Cognitive Function and General Anesthesia Exposure: A Cognitive Impairment Stage- Dependent Inverse Relationship

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Abstract

The relationship between general anesthesia (GA) exposure and cognition remains controversial. Using data from the Korea Dementia Research Center's Trial Ready Registry, we examined the associations between a history of GA after the age of 50 and cognitive function, as measured using the Clinical Dementia Rating-Sum of Boxes (CDR-SB) and Global Deterioration Scale (GDS) scores, across the normal, mild cognitive impairment (MCI), and dementia groups. Ordinal logistic regression and subgroup analyses were performed on 688 participants (258 cognitively normal, 245 with MCI, and 185 with dementia). In the normal group, a history of GA was associated with higher CDR-SB (odds ratio [OR] = 2.20, $P = 0.031$) and GDS scores (OR = 1.87, $P = 0.053$). However, in the dementia group, GA was associated with lower CDR-SB (OR = 0.43, $P = 0.032$) and GDS scores (OR = 0.40, $P = 0.022$). Participants with a history of GA had higher CDR-SB and GDS scores in the normal group, but lower scores in the dementia group. No significant associations were observed in the MCI group. Thus, the relationship between GA exposure and cognitive function may differ depending on the stage of cognitive impairment, highlighting the need for stage-specific approaches in future research.

Introduction

Dementia is a progressive neurodegenerative disorder characterized by cognitive decline and impaired daily functioning[1]. Its global prevalence is rising rapidly, with an estimated 55 million people being affected in 2020, and is projected to increase to 78 million by 2030 and 139 million by 2050[2]. This dramatic increase presents a notable challenge to healthcare systems and societies worldwide.

The clinical evaluation of dementia typically involves the use of standardized cognitive assessment tools, such as the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Global Deterioration Scale (GDS). These instruments assess the cognitive, functional, and behavioral aspects of dementia severity across various stages of cognitive decline[3–5] and are essential for early disease detection, monitoring of disease progression, and evaluation of the effectiveness of therapeutic interventions[6,7].

Numerous risk factors have been implicated in the development and progression of dementia. Aging remains the most critical determinant, with the prevalence doubling approximately every five years after the age of 65[8]. Other factors include genetic predisposition (e.g., E4 variant of apolipoprotein E [APOE4]), cardiovascular disease, diabetes mellitus, obesity, smoking, and low educational attainment[9–11]. However, the roles of certain potential risk factors remain controversial. For instance, previous studies have reported conflicting findings regarding the association between hypertension and dementia[12] and that between general anesthesia (GA) exposure and subsequent cognitive decline or dementia. Although some studies have suggested a positive association[13,14], others have reported no significant relationship[15,16].

In the present study, we aimed to examine the factors associated with cognitive impairment, as assessed by the CDR and GDS scores, across distinct cognitive diagnostic groups.

Results

Comparison of participant characteristics between the diagnostic groups

A total of 688 participants were enrolled in the present study, of whom 433 (62.9%) were women, with a median age of 74 years (Table 1). Among the participants, 258 (37.5%), 245 (35.6%), and 185 (26.9%) were classified as normal subjects, participants with mild cognitive impairment (MCI), and participants with dementia, respectively. The median number of years of education was 12 across all groups; however, the distribution differed significantly among the groups ($P = 0.013$). There was no significant difference in the prevalence of a family history of dementia. A total of 186 participants (26.6%) had a history of GA after 50 years of age, 135 (19.6%) had diabetes mellitus, 313 (45.5%) had hypertension, 294 (42.7%) had dyslipidemia, 72 (10.5%) had a history of malignancy, and 258 (37.5%) were APOE4carriers. Variables that showed significant differences among the normal, MCI, and dementia groups ($P < 0.05$) included age, years of education, presence of diabetes mellitus, and APOE4 carrier status. The MMSE scores decreased progressively from the MCI to the dementia group, whereas both the CDR-SB and GDS scores increased significantly ($P < 0.001$). In addition, the proportion of amyloid Positron Emission Tomography (PET) positivity and the standardized uptake value ratios (SUVRs) were significantly higher in the dementia group ($P < 0.001$).

