Am J Transl Res 2025;17(11):8675-8683
www.ajtr.org /ISSN:1943-8141/AJTR0167861

Original Article

Superior neuroprotective effect of ciprofol over propofol in elderly patients undergoing laparoscopic radical gastrectomy

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Received August 1, 2025; Accepted October 27, 2025; Epub November 15, 2025; Published November 30, 2025

Abstract: Objectives: To investigate the effects of ciprofol or propofol anesthesia on cognitive function in elderly patients undergoing laparoscopic radical gastrectomy for gastric cancer. Methods: Data of 100 elderly patients were retrospectively collected and cases were assigned to the observation group (ciprofol, n=50) and the control group (propofol, n=50) according to the anesthesia method. Heart rate (HR), mean arterial pressure (MAP), and bispectral index (BIS) were recorded at anesthesia induction and intraoperative time points. Post-anesthesia recovery findings, visual analogue scale (VAS) scores, incidence of agitation, and postoperative cognitive dysfunction (POCD) were compared. Mini-Mental State Examination (MMSE) scores were assessed preoperatively and postoperatively. Serum levels of aldosterone (ALD), cortisol (COR), adrenocorticotropic hormone (ACTH), S100β protein, neuron-specific enolase (NSE), and oxidative stress markers [reactive oxygen species (ROS), malondialdehyde (MDA), superoxide dismutase (SOD)] were measured before and after surgery. Results: HR, MAP, and BIS values were significantly lower in the observation group than in the control group at corresponding time points. The observation group also had better recovery profiles, lower VAS scores, and reduced incidence of POCD and adverse reactions ($P < 0.05$). Postoperative MMSE scores were significantly higher in the observation group ($P < 0.05$). Although postoperative serum ALD, COR, ACTH, ROS, MDA, SOD, S100β, and NSE levels increased in both groups, the elevation was less pronounced in the observation group ($P < 0.05$). Conclusions: Ciprofol anesthesia effectively reduces intraoperative physiological fluctuations, alleviates postoperative stress response, and improves postoperative cognitive function in elderly patients undergoing laparoscopic radical gastrectomy for gastric cancer.

Keywords: Ciprofol, propofol, laparoscopy, gastric cancer, cognitive function

Introduction

With ongoing aging of the population, the proportion of elderly patients with gastric cancer is steadily increasing. Laparoscopic radical gastrectomy has become a common surgical approach in this population due to its merits of minimal invasiveness, reduced tissue trauma, and faster postoperative recovery [1-3]. However, elderly patients generally exhibit diminished physiological reserves and decreased tolerance to surgical and anesthetic stress, making them more susceptible to postoperative cognitive dysfunction (POCD). POCD can impede postoperative recovery, reduce quality of life, and impose significant burdens on caregivers and healthcare systems [4-6]. Therefore, optimizing the choice of anesthetic agents to reduce the incidence of POCD has become a critical issue in clinical practice.

Anesthetic agents play a central role during surgery, significantly affecting physiologic homeostasis and postoperative recovery. Propofol, a commonly used intravenous anesthetic, is favored for its rapid onset, timely awakening, and short duration of action, making it widely applied for anesthesia induction and maintenance across various surgical procedures [7, 8]. However, studies have indicated that the use of propofol in elderly patients may still be associated with a certain degree of POCD. The under-

https://doi.org/10.62347/OEEB5164

lying mechanisms are thought to involve direct neurotoxic effects, disruption of neurotransmitter release and metabolism, and the induction of a systemic stress response [9, 10].

Compared to propofol, ciprofol exhibits distinct pharmacokinetic and pharmacodynamic properties. Although its onset and recovery times are comparable to propofol, ciprofol demonstrates superior hemodynamic stability and a lower incidence of adverse reactions [11, 12]. Theoretically, ciprofol may confer neuroprotective effects in elderly patients by modulating stress responses and attenuating neuroinflammation and oxidative stress, thereby reducing the risk of POCD. While previous studies have explored the safety and efficacy of ciprofol in other surgical contexts and patient populations, its application in elderly patients undergoing laparoscopic radical gastrectomy remains underreported [13].

Thus, the present study aimed to compare the effects of ciprofol and propofol on cognitive function in elderly patients undergoing laparoscopic radical gastrectomy for gastric cancer to provide clinical evidence to help reduce the incidence of POCD in this population.

