Increased Risk of Dementia after Anesthesia and Surgery

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ABSTRACT

Background: The potential relationship between anesthesia, surgery, and onset of dementia remains elusive.

Aims: To determine whether the risk of dementia increases after surgery with anesthesia, and to evaluate possible associations among age, mode of anesthesia, type of surgery, and risk of dementia.

Method: The study cohort included an anesthetized group of patients aged 50 years and older who were anesthetized between January 1, 2004 and December 31, 2007, and a control group of randomly selected age- and sex-matched patients. Patients were followed until December 31, 2010 to identify signs of early dementia.

Results: Relative to control patients who were not anesthetized, patients who underwent anesthesia and surgery exhibited an increased risk of dementia (HR = 1.99) and a reduced mean interval to dementia diagnosis. The risk of dementia increased in patients who received intravenous (IV) or intramuscular (IM) anesthesia, regional anesthesia (RA), and general anesthesia (GA).

Conclusions: The results of our nationwide population-based study suggest that patients who undergo anesthesia and surgery are at increased risk for dementia.

Keywords: anesthesia, surgery, dementia, Alzheimer's disease

Competing interests: The authors have reported no conflicts of interest.

INTRODUCTION

Generally considered safe and effective, anesthetics have bestowed enormous clinical benefits. However, there is growing concern that they may have neurodegenerative complications. Evidence from *in vitro* studies suggests that inhaled anesthetics interact with pathways of neurodegeneration.[1] Animal studies also provide evidence that exposure to inhaled anesthetics can impair memory,[2] and increase risk of Alzheimer's disease (AD) pathology.[3] Postoperative cognitive decline (POCD) in human patients is generally considered to be a short-lived condition with normal function returning within days; but cognitive changes may persist for weeks or more.[4] It is not yet clear whether POCD represents an unmasking of early dementia, or a predictor of later dementia. Regardless, with clinical features similar to those observed in demented patients, post-operative long-term cognitive impairment raises concerns that anesthesia and surgery may accelerate the onset and progression of neurodegenerative dementia.[5]

Whether anesthesia and surgery contributes to the development of long-term cognitive decline, however, remains controversial. One study showed declined cognitive function 5 years after coronary arterial bypass graft (CABG) operations.[6] Another retrospective study showed that patients who underwent CABG operations had a higher incidence of AD in the following 5 to 6 years.[5] However, another study found that similar portions of AD and control groups had been subjected to CABG operations.[7] Moreover, others have reported no link between anesthesia, surgery, and long-term cognitive decline. It is possible that small cohorts, biased study populations, and confounding coincident illnesses may have contributed to the contradictory results.[7] Thus, the consensus statement from the First International Workshop on Anesthetics and Alzheimer's Disease in 2009 suggested that statistically sound prospective and retrospective human studies of the risk of AD after anesthesia are needed.[9]

The Taiwan National Health Insurance Research Database (NHIRD) provides data from a large and representative Taiwanese population that has been followed for over a decade.[10] Thus, in this study we analyzed the NHIRD retrospectively to determine whether the risk of neurodegenerative dementia increases after anesthesia and surgery, and to evaluate possible associations between the risk of dementia and patient age, mode of anesthesia, and type of surgery.

SUBJECTS/MATERIALS AND METHODS

Database

At the time of our analysis, the NHIRD contained records for approximately 23 million enrollees dating back to March 1995, representing almost 99% of the total population in Taiwan.[10] We reviewed records from the Longitudinal Health Insurance Database (LHID), which includes records derived from the NHIRD by systematic random sampling. The LHID includes claims data for 1 million patients. We observed no significant differences in sex, age, or average income distributions between the LHID and the NHIRD.[10]

Study samples

We extracted the records of patients 50 years or older who underwent anesthesia for the first time since 1995, between January 1, 2004, and December 31, 2007, based on the Ninth Edition of the International Classification of Diseases' Clinical Modification (ICD-9-CM) codes. To avoid the influence of chemotherapy and brain metastasis, we excluded patients who had any diagnosis of cancer (ICD-9-CM: 140-208). Similarly, we excluded patients with a history of dementia, Parkinsonism (ICD-9-CM: 332), stroke (ICD-9-CM: 430-434), or brain operations (ICD-9-CM op-code 01-04). We tracked each participant in the study cohort from the date of anesthesia until December 31, 2010.

The control cohort was selected from the remaining patients with no anesthesia since 1995, and excluded those with a history of cancer, dementia, Parkinsonism, or stroke. For each of the anesthesia group participants, we selected 4 or 5 control participants randomly, but matched for exact age and sex.

