD seven days and three months after CCS

Risk factors	7 days after CCS			3 months after CCS		
	Patients without POCD	Patients with POCD	*p*	Patients without POCD	Patients with POCD	*p*
Age (years)						
< 65	5 (62.5)	36 (34.3)	0.110	32 (47.1)	9 (20.0)	0.003
≥ 65	3 (37.5)	69 (65.7)		36 (52.9)	36 (80.0)	
Level of education (years)						
≤ high school	6 (75.0)	68 (64.8)	0.712	46 (67.6)	28 (62.2)	0.686
> high school	2 (25.0)	37 (35.2)		22 (32.4)	17 (37.8)	
BMI (kg/m^2)						
0–19	0 (0)	3 (2.9)	0.532	2 (2.9)	1 (2.2)	0.946
20–24	2 (25.0)	44 (41.9)		27 (39.7)	19 (42.2)	
> 24	6 (75.0)	58 (55.2)		39 (57.4)	25 (55.6)	
Duration of anesthesia (hrs)						
0–4	3 (37.5)	65 (61.9)	0.262	39 (57.4)	29 (64.4)	0.557
> 4	5 (62.5)	40 (38.1)		29 (42.6)	16 (35.6)	
Duration of hospitalization (days)						
0–10	0 (0)	3 (2.9)	1.000	3 (4.4)	0 (0)	0.275
> 10	8 (100)	102 (97.1)		65 (95.6)	45 (100)	
Amount of blood during surgery (mL)						
0–600	6 (75.0)	81 (77.1)	1.000	53 (77.9)	34 (75.6)	0.821
> 601	2 (25.0)	24 (22.9)		15 (22.1)	11 (24.4)	
Total amount of blood during hospitalization (mL)						
0–600	5 (62.5)	49 (46.7)	0.476	33 (48.5)	21 (46.7)	1.000
> 601	3 (37.5)	56 (53.3)		35 (51.5)	24 (53.3)	
Intraoperative fluid replacement (mL)						
0–2,000	0 (0)	8 (7.6)	0.629	7 (10.3)	1 (2.2)	0.249
2,001–4,000	8 (100)	94 (89.5)		59 (86.8)	43 (95.6)	
> 4,000	0 (0)	3 (2.9)		2 (2.9)	1 (2.2)	

Table 3 (continued)

Risk factors	7 days after CCS			3 months after CCS		
	Patients without POCD	Patients with POCD	*p*	Patients without POCD	Patients with POCD	*p*
Postoperative fluid replacement (mL)						
0–2,000	0 (0)	2 (1.9)	0.889	1 (1.5)	1 (2.2)	0.687
2,001–4,000	8 (100)	102 (97.1)		66 (97.1)	44 (97.8)	
> 4,000	0 (0)	1 (1.0)		1 (1.59)	0 (0)	
APOE ε4 allele						
yes	6 (54.5)	88 (89.8)	0.007	58 (89.2)	36 (81.8)	0.270
no	5 (45.5)	10 (10.2)		7 (10.8)	8 (18.2)	

Values are given as numbers (percentages). For abbreviations, see Tables 1 and 2.
Chi-squared test; $p < 0.05$ statistical significance.

Discussion

To our knowledge, this is the first study to investigate the relationship between the APOE ε4 allele and POCD in CCS patients under GA. In addition, the influence of other sociodemographic and clinical factors on POCD incidence was assessed. We found that the APOE ε4 allele and age could significantly increase the incidence of POCD seven days and three months after CCS under GA, respectively.

The primary approach for treating patients with CC is surgical treatment. Considering that the incidence of CC increases in the aging population, an increase in the incidence of POCD can be expected since older patients are more susceptible to the effects of surgery and anesthesia, which was confirmed in our study. Activation of the immune system and inflammation during surgery are key factors in the development of POCD [18, 19]. These mechanisms are triggered during the surgical procedure and anesthesia, leading to the release of peripheral inflammatory cytokines that can directly compromise the integrity of the blood-brain barrier while also increasing the infiltration of inflammatory factors and macrophages into the brain. This ultimately leads to microglial activation and the initiation of an inappropriate inflammatory response in the hippocampus, contributing to POCD. This cascade of events can subsequently cause synaptic damage and neuronal death [20]. Another important factor associated with the development of POCD is anesthesia. The effects of anesthetics during surgery can lead to mitochondrial damage, further inducing oxidative damage to neurons [21]. As a result, microglial activation occurs, leading to neuroinflammation and neuronal apoptosis, which significantly contributes to POCD [20]. However, the multifactorial etiology of POCD has been proposed. It is essential to identify risk factors for POCD so that the success rate of surgical interventions can be improved and complications prevented. Recently, genetic risk factors associated with POCD have garnered significant research interest [22, 23]. Therefore, the present study investigates the possible effect of the APOE ε4 allele on POCD incidence following CCS under GA, besides the patient's sociodemographic and clinical factors. In this study, the MMSE was chosen to assess POCD. This test is one of the most widely used tools for measuring cognitive function, including cognitive function measurement after surgical procedures, due to its simplicity and ease of administration, with sensitivity from 80% to 95% and specificity from 86% to 100% [24–26].