Table 1
Demographic, clinical, and neuroimaging characteristics of study participants among the different diagnostic groups.

	Total participants (N = 688)			*P*-value
	Normal (N = 258, 37.5%)	MCI (N = 245, 35.6%)	Dementia (N = 185, 26.9%)	
Demographics				
Age, years (Median [range])	73 (50–90)	74 (51–87)	74 (51–87)	0.013
Female, N (%)	156 (60.5%)	156 (63.7%)	121 (65.4%)	0.544
Education, years (Median [IQR])	12 (9.0–16.0)	12 (6.0–16.0)	12 (6.0–14.0)	< 0.001
Family history of dementia, N (%)	77 (29.8%)	88 (35.9%)	61 (33.0%)	0.349
Medical history, N (%)				
GA history	59 (22.9%)	71 (29.0%)	53 (28.6%)	0.229
Diabetes mellitus	37 (14.3%)	59 (24.1%)	39 (21.1%)	0.019
Hypertension	132 (51.2%)	100 (40.8%)	81 (43.8%)	0.057
Dyslipidemia	115 (44.6%)	113 (46.1%)	66 (35.7%)	0.072
Malignancy	20 (7.8%)	31 (12.7%)	21 (11.4%)	0.180
APOE4 carrier	48 (18.6%)	113 (46.1%)	97 (52.4%)	< 0.001
Clinical assessment measures (Median [IQR])				
MMSE, score	28 (27.0–29.0)	26 (23.0–28.0)	18 (15.0–22.0)	< 0.001
MMSE, Z-score	0.46 (-0.14–1.02)	-0.75 (-1.90–0.08)	-4.26 (-6.63–-2.21)	< 0.001
CDR total	0.0 (0.0–0.0)	0.5 (0.5–0.5)	1.0 (0.5–1.0)	< 0.001
CDR-SB	0.0 (0.0–0.0)	1.0 (0.5–2.0)	5.0 (3.5–7.0)	< 0.001
GDS[a]	1.0 (1.0–2.0)	3.0 (3.0–3.0)	4.0 (4.0– 5.0)	< 0.001
Amyloid PET				

[a]GDS data were unavailable for nine participants who were excluded from the GDS-related analysis.

	Total participants (N = 688)			*P*-value
	Normal (N = 258, 37.5%)	MCI (N = 245, 35.6%)	Dementia (N = 185, 26.9%)	
Positive for amyloid	45 (17.4%)	129 (52.7%)	150 (81.1%)	< 0.001
SUVR (Median [IQR])	0.64 (0.56–0.92)	1.06 (0.78–1.37)	1.37 (1.13–1.56)	< 0.001

[a]GDS data were unavailable for nine participants who were excluded from the GDS-related analysis.

Abbreviations: MCI, mild cognitive impairment; IQR, interquartile range; GA, general anesthesia; APOE4, E4 variant of apolipoprotein E; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; GDS, Global Deterioration Scale; PET, positron emission tomography; SUVR, standardized uptake value ratio.

Variables associated with the CDR-SB scores

In the normal group, multivariate analysis revealed that a history of GA was significantly associated with higher CDR-SB scores (OR = 2.20 [95% confidence interval (CI): 1.07–4.51, $P = 0.031$]; Table 2). Dyslipidemia and amyloid PET positivity were independently associated with increased CDR-SB scores (dyslipidemia: odds ratio (OR) = 2.04, $P = 0.040$; amyloid PET: OR = 8.62, $P < 0.001$). Although the education level showed a protective effect in the univariate analysis (OR = 0.91, $P = 0.002$), this association was not found to be statistically significant in the multivariate model.