Materials and methods

Case selection

This study adopted a retrospective cohort design. Data of patients who underwent laparoscopic radical gastrectomy at Mianyang Central Hospital between May 2022 and May 2024 were collected. According to the anesthesia methods, patients were divided into the observation group (cyclopofol anesthesia) or the control group (propofol anesthesia), with 50 cases in each group. The study was approved by the Ethics Committee of Mianyang Central Hospital (S-2020-019).

Inclusion and exclusion criteria

Patients were included if they (1) met the diagnostic criteria and surgical indications for laparoscopic radical gastrectomy described in the Guidelines for the Diagnosis and Treatment of Gastric Cancer (2022 edition), with a preoperative American Society of Anesthesiologists (ASA) physical status of grade I-II [14]; (2) had not taken psychotropic medications within 90 days before surgery; (3) had no history of psychiatric or psychological disorders; (4) had a tumor stage of I-II; (5) had complete clinical data.

Patients were excluded if they (1) had a history of cerebral hemorrhage or traumatic brain injury; (2) were unable to complete cognitive function assessments; (3) had received anesthesia within the previous 90 days; (4) had severe comorbidities; (5) were participating in other studies; or (6) showed poor compliance.

Anesthesia protocol

For anesthesia induction, patients in the control group received propofol (Xi'an Libang Pharmaceutical Co., Ltd., H19990282) 1-1.5 mg/kg combined with rocuronium bromide (Zhejiang Xianju Pharmaceutical Co., Ltd., H20090070) 0.6 mg/kg and sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., H20050580) 0.2 μg/kg. Patients in the observation group received ciprofol (Liaoning Haisco Pharmaceutical Co., Ltd., H20210007) 0.4 mg/kg combined with rocuronium bromide 0.6 mg/kg and sufentanil 0.2 μg/kg.

For anesthesia maintenance, patients in the control group received continuous intravenous infusion of propofol 4-8 mg/kg·h, together with remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., H20030200) 0.05-0.2 μg/kg·min and rocuronium bromide 5 μg/kg·min. In the observation group, propofol was replaced by ciprofol at 0.2 mg/kg·h, while the doses of remifentanil and rocuronium bromide remained the same. During anesthesia, the bispectral index (BIS) was maintained between 40 and 60.

Observation indicators

Primary indicators: Hemodynamics and BIS were recorded by measuring heart rate (HR), mean arterial pressure (MAP), and BIS values at the following time points: upon entry to the operating room, during anesthesia induction, at tracheal intubation, at skin incision, at 10, 30, and 60 minutes intraoperatively, and at the end of surgery. Cognitive function was assessed using Mini-Mental State Examination (MMSE) scores, which were collected at 1 day before surgery and at 6 hours, 12 hours, 1 day, 3 days, and 7 days postoperatively. Stress and oxidative stress biomarkers were determined by col-

Table 1. Comparison of general characteristics between the two groups

Variable	Control (n=50)	Observation (n=50)	t/χ^2	*P*
Age (years)	68.9±5.7	69.4±6.1	0.423	0.673
Gender			0.437	0.509
Male	34 (68.00)	37 (74.00)		
Female	16 (32.00)	13 (26.00)		
BMI (kg/m^2)	23.07±2.15	23.28±1.96	0.510	0.611
ASA			0.713	0.398
I	31 (62.00)	35 (70.00)		
II	19 (38.00)	15 (30.00)		

lecting venous blood samples 1 day before and 1 day after surgery. ELISA was used to measure serum levels of aldosterone (ALD), cortisol (COR), adrenocorticotropic hormone (ACTH), S100β, and neuron-specific enolase (NSE), as well as oxidative stress markers including reactive oxygen species (ROS), malondialdehyde (MDA), superoxide dismutase (SOD). All ELISA kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd., (ALD: MLB-ALD-001; COR: MLB-COR-002; ACTH: ml060657; S100β: ml057716; NSE: ml057772; ROS: ml057611; MDA: ml058173; SOD: ml060511).