Events

The first occurrence of dementia diagnosis was identified. We accepted the diagnoses of presenile dementia, senile dementia (ICD-9-CM: 290.0-290.3), and Alzheimer's dementia (ICD-9-CM code 331.0) as forms of neurodegenerative dementia. Such diagnoses were established mostly by board certified neurologists or psychiatrists after routine blood count, blood chemistry, thyroid hormone, folate, vitamin B12, syphilis, neuropsychological, and brain imaging (computed tomography or magnetic resonance imaging) tests to exclude dementia due to other causes and accepted in light of applications for reimbursement for dementia prescription medication. Because perioperative stroke is a surgical complication that could potentially contribute to the development of vascular dementia, we excluded potential subjects with a diagnosis of atherosclerotic dementia (ICD-9-CM: 290.4). In contrast to POCD, a transient and reversible condition, dementia is a slowly developing and progressive neurodegenerative process. Therefore, patients were considered eligible for the study cohort if a diagnosis of dementia had been recorded at least twice, with the first diagnosis occurring at least 3 months after the first anesthesia experience.

Covariates

We extracted demographic information, including age and sex, and the following potentially confounding factors: hypertension (ICD-9-CM: 401), hyperlipidemia (ICD-9-CM: 272), and depression (ICD-9-CM: 296.2-296.3, 300.4, 311). Among patients with depression, those treated by electroconvulsive therapy (ECT) (ICD-9-CM procedure-code 9426, 9427) were identified. We calculated the Charlson index to account for 22 comorbidities (e.g. myocardial infarction, liver disease, or diabetes mellitus) using a total score that was weighted according to the presence of the various conditions.[11]

To assess the differences in the risks for dementia based on covariates, we divided the subjects into two age-band categories: middle-aged (50–65 y) and seniors (> 65 y). The modes of anesthesia received were classified into three groups: intravenous (IV) or intramuscular (IM) anesthesia, regional anesthesia (RA), and general anesthesia (GA). Patients in the IV/IM group typically received combined regimens that included propofol, midazolam, thiopental, or ketamine as sedatives for operations that were relatively short in duration. The RA group included patients that had been given epidural, spinal, or local anesthesia. The GA group included patients that were given hypnotics, such as propofol, barbiturates, or etomidate as sedatives prior to administration of inhaled or IV anesthetics for maintenance. The number of separate anesthesia treatments that participants received within a year was used as a covariate, with one level of the covariate indicating only a single exposure to anesthesia and a second level indicating two or more exposures. We also grouped participants according to the type of surgery they received as follows: eye surgery (ICD-9-CM op-code 08-16), ear-nose-throat (ENT) surgery (ICD-9-CM op-code 18-29), respiratory surgery (ICD-9-CM op-code 30-34), cardiovascular surgery (ICD-9-CM op-code 35-39), digestive surgery (ICD-9-CM op-code 42-54), genitourinary surgery (ICD-9-CM op-code 55-71), musculoskeletal surgery (ICD-9-CM op-code 76-84), or dermatologic surgery (ICD-9-CM op-code 86). All surgical groups were mutually exclusive.

Statistical analysis

All statistical analyses were performed with the SAS statistical software package for Windows (version 9.2.; SAS Institute Inc., Cary, NC). Clinical variables were compared between study and control groups using the chi-square test. Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We adjusted the models for possible confounding factors, including hypertension, hyperlipidemia, depression, and the Charlson index; the values of the confounding factors were at baseline. All tests were two-tailed, and a *P* value of less than .05 was considered statistically significant.

RESULTS

A total of 24,901 patients were included in the anesthetized-study group, and 110,972 subjects were included in the control group. Table 1 shows the characteristics of the samples of anesthetized patients and nonanesthetized subjects. Relative to the control group, the anesthetized participants were slightly older (63 y vs. 61 y, $P < .001$) and more frequently men (49.5% vs. 48.2%, $P < .001$). The prevalence of comorbidity, including hypertension, hyperlipidemia, and depression, was higher in the anesthetized group ($P < .001$). The Charlson index was also higher in the anesthetized group (mean 2.15 vs 1.49, $P < .001$).

GA was the most commonly used (55.1%) mode of anesthesia in the anesthetized patient group, followed by RA (35.2%), and IV/IM (6.8%) (Table 2); 42.9% of anesthetized patients received anesthesia at least twice within a single year. The most frequent surgery types were musculoskeletal surgery (39.5%), digestive surgery (20.5%), and genitourinary surgery (16.3%). A summary of the distribution of anesthesia type in relation to surgery type is provided in Table 3.