Table 2
Ordinal logistic regression analysis of variables associated with CDR-SB scores among the different diagnostic groups.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Normal participants				
Age	1.03 (1.00–1.08)	0.084	1.01 (0.97–1.06)	0.571
Sex (female)	1.69 (0.94–3.16)	0.088	1.74 (0.87–3.60)	0.127
Education, year	0.91 (0.85–0.96)	0.002	0.95 (0.89–1.02)	0.192
Family history of dementia	1.52 (0.83–2.77)	0.170	1.47 (0.74–2.88)	0.266
GA history	2.33 (1.24–4.31)	0.007	2.20 (1.07–4.51)	0.031
Diabetes mellitus	1.16 (0.49–2.54)	0.717	1.02 (0.40–2.41)	0.966
Hypertension	1.15 (0.65–2.03)	0.630	0.74 (0.38–1.43)	0.374
Dyslipidemia	1.82 (1.03–3.24)	0.039	2.04 (1.04–4.07)	0.040
Cancer history	1.42 (0.49–3.66)	0.486	1.10 (0.32–3.36)	0.872
APOE4 carrier	1.89 (0.94–3.67)	0.065	0.86 (0.37–1.90)	0.722
PET-amyloid+	8.58 (4.43–16.88)	< 0.001	8.62 (4.09–18.64)	< 0.001
MCI group				
Age	1.02 (0.99–1.05)	0.277	1.02 (0.98–1.06)	0.347
Sex (female)	1.25 (0.76–2.09)	0.380	1.23 (0.68–2.23)	0.495
Education, year	0.95 (0.90–0.99)	0.030	0.94 (0.88–0.99)	0.032
Family history of dementia	1.13 (0.68–1.87)	0.628	0.99 (0.57–1.72)	0.972
GA history	0.66 (0.38–1.13)	0.134	0.57 (0.31–1.04)	0.070
Diabetes mellitus	1.10 (0.62–1.91)	0.750	1.30 (0.69–2.45)	0.418
Hypertension	1.16 (0.70–1.90)	0.561	1.08 (0.60–1.92)	0.803
Dyslipidemia	0.98 (0.60–1.59)	0.920	0.95 (0.54–1.66)	0.847
Cancer history	0.58 (0.25–1.24)	0.172	0.79 (0.31–1.89)	0.601

Abbreviations: CDR-SB, Clinical Dementia Rating-Sum of Boxes; OR, odds ratio; CI, confidence interval; MCI, mild cognitive impairment; GA, general anesthesia; APOE4, E4 variant of apolipoprotein E; PET, positron emission tomography.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
APOE4 carrier	2.12 (1.29–3.49)	0.003	1.61 (0.88–2.93)	0.121
PET-amyloid+	3.43 (2.05–5.81)	< 0.001	3.12 (1.73–5.73)	< 0.001
Dementia group				
Age	1.00 (0.97–1.04)	0.925	1.01 (0.97–1.05)	0.808
Sex (female)	1.34 (0.69–2.64)	0.388	1.17 (0.52–2.66)	0.703
Education, year	0.97 (0.91–1.03)	0.367	0.96 (0.89–1.04)	0.345
Family history of dementia	0.60 (0.30–1.18)	0.138	0.88 (0.42–1.80)	0.718
GA history	0.41 (0.20–0.84)	0.015	0.43 (0.20–0.92)	0.032
Diabetes mellitus	1.18 (0.54–2.61)	0.681	1.62 (0.69–3.85)	0.267
Hypertension	0.55 (0.28–1.05)	0.074	0.60 (0.29–1.24)	0.170
Dyslipidemia	0.50 (0.25–0.98)	0.046	0.55 (0.27–1.12)	0.102
Cancer history	0.76 (0.29–2.05)	0.583	1.15 (0.41–3.29)	0.790
APOE4 carrier	0.74 (0.38–1.40)	0.350	0.64 (0.32–1.27)	0.208
PET-amyloid+	1.55 (0.70–3.40)	0.277	1.89 (0.78–4.61)	0.159

Abbreviations: CDR-SB, Clinical Dementia Rating-Sum of Boxes; OR, odds ratio; CI, confidence interval; MCI, mild cognitive impairment; GA, general anesthesia; APOE4, E4 variant of apolipoprotein E; PET, positron emission tomography.