Secondary indicators: Anesthesia recovery indices were recorded, including the time from discontinuing anesthetic infusion to eye-opening (defined as recovery of consciousness), the time to tracheal extubation, and the time to discharge from post-anesthesia care unit. Postoperative pain was evaluated at different time points using the visual analogue scale (VAS), where 0 represented no pain and 10 represented severe pain. Postoperative agitation and complications were analyzed by applying an agitation scoring scale, and the incidences of POCD and other complications were documented.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0. Categorical variables were expressed as n (%), and comparisons were conducted using the chi-square test. Continuous variables were expressed as mean ± standard deviation. The comparison between two time points was conducted using the paired t-test. One-way analysis of variance followed by LSD test was used for comparisons among multiple groups. *P*-value < 0.05 was considered significant.

Results

Comparison of general characteristics

There were no significant differences in general characteristics between the two groups in terms of age, sex, body mass index (BMI), or ASA classification ($P > 0.05$). Details are presented in **Table 1**.

Comparison of hemodynamics and BIS at different time points

At anesthesia induction, post-tracheal intubation, skin incision, 10 min, 30 min, 60 min intraoperatively, and at the end of surgery, the observation group showed significantly lower HR, MAP, and BIS values compared to the control group ($P < 0.05$). Detailed results are presented in **Figure 1**.

Comparison of anesthesia recovery times

The observation group exhibited significantly shorter times to consciousness recovery, tracheal extubation, and discharge from the post-anesthesia care unit compared to the control group ($P < 0.05$). See **Table 2** for details.

Comparison of postoperative pain scores and incidence of POCD

At 12 and 24 hours postoperatively, the observation group demonstrated significantly lower VAS pain scores than the control group. Additionally, the incidence of POCD at all assessed time points was significantly lower in the observation group ($P < 0.05$). Detailed data are shown in **Table 3**.

Comparison of MMSE scores at different time points

There were no significant differences in MMSE scores between the two groups preop-