During 3–7 y of follow-up, 661 of the 24,901 (2.65%) anesthetized participants and 1539 of the 110,972 (1.39%) nonanesthetized participants were diagnosed with dementia. The mean duration of dementia diagnosis from the date of the first anesthesia exposure was shorter in the anesthetized group than in the nonanesthetized group (906.7 ± 623.5 d vs 1104.3 ± 609.8 d, $P < .0001$). Adjusting for hypertension, hyperlipidemia, depression, and Charlson index values yielded an estimated 1.99-fold increased risk for developing dementia in the anesthesia group (95% CI, 1.81–2.17; P < .001). The risk of dementia after anesthesia was increased similarly in men (HR, 2.30; 95% CI, 2.00–2.65) and women (HR, 1.80; 95% CI, 1.60–2.03). Significant associations between the emergence of dementia and exposure to anesthesia were observed in both middle-aged patients (HR, 1.90; 95% CI, 1.49–2.42) and

seniors (HR, 1.79; 95% CI, 1.62–1.97). The increased risk of dementia was observed for patients with a Charlson index less than 3 (HR, 1.90; 95% CI, 1.6–2.16), as well as for those with a Charlson index greater than 3 (HR, 1.67; 95% CI, 1.45–1.91) (Table 4). Of the 18 (1.7%) subjects in the anesthetized group with a diagnosis of depression (N = 1046) that received ECT, none developed dementia. However, among depressed patients who did not receive ECT, the HR of dementia after anesthesia and surgery was 6.34 (95% CI, 4.24–9.49).

Table 5 shows, in summary form, the associations of dementia with mode of anesthesia and number of anesthesia treatments within any single year. The adjusted HR of incident dementia was greatest in patients that received RA anesthesia (HR, 1.80; 95% CI, 1.57–2.07), followed by IV or IM anesthesia (HR, 1.60; 95% CI, 1.11–2.30) and GA (HR, 1.46; 95% CI, 1.28–1.68). Compared to the GA group, the RA group, but not IV/IM anesthesia group, had a higher risk of dementia (HR, 1.42; 95% CI, 1.20–1.66). Exposure to anesthesia at least twice within a year yielded a 1.75-fold increased risk of dementia (95% CI, 1.53–2.01), whereas exposure to anesthesia only once within a year yielded a 1.73-fold increased risk of dementia (95% CI, 1.53–1.96), with no significant difference in risk between these two groups.

As reported in Table 6, five of the eight types of surgery were associated with an increased risk for dementia, including dermatologic surgery (HR, 2.36; 95% CI, 1.46–3.80), musculoskeletal surgery (HR, 1.88; 95% CI, 1.65–2.15), genitourinary surgery (HR, 1.93; 95% CI, 1.50–2.49), digestive surgery (HR, 1.75; 95% CI, 1.41-2.17), and eye surgery (HR, 1.55; 95% CI, 1.05–2.31). In contrast, the incidences of dementia after ENT, respiratory, and cardiovascular surgery did not differ significantly from the incidence observed for the nonanesthetized control group.

DISCUSSION

The current study showed a 1.99-fold increased risk for development of dementia within 3 to 7 y of anesthesia and surgery. The mean duration of dementia diagnosis was shorter in the patients who underwent anesthesia and surgery than in those in the control group. These findings suggest a significant association between surgery with anesthesia and subsequent dementia. The increased risk of dementia was independent of age, sex, Charlson index, mode of anesthesia, and number of anesthesia exposures within a year. In contrast to prior conflicting studies,[7] in this nationwide population-based analysis, we examined a large number of cases, including 4 or 5 age- and sex-matched control subjects per anesthetized group subject, and made adjustments for potential confounding factors. Owing to our study design, the present results provide statistically sound evidence for the putative association of dementia with anesthesia and surgery.

Because the diagnosis of dementia requires the presence of persistent cognitive decline, our study used dementia as a marker of clinically significant brain dysfunction to investigate whether anesthesia would cause long-term detrimental effects on the brain. After excluding vascular dementia and Parkinsonism with dementia, AD accounted for the majority of dementia cases in our cohort. Therefore, our findings suggest that exposure to anesthesia with surgery may increase patients' risk of developing AD-type dementia. The long interval between anesthesia exposure and dementia diagnosis in both our anesthetized and control groups should provide confidence that our results were not confounded by POCD. The Taiwanese NHIRD is a nationwide medical claim database, and it is possible some AD patients have gone misdiagnosed. However, it is likely that variability in diagnosis of dementia would be similar in both the anesthetized and control groups.