In the MCI group, education level and amyloid PET positivity were significantly associated with CDR-SB scores in the multivariate analysis (education, OR = 0.94, $P = 0.032$; amyloid PET, OR = 3.12, $P < 0.001$). In the dementia group, a history of GA was significantly associated with lower CDR-SB scores in multivariate analysis (OR = 0.43 [95% CI: 0.20–0.92, $P = 0.032$]).

Variables associated with the GDS Scores

In the normal group, a history of GA was associated with higher GDS scores in the univariate analysis (OR = 2.34 [95% CI: 1.32–4.11, $P = 0.003$]), with borderline significance in the multivariate model (OR = 1.87 [95% CI: 0.99–3.51, $P = 0.053$]; Table 3). Amyloid PET positivity was independently associated with higher GDS scores (OR = 6.49, $P < 0.001$). While age, education level, and cancer history were significantly associated with GDS scores in the univariate analysis (age: OR = 1.04, $P = 0.016$; education: OR = 0.91, $P = 0.001$; cancer history: OR = 2.39, $P = 0.039$), these associations were not significant after adjustment.

Table 3
Ordinal logistic regression analysis of variables associated with GDS scores among the different diagnostic groups.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Normal participants				
Age	1.04 (1.01–1.08)	0.016	1.03 (0.99–1.07)	0.223
Sex (female)	1.66 (0.98–2.86)	0.063	1.65 (0.90–3.06)	0.107
Education, year	0.91 (0.86–0.96)	0.001	0.95 (0.90–1.01)	0.131
Family history of dementia	1.34 (0.78–2.30)	0.287	1.40 (0.77–2.52)	0.262
GA history	2.34 (1.32–4.11)	0.003	1.87 (0.99–3.51)	0.053
Diabetes mellitus	1.70 (0.83–3.39)	0.135	1.42 (0.66–2.95)	0.356
Hypertension	1.43 (0.86–2.39)	0.169	0.90 (0.50–1.61)	0.714
Dyslipidemia	1.69 (1.02–2.82)	0.044	1.60 (0.89–2.89)	0.115
Cancer history	2.39 (1.03–5.46)	0.039	2.13 (0.82–5.42)	0.113
APOE4 carrier	1.55 (0.81–2.93)	0.180	0.84 (0.39–1.74)	0.651
PET-amyloid+	6.79 (3.5–13.46)	< 0.001	6.49 (3.14–13.75)	< 0.001
MCI group				
Age	1.02 (0.98–1.05)	0.385	1.01 (0.97–1.05)	0.725
Sex (female)	1.01 (0.57–1.77)	0.973	1.16 (0.61–2.20)	0.657
Education, year	1.00 (0.94–1.05)	0.882	0.98 (0.92–1.05)	0.566
Family history of dementia	1.39 (0.78–2.49)	0.269	1.15 (0.61–2.16)	0.665
GA history	1.13 (0.62–2.07)	0.693	0.96 (0.48–1.89)	0.896
Diabetes mellitus	1.10 (0.59–2.08)	0.776	1.27 (0.64–2.55)	0.499
Hypertension	1.79 (1.02–3.20)	0.046	2.03 (1.08–3.90)	0.030
Dyslipidemia	1.09 (0.63–1.89)	0.759	0.76 (0.40–1.44)	0.405
Cancer history	1.23 (0.56–2.77)	0.619	1.35 (0.54–3.43)	0.519

Abbreviations: GDS, Global Deterioration Scale; OR, odds ratio; CI, confidence interval; MCI, mild cognitive impairment; GA, general anesthesia; APOE4, E4 variant of apolipoprotein E; PET, positron emission tomography