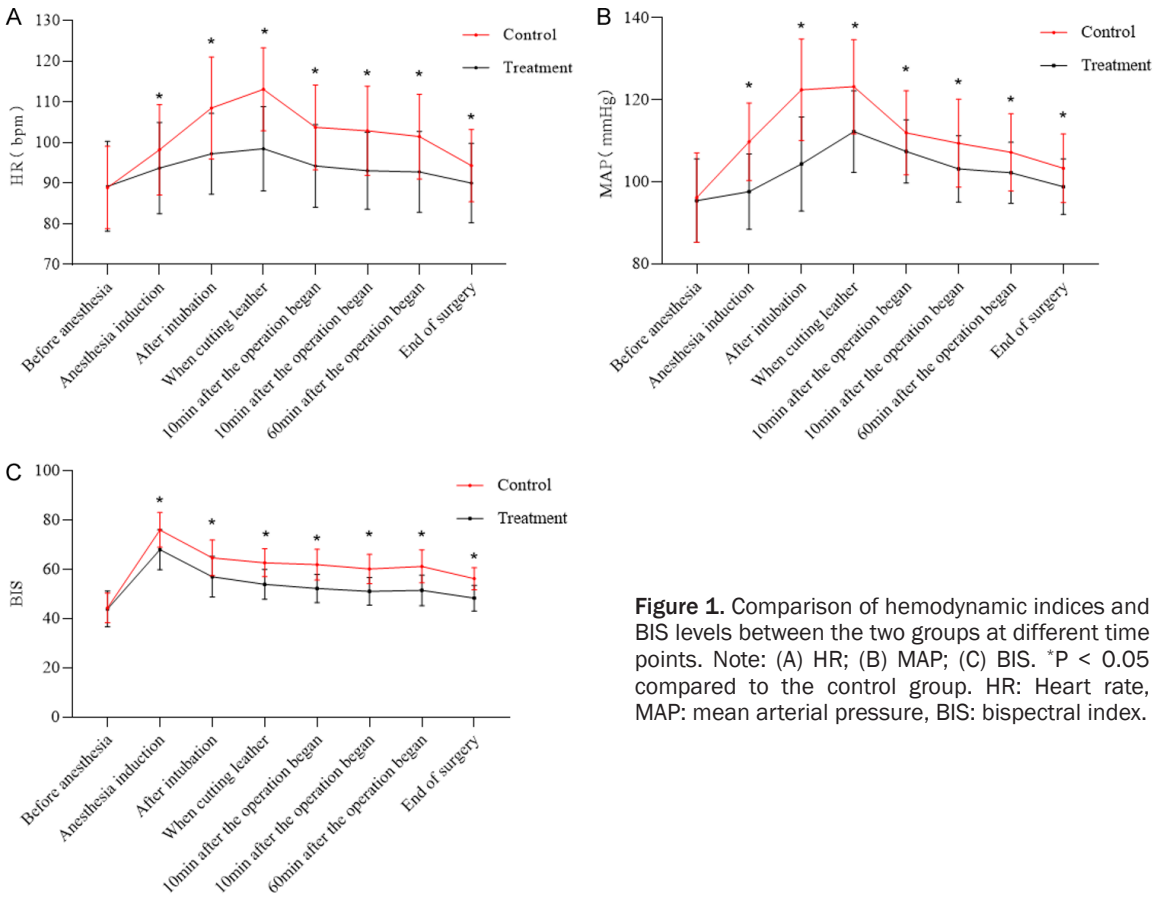

Figure 1. Comparison of hemodynamic indices and BIS levels between the two groups at different time points. Note: (A) HR; (B) MAP; (C) BIS. *P < 0.05 compared to the control group. HR: Heart rate, MAP: mean arterial pressure, BIS: bispectral index.

Table 2. Comparison of anesthesia recovery times between the two groups

Variables	Control (n=50)	Observation (n=50)	*t*	*P*
Recovery time of consciousness (min)	12.87±3.31	9.29±3.01	5.658	< 0.001
Extubation time (h)	14.76±2.24	12.09±2.14	6.094	< 0.001
Time to leave the resuscitation room (min)	38.75±5.62	33.14±3.49	5.996	< 0.001

Table 3. Comparison of postoperative VAS scores and incidence of POCD between the two groups

Groups	Control (n=50)	Observation (n=50)	t/χ^2	*P*
VAS				
1 d before surgery	0.79±0.22	0.83±0.24	0.869	0.387
12 h after surgery	4.78±0.94	2.91±0.86	10.379	< 0.001
1 d after surgery	2.25±0.51	1.26±0.43	10.494	< 0.001
The occurrence of POCD				
6 h after surgery	12	4	4.762	0.029
12 h after surgery	16	7	4.574	0.033
1 d after surgery	15	6	4.883	0.027

visual analogue scale (VAS) scores, postoperative cognitive dysfunction (POCD).

eratively and on postoperative day 7 ($P > 0.05$). However, at 6 hours, 12 hours, 1 day, and 3 days postoperatively, the observation group demonstrated significantly higher MMSE scores than the control group ($P < 0.05$). See **Figure 2** for details.

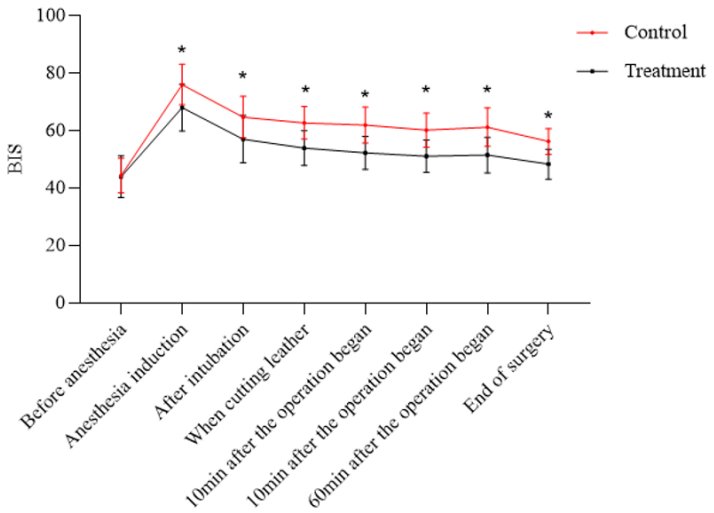

Figure 2. Comparison of MMSE scores between the two groups at different time points. Note: *P < 0.05 compared to the control group. MMSE: Mini-Mental State Examination.

Comparison of adverse event incidence

The overall incidence of adverse events was 26.0% in the control group and 10.0% in the observation group ($P < 0.05$). Detailed adverse event data are provided in **Table 4**.

Comparison of oxidative stress markers

On postoperative day 1, levels of ROS, MDA, and SOD increased in both groups, with significantly higher levels observed in the control group compared to the observation group (all $P < 0.05$). Detailed data are presented in **Table 5**.