In our study of patients undergoing CCS under GA, the incidence of POCD seven days and three months after surgery was 92.9% and 39.8%, respectively. The prevalence of POCD after various surgical interventions varies significantly across studies. Specifically, the incidence of POCD following noncardiac surgery ranges from 41% to 75% seven days after surgery and from 18% to 45% three months after surgery. Conversely, higher rates of POCD are observed following cardiac surgery [26–29]. POCD obtained in the present study is higher than that found in other types of noncardiac surgery studies, especially in the early postoperative period (seven days). The possible explanation for this variation in the results of present and previous studies can be partially explained by some methodological differences, such as the tool used to define POCD, time of POCD testing, primary diagnosis, type of surgical intervention, as well as sample characteristics. The sample in this study is characterized by a higher percentage of older patients and those with a lower level of education. The incidence of POCD decreases over time, as demonstrated in this study. This reduction may be attributed to the overall improvement in the patient's health status following the resolution of the primary disease and its associated symptoms.

Of all patients carrying at least one APOE ε4 allele (94 out of 113 in total), the largest proportion of participants, i.e., 67 patients (59.3%), had the ε3/ε4 allele, 27 (23.9%) had the ε2/ε4 allele, while no participants had the ε4/ε4 allele. The present study showed a significant relationship between the APOE ε4 allele and POCD seven days after surgery ($p = 0.007$) but not three months after surgery ($p = 0.270$). Some studies found that the APOE ε4 allele is a risk factor for POCD one week after surgery. In contrast, others found a significant relationship between the APOE ε4 allele and POCD three months after surgery [30, 31]. Other authors found no association between POCD and APOE ε4 allele status one week or three months after surgery [32]. The meta-analysis conducted by Cao et al. [10], which included nine independent studies, found a significant association between the APOE ε4 allele and POCD one week after surgery; however, no such association was observed one to three months or one year following surgery. A possible explanation for the predominantly short-term effect of the APOE ε4 allele on POCD is that the incidence of POCD is

notably higher in the first seven days following surgery. Additionally, the APOE ε4 allele may exacerbate the negative effects of surgery by influencing neuronal repair mechanisms, altering neuronal susceptibility to injury, or increasing embolic load. A recent meta-analysis including 22 studies showed that the APOE ε4 allele was significantly associated with POCD within one week and one to three months after surgery, but not one year after surgery [9]. Furthermore, this meta-analysis included trial sequential analysis according to the surgery type to strengthen the conclusiveness of the results. After excluding patients who underwent cardiovascular surgery, it was found that POCD was not significantly associated with the APOE ε4 allele. Furthermore, excluding both studies that included participants with cognitive impairment as well as retrospective studies, this sensitive analysis revealed a significant association between POCD and the APOE ε4 allele only one week after surgery, which is consistent with the findings of the present study. Several mechanisms might be responsible for the APOE ε4 allele-related POCD. Older APOE ε4 allele carriers may experience reduced cerebral blood flow, which could contribute to the risk of developing POCD [33]. In addition, the clearance of amyloid-β, an essential factor in Alzheimer's disease, is reduced in APOE ε4 allele carriers, predisposing the individuals to POCD. Moreover, the APOE ε4 allele has been linked to the impairment of the blood-brain barrier in Alzheimer's patients, a mechanism that can be significant in the context of POCD [11].

The current understanding is that the risk of developing POCD increases with age [2]. In this study, patients aged 65 years or above had a significant risk of POCD three months after surgery ($p = 0.003$). This result is consistent with previous studies, which indicate that age is one of the most important factors for POCD [34]. The possible reason for the fact that age has only a medium-term effect (three months) in the present study can be explained by the fact that we recruited older patients (mean age 66.6). Although POCD can affect surgical patients in all age groups on a short-term basis, it resolves faster in the younger age group [35]. A decrease in brain volume and cerebral blood flow, with subsequent reduced oxygen delivery and metabolism, advancing age, and age-induced central nervous system apoptosis, may increase the incidence of POCD in elderly patients [36]. Moreover, older patients may experience the progression of their underlying medical comorbidities or develop new health problems between the two testing periods.

Other clinical and sociodemographic factors previously associated with the incidence of POCD, including gender, educational level, duration of surgery and anesthesia, blood loss, and length of hospitalization, did not demonstrate a significant relationship with POCD in this study. The most plausible explanations for this lack of association may stem from the overall higher incidence of POCD observed in both investigated time intervals and the limited sample size.

This study has several limitations that should be taken into account. Firstly, the findings may be limited to patients undergoing CCS under GA. The potential application of laparoscopic techniques should be considered a less stressful option. Additionally, we did not assess which specific cognitive domains (memory, attention, information processing, visuospatial skills, and cognitive flexibility) were most affected in the postoperative period. Furthermore, the relatively small sample size of our study restricts a comprehensive analysis of the relationship between the APOE ε4 allele and POCD. Future prospective studies with larger cohorts and more detailed psychometric assessments are warranted to enhance our understanding of the factors contributing to the development of POCD.

Conclusion

The present study indicates that the presence of the apolipoprotein E ε4 allele may serve as a potential risk predictor for the occurrence of postoperative cognitive dysfunction seven days after surgery. Additionally, age emerges as a significant sociodemographic factor influencing the incidence of postoperative cognitive dysfunction three months after colon cancer surgery performed under general anesthesia. These findings highlight the importance of genetic and demographic factors in assessing the risk of postoperative cognitive dysfunction. Targeted interventions and monitoring may be beneficial for the population at risk. Further research is needed to explore the underlying mechanisms and develop strategies for reducing the impact of these risk factors on cognitive outcomes after surgery.

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Received on October 9, 2024
Revised on November 11, 2024
Revised on January 17, 2025
Accepted on January 28, 2025
Online First April 2025