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
APOE4 carrier	3.77 (2.07–7.15)	< 0.001	2.25 (1.13–4.63)	0.024
PET-amyloid+	7.16 (3.71–14.83)	< 0.001	5.43 (2.64–11.87)	< 0.001
Dementia group				
Age	1.02 (0.98–1.06)	0.377	1.03 (0.99–1.08)	0.161
Sex (female)	1.21 (0.58–2.54)	0.609	1.30 (0.53–3.20)	0.563
Education, year	1.00 (0.94–1.07)	0.992	1.01 (0.93–1.10)	0.817
Family history of dementia	0.71 (0.34–1.50)	0.372	1.07 (0.48–2.39)	0.868
GA history	0.40 (0.18–0.87)	0.022	0.44 (0.19–1.00)	0.052
Diabetes mellitus	1.34 (0.56–3.35)	0.520	1.76 (0.69–4.65)	0.243
Hypertension	0.52 (0.25–1.07)	0.081	0.54 (0.24–1.20)	0.137
Dyslipidemia	0.63 (0.30–1.33)	0.225	0.67 (0.30–1.48)	0.325
Cancer history	0.48 (0.17–1.43)	0.171	0.59 (0.20–1.87)	0.363
APOE4 carrier	0.60 (0.29–1.23)	0.168	0.54 (0.24–1.15)	0.113
PET-amyloid+	1.35 (0.55–3.24)	0.510	1.75 (0.65–4.65)	0.265

Abbreviations: GDS, Global Deterioration Scale; OR, odds ratio; CI, confidence interval; MCI, mild cognitive impairment; GA, general anesthesia; APOE4, E4 variant of apolipoprotein E; PET, positron emission tomography

In the MCI group, hypertension, APOE4 carrier status, and amyloid PET positivity were significantly associated with higher GDS scores in the multivariate model (hypertension, OR = 2.03, $P = 0.030$; APOE4 carrier, OR = 2.25, $P = 0.024$; amyloid PET, OR = 5.43, $P < 0.001$), whereas history of GA showed no significant relationship. In the dementia group, a history of GA was associated with lower GDS scores in the univariate analysis (OR = 0.40 [95% CI: 0.18–0.87, $P = 0.022$]) and showed a borderline significance towards an inverse association in the multivariate model (OR = 0.44 [95% CI: 0.19–1.00, $P = 0.052$).

Comparison of CDR-SB and GDS scores by history of GA within each diagnostic group

Within each diagnostic group, the CDR-SB and GDS scores were compared between participants with and without a history of GA (Fig. 1). In the normal group, the mean CDR-SB and GDS scores were higher for participants with, than for those without, a history of GA (0.47 vs. 0.23 for CDR-SB, 1.66 vs. 1.40 for

GDS; all, $P < 0.05$). In the MCI group, the mean CDR-SB and GDS scores of participants with and without a history of GA showed no significant differences (1.24 vs. 1.49 for CDR-SB, 2.88 vs. 2.86 for GDS; all, $P > 0.05$).

In contrast, in the dementia group, the mean CDR-SB and GDS scores were lower for participants with, than for those without, a history of GA (4.78 vs. 5.71 for CDR-SB, 4.06 vs. 4.36 for GDS; all, $P < 0.05$).

Discussion

In the present study, we explored the relationship between GA exposure and cognitive function in three diagnostic groups: the cognitively normal, MCI, and dementia groups. Contrary to the assumption that GA exacerbates cognitive decline, our findings reveal a stage-specific pattern. In cognitively normal individuals, a history of GA was associated with higher CDR-SB and GDS scores. In contrast, no significant relationship was observed in the MCI group, and intriguingly, a history of GA was associated with lower CDR-SB and GDS scores in individuals with dementia.

The observed association between GA and higher cognitive burden (as measured by the CDR-SB and GDS) in the normal group is consistent with previous studies reporting that GA exposure may accelerate subtle cognitive changes or unmask the underlying neuropathological processes[17,18]. Such processes can involve inflammation, disruption of the blood–brain barrier, or exacerbation of preclinical neurodegenerative changes[17]. These effects may vary depending on the type of anesthetic agent used; a recent study has indicated that the use of desflurane and midazolam may be linked to a higher risk of dementia, whereas propofol appears to have no significant association[19].