Comparison of stress-related biomarkers

On postoperative day 1, serum levels of ALD, COR, ACTH, NSE, and S100β protein increased in both groups, with significantly higher levels in the control group than in the observation group ($P < 0.05$). See **Table 6** for specific values.

Discussion

With the accelerated aging of the population in China, the number of elderly patients with gastric cancer is continuously increasing. Due to its minimally invasive advantages, laparoscopic radical gastrectomy has become the preferred surgical approach for this patient population [15]. However, elderly patients often exhibit diminished physiological reserves and reduced tolerance to anesthesia and surgical stress, resulting in a higher incidence of POCD, which subsequently delays recovery and adversely affects quality of life [16]. Therefore, optimizing anesthesia protocols for high-risk populations is especially crucial. As a new-generation intravenous anesthetic, ciprofol offers advantages over traditional agents like propofol due to its superior pharmacokinetic and pharmacodynamic properties. However, research on its application in elderly patients undergoing laparoscopic radical gastrectomy for gastric cancer remains limited [17].

HR and MAP are key clinical indicators used to assess cardiovascular function and the degree of stress response, while the BIS provides real-time monitoring of cortical suppression. The results showed no significant differences in baseline HR, MAP, or BIS values between the two groups upon admission to the operating room, indicating comparable preoperative physiological status. At critical time points, including anesthesia induction, tracheal intubation, skin incision, 10, 30, and 60 minutes intraoperatively, and at the end of surgery-the ciprofol group exhibited consistently lower HR, MAP, and BIS values than the propofol group. These findings suggest that ciprofol produces a more stable cardiovascular inhibitory effect, attenuating stress-induced fluctuations during surgical procedures [18]. Meanwhile, the lower BIS values maintained in the ciprofol group demonstrate its advantage in anesthesia depth regulation, providing more comprehensive suppression of cortical excitability and reducing the risk of intraoperative awareness [19]. Additionally, the ciprofol group exhibited shorter times to postoperative consciousness recovery, tracheal extubation, and discharge from the recovery room. This phenomenon is closely related to ciprofol's rapid onset, short half-life, and fast metabolic clearance, which collectively accelerate the restoration of patients' consciousness and spontaneous respiration. Adequate postoperative analgesia directly influences the speed and quality of patient recovery. The results of this study demonstrated that the ciprofol group consistently exhibited lower VAS pain scores at all postoperative

Table 4. Comparison of the incidence of adverse reactions between the two groups

Group	Control (n=50)	Observation (n=50)	χ^2	*P*
Restlessness	6 (12.00)	2 (4.00)	4.336	0.037
Disgusting	5 (10.00)	2 (4.00)		
Vomiting	2 (4.00)	1 (2.00)		
Total incidence of adverse reactions	13 (26.00)	5 (10.00)		

Table 5. Comparison of oxidative stress marker levels between the two groups

Group	Control (n=50)	Observation (n=50)	*t*	*P*
ROS (μmol/mL)				
Before surgery	83.44±13.37	82.97±12.31	0.183	0.855
1 d after surgery	131.94±17.45#	114.58±14.29#	5.443	< 0.001
MDA (mmol/mL)				
Before surgery	2.18±0.41	2.25±0.37	0.896	0.372
1 d after surgery	4.17±0.51#	3.06±0.45#	11.54	< 0.001
SOD (U/mL)				
Before surgery	62.03±8.13	61.55±7.82	0.301	0.764
1 d after surgery	83.41±8.31#	75.68±9.22#	4.404	< 0.001

Note: Compared to before treatment within the same group, #P < 0.05. ROS: Reactive oxygen species, MDA: malondialdehyde, SOD: superoxide dismutase.

Table 6. Comparison of stress-related indicators between the two groups

Group	Control (n=50)	Observation (n=50)	*t*	*P*
ALD (pg/mL)				
Before surgery	219.84±49.51	221.07±44.58	0.131	0.896
1 d after surgery	274.18±56.27#	235.40±41.47#	3.923	< 0.001
COR (noml/L)				
Before surgery	128.79±24.61	130.22±31.94	0.251	0.803
1 d after surgery	244.32±40.14#	185.93±38.49#	7.424	< 0.001
ACTH (ng/mL)				
Before surgery	17.16±2.48	16.73±3.42	0.72	0.474
1 d after surgery	56.27±8.89#	42.11±7.31#	8.699	< 0.001
NSE (ng/mL)				
Before surgery	8.08±1.44	8.25±1.37	0.605	0.547
1 d after surgery	12.98±2.01#	10.84±1.72#	5.72	< 0.001
S-100β (pg/mL)				
Before surgery	205.43±22.72	202.19±24.50	0.686	0.495
1 d after surgery	289.75±33.42#	241.19±35.21#	7.073	< 0.001

Note: Compared to before treatment within the same group, #P < 0.05. ALD: Aldosterone, COR: cortisol, ACTH: adrenocorticotropic hormone, S100β protein.

assessment time points compared to the propofol group, indicating a superior analgesic effect of ciprofol [20]. Furthermore, the cardiovascular stability provided by ciprofol may help mitigate pain sensitization caused by tissue ischemia or hypoxia, thereby enhancing postoperative analgesia.

Clinical data indicate that the incidence of POCD and the occurrence of adverse postoperative events were lower in the ciprofol anesthesia group compared to the propofol group. The pathogenesis of POCD is known to involve neuroinflammation, oxidative stress injury, and neurotransmitter metabolism imbalance.

Elderly patients, with diminished neural tolerance, exhibit increased sensitivity to surgical trauma and anesthetic stimuli. Ciprofol maintains more stable intraoperative hemodynamics, ensuring continuous and effective cerebral perfusion, thereby reducing the risk of ischemic neuronal injury [21]. Additionally, ciprofol's antioxidant and anti-inflammatory properties help mitigate oxidative stress and neuroinflammation induced during surgery and anesthesia, exerting neuroprotective effects [22]. Study data further confirmed that MMSE scores at all postoperative time points were significantly higher in the ciprofol group compared to the propofol group ($P < 0.05$), highlighting ciprofol's pronounced advantage in preserving postoperative cognitive function in elderly patients.

Surgical procedures and anesthesia both induce physiological stress responses, leading to alterations in various hormone levels. Among these, ALD, COR, and ACTH are key biomarkers for assessing the body's stress status. Surgery, as a significant physiological stimulus, activates the hypothalamic-pituitary-adrenal axis, resulting in increased secretion of ALD, COR, and ACTH [23, 24]. In this study, postoperative levels of ALD, COR, and ACTH were elevated in both groups; however, the ciprofol group exhibited significantly lower levels of these hormones than the propofol group. This phenomenon may be attributed to ciprofol's stabilizing effects on the cardiovascular system and its moderate inhibitory action on the cerebral cortex, which collectively reduce excessive activation of the hypothalamic-pituitary-adrenal axis through neural pathways triggered by surgical stimuli, thereby lowering the secretion of stress hormones. Additionally, S100β protein and NSE serve as sensitive biomarkers for neuronal injury. Although postoperative levels of S100β and NSE increased in both groups, the ciprofol group exhibited significantly lower levels than the propofol group, suggesting that while surgery and anesthesia caused some degree of neuronal damage, ciprofol was associated with less neuronal injury.

Oxidative stress is closely associated with POCD [25]. Surgical trauma and anesthesia can induce oxidative stress responses characterized by elevated levels of ROS and MDA, alongside the suppression of key antioxidant enzymes such as SOD. In this study, the ciprofol group exhibited lower ROS and MDA levels and relatively higher SOD activity compared to the propofol group, indicating that ciprofol possesses antioxidant properties that may mitigate oxidative stress-induced damage caused by surgery [26].

In summary, the findings of this study indicate that the use of ciprofol for anesthesia in elderly patients undergoing laparoscopic radical gastrectomy offers significant advantages. These include maintaining cardiovascular stability, accelerating postoperative recovery, alleviating postoperative pain, reducing the risk of complications, protecting postoperative cognitive function, and mitigating both stress responses and oxidative stress-induced damage.

However, this study has several limitations. First, the sample size was relatively small, possibly introducing selection bias. Second, cognitive function was only assessed within 7 days postoperatively, and the long-term effects remain unclear. Therefore, further large-scale, multicenter studies with extended follow-up are expected to validate these findings.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (No. 823-00629), The Human Welfare Special Research Project of Sichuan Medical Association (No. 2024RF01) and Open Project of the Key Laboratory of Nuclear Technology for Medical Transformation of the National Health Commission (Nos. 2024HYX019, 2024HYX018).

Disclosure of conflict of interest

None.

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