However, in the dementia group, the inverse association between a history of GA and dementia severity was unexpected; several possible explanations for this occurrence may be considered. First, certain anesthetic regimens or perioperative management strategies may help preserve or stabilize cognitive function in patients with advanced neurodegenerative diseases. Some studies have suggested that anesthetic protocols may attenuate the postoperative systemic inflammatory response[20] and that perioperative administration of agents such as dexmedetomidine may notably suppress the production of pro-inflammatory cytokines, such as IL-6, IL-8, and TNF-α[21]. However, in our study, we did not collect information regarding the specific indications for GA or the types of surgical procedures performed; this limited our ability to assess the potential role of cancer- or other disease-specific factors in these associations. Second, the inverse association may reflect improvements in cognition following the surgical treatment of an underlying condition. For example, cognitive improvement after coronary artery bypass grafting (CABG) surgery may occur because of improved general health, enhanced quality of life, and a reduction in the number of previously prescribed medications. In such cases, surgical intervention may alleviate the underlying pathology that caused the cognitive impairment; the resulting improvement in the quality of life may contribute to the improvement of cognitive outcomes[22]. Therefore, this hypothesis may not reflect the effects of GA itself, but rather, the impact of treating the primary pathology through surgery.

Moreover, the observed inverse association may have been influenced by selection or survivorship bias. Individuals with dementia who undergo GA may systematically differ from those who do not, possibly having fewer comorbidities, better general health, or greater healthcare access. While our findings raise intriguing possibilities, the above interpretations remain speculative and warrant further investigation through prospective studies with detailed anesthetic and surgical data. Therefore, future studies should assess potential modifiers, such as GA type (e.g., inhalational vs. intravenous), the type and duration of surgery, and perioperative complications to better characterize these divergent outcomes. Additionally, prospective studies incorporating not only neuroimaging modalities (e.g., amyloid or tau PET) but also blood-based biomarkers of Alzheimer's disease, inflammatory biomarkers, and more comprehensive medical records, could also help elucidate the mechanisms whereby GA exerts variable effects on cognitive function[23,24].

This study has a few limitations. First, the retrospective design of our study and reliance on an anonymized database limited our ability to establish definitive causal relationships. Second, detailed information on the type of GA, its duration, and intraoperative management was not available; all these parameters may have independently influenced the cognitive outcomes. Third, the temporal relationship between GA exposure and assessment of cognitive function (CDR and GDS scores) was not clearly defined. Because the dataset merely indicated whether the participants had undergone GA after the age of 50, we were unable to evaluate the potential risk of cognitive impairment in relation to the specific timing of GA. Despite these limitations, the relatively large sample size enabled us to identify statistically significant associations between GA exposure and cognitive measures across the diagnostic groups. Unlike previous studies, our analysis stratified participants according to their cognitive status and incorporated a wide range of relevant covariates, including educational level, family history of dementia, APOE4 carrier status, and amyloid PET findings; this enhanced the robustness and clinical relevance of our findings.

In conclusion, our findings suggest that the association between GA exposure and dementia severity differs depending on the stage of cognitive impairment. While GA may contribute to a higher cognitive burden among individuals who are cognitively normal, it appears to have an inverse relationship with the CDR-SB and GDS scores in those with established dementia. Our findings call for further prospective investigations, with an emphasis on mechanistic studies and stratified analyses that consider disease stage, GA type, and comorbidities.

Methods

Study participants and exclusion criteria

The data for this study were provided by the Korea Dementia Research Center's Trial Ready Registry (KDRC TRR), supported by the Ministry of Health and Welfare and Ministry of Science and ICT, Republic of Korea[25]. The registry contains comprehensive anonymized clinical information, including that regarding demographic characteristics, diagnostic classifications, medical history, clinical assessments,

laboratory results, and neuroimaging findings. MCI and dementia were diagnosed in accordance with the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria[26].

The following exclusion criteria were applied in this platform: individuals with psychiatric disorders, major neurological or severe systemic illnesses potentially affecting cognitive function, and/or severe visual or hearing impairments that could interfere with neuropsychological evaluation were excluded. Participants who were unable to undergo brain Magnetic Resonance Imaging (MRI) or PET imaging were also excluded from the study. In addition, individuals with secondary causes of cognitive impairment were identified via findings of laboratory tests, such as those for vitamin B12 deficiency, positive syphilis serology, or abnormal thyroid, renal, or hepatic function. Patients with structural brain abnormalities evident on MRI, including territorial infarctions, multiple lacunar infarcts, intracranial hemorrhages, more than five cerebral microbleeds, large hemorrhages (≥ 10 mm), brain tumors, hydrocephalus, or severe white matter hyperintensities (assessed using the modified Fazekas scale), were also excluded.

All experimental protocols were approved by the Institutional Review Board of Veterans Health Service Medical Center, Seoul, Republic of Korea (Approval No. 2024-02-019), in accordance with relevant guidelines and regulations. This study was conducted in compliance with the Declaration of Helsinki. The initial IRB approval included a waiver of the requirement to obtain informed consent due to the retrospective nature of the study.

Variables for analysis of cognitive function

The following variables were extracted for analysis: age, sex, years of education, family history of dementia, history of GA after the age of 50 years, medical history of diabetes mellitus, hypertension, dyslipidemia, and/or cancer, APOE4 carrier status, MMSE, CDR-Sum of Boxes (CDR-SB), and GDS scores, and amyloid PET results (the amyloid status and SUVR).

Both the CDR-SB and GDS scores were categorized into three ordinal levels — low, intermediate, and high — based on the diagnostic group (normal, MCI, and dementia groups) for statistical analysis. In the normal group, a CDR-SB score of 0 was classified as low, 0.5 as intermediate, and any value above 0.5 as high. In the MCI group, scores ≤ 1.0 were considered low, 1.5 to 2.5 as intermediate, and > 2.5 as high. In the dementia group, scores ≤ 3.0 were classified as low, 3.5 to 10.0 as intermediate, and > 10.0 as high. For GDS, a score of 1 in the normal group was considered low, 2 as intermediate, and > 2 as high. In the MCI group, scores ≤ 2 were low, 3 was intermediate, and > 3 was high. In the dementia group, scores ≤ 3 were low, 4 to 5 were intermediate, and > 5 were high. Nine participants lacked GDS measurements and were excluded from the GDS-based analysis.

Statistical analysis

Group comparisons among the normal subjects and patients with MCI and dementia were performed using the Kruskal–Wallis tests for continuous variables (age, years of education, MMSE, CDR-SB, and GDS scores, and SUVRs) and chi-square tests for categorical variables (sex, family history of dementia, history of GA, diabetes mellitus, hypertension, dyslipidemia, cancer history, APOE4 carrier status, and amyloid PET results).

Univariate and multivariate ordinal logistic regression analyses were performed using the categorized CDR-SB and GDS scores as dependent variables. The covariates included in the models were selected from the same set of demographic and clinical variables used for the group comparisons. The MMSE scores and SUVRs were excluded as predictors because the MMSE score is closely correlated with both the CDR-SB and GDS scores and the SUVRs were derived from the amyloid PET results. The ORs and corresponding 95% CIs were reported.

Subgroup analyses were performed for each diagnostic category to explore the potential effects of GA on cognitive function. The CDR-SB and GDS scores of the participants with and without a history of GA were compared and the score distributions were visualized using box plots. Intergroup differences were assessed using the Wilcoxon rank-sum test. All statistical analyses and data visualizations were performed using R software (version 4.3.0).

Abbreviations

MCI
mild cognitive impairment
IQR
interquartile range
GA
general anesthesia
APOE4
E4 variant of apolipoprotein E
MMSE
Mini-Mental State Examination
CDR-SB
Clinical Dementia Rating-Sum of Boxes
GDS
Global Deterioration Scale
PET
positron emission tomography
SUVR
standardized uptake value ratio.

Declarations

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Author contributions

Song K, Conceptualization, Methodology, Writing – review and editing, and Project administration; Park M-S, Formal analysis, writing–original draft and Visualization; Kim S-Y, Supervision, Writing – review, and editing

Competing Interests

The authors have no potential conflicts of interest to disclose

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Figures

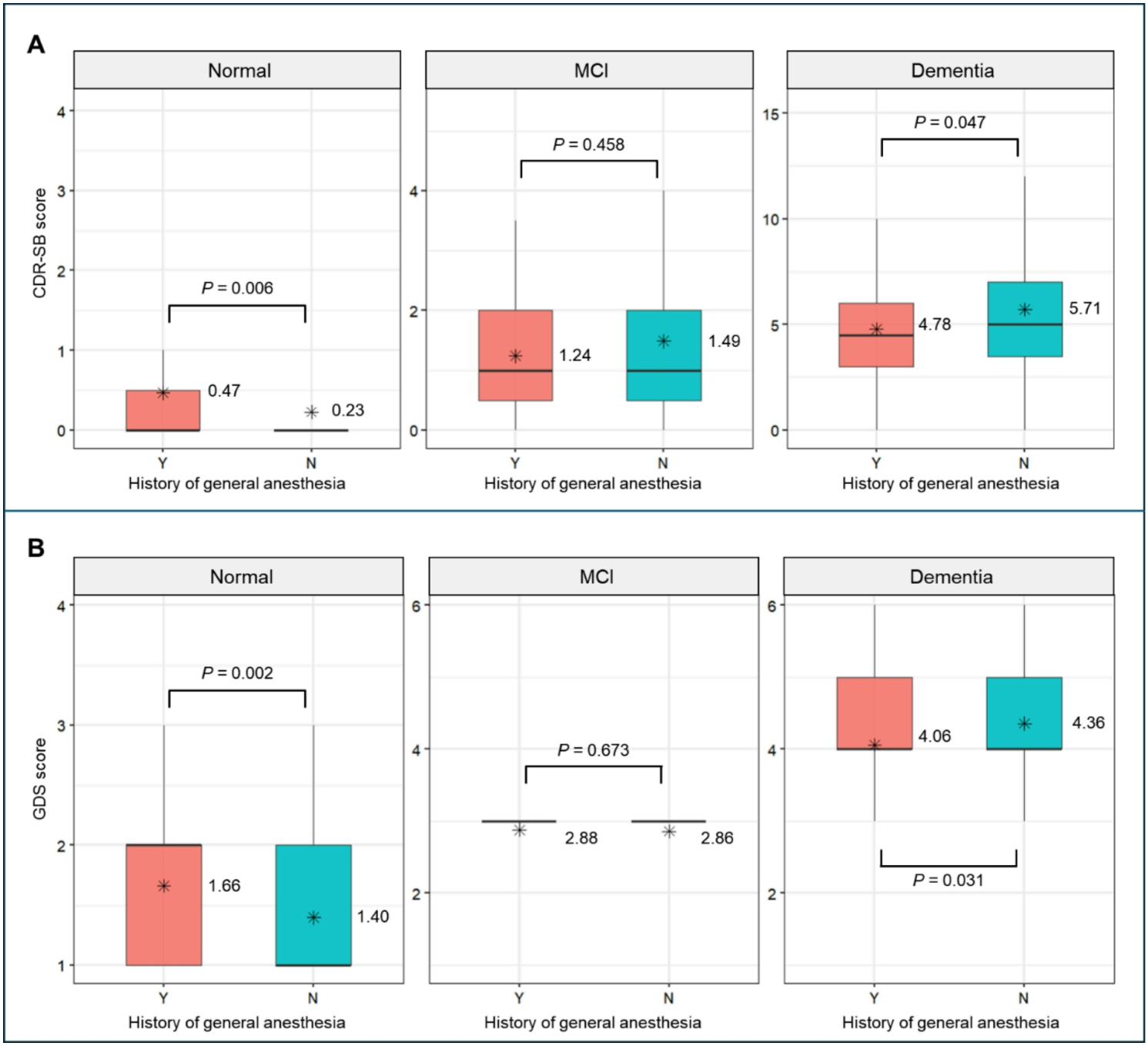

Figure 1

Comparison of CDR-SB (A) and GDS (B) scores between participants with (Y) and without (N) a history of general anesthesia, stratified by diagnostic group. Box plots display the median (horizontal line), interquartile range (box), and mean (asterisk).