Anesthesia and surgery are inseparable in clinical settings. Thus, it is difficult to establish with certainty whether the increased risk of dementia development observed was attributable to the anesthesia per se, the surgical process, or both. However, it is noteworthy, that there is a growing body of laboratory evidence suggesting that anesthetics may be neurotoxic. For example, exposure of rats to a volatile anesthetic induced caspase-3 activation and increased levels of amyloid β peptide (Aβ).[12] *In vitro*[1] and multidimensional NMR studies[13] have shown that exposing Aβ to inhaled anesthetics can promote Aβ oligomerization, a process which enhances Aβ-induced neurotoxicity. Others have identified calcium dysregulation as a possible mechanism of anesthetic-induced neurotoxicity.[14] Although there is evidence that suggests anesthetics may interact with AD neuropathology at multiple levels in the involved pathways, human evidence has been lacking.

Another plausible mechanism of dementia development after anesthesia and surgery is the occurrence perioperative events. To help control for this possibility, we excluded patients with vascular dementia from our study. The association of overt perioperative stroke with dementia was beyond the scope of our study. Nevertheless, microvascular perioperative brain damages, such as white matter hyperintensities and silent small infarctions, might influence the risk of dementia development. AD has also been linked to hypoxia and hypocapnia events,[15] although other studies have shown no connection.[16] Deliberate or unintended hypothermia in the perioperative period might also be a risk factor.[9] In animal studies, anesthesia-induced hypothermia has been shown to produce tau hyperphosphorylation, a biochemical process that may play a role in AD pathogenesis.[3]

However, caution must be exercised in asserting causality because surgery with anesthesia shares some common features with dementia pathology, such as old age and involvement of inflammatory processes. The other possible explanation for the observed association between having surgery under anesthesia and subsequent dementia is that dementia patients are more susceptible to

surgical illness prior to clinical diagnosis of dementia. Thus, some AD-associated comorbidities might cause patients to be prone to surgical interventions.[17] However, it is noteworthy that some illnesses (i.e. cancer) have been shown to have an inverse association with AD.[18] Unfortunately, clinical evidence of susceptibility to surgical illness during the preclinical period of AD is scant.

Thus far, most *in vitro* and animal studies whose results support the proposition of anesthetic-induced neurotoxicity have examined inhaled anesthetics. Limited data are available in relation to the effects of IV anesthetics. IV anesthetics are generally considered less neurotoxic than inhaled anesthetics. Propofol only enhances Aβ oligomerization at high concentrations,[1] and did not impair memory in rats.[22] Some human studies have shown that the risk of long-term cognitive decline was increased after either GA or RA,[23] while others found no association between GA or RA and risk of developing AD.[24] One study demonstrated that Aβ and tau in cerebrospinal fluid changed in a manner consistent with AD 6 months after CABG, regardless of whether the patient received inhaled or IV anesthesia.[25] There has been an ongoing debate as to whether RA is superior to GA in relation to the incidence of cognitive decline; previous studies have shown inconsistent results. One study showed that patients exposed to GA had a lower risk of dementia 5 years after prostate or hernia surgery than did RA patients,[4] but other studies demonstrated no significant differences betweeen these types of anesthesia. In our study, all three modes of anesthesia were associated with an increased risk of dementia, and the HR for dementia development was higher in the RA group than in the GA group, while there was no significant difference between the IV/IM group and the GA group. It may be that anesthetic-induced neurotoxicity does not play a key role in the onset or acceleration of AD pathogenesis after anesthesia and surgery. Other peri-anesthesia factors, such as duration and depth of anesthesia,[26] might also modulate AD pathogenesis.

There is a bidirectional link between depression and dementia. ECT is sometimes administered with IV/IM anesthesia in severely depressed patients, and has been reported to cause cognitive decline.[27] However, in our study, we found that none of the 18 patients that had received ECT developed dementia. Therefore, we can conclude that our finding of increased risk of dementia after IV/IM anesthesia was not biased by inclusion of these depressed patients. On the other hand, given the small number of cases of ECT-treated patients with depression, we cannot elaborate on the possible association of exposure to IV/IM anesthesia during ECT with dementia development in depressed patients.

Our data do not support the hypothesis that two or more exposures to anesthesia within a year increase risk of AD development beyond that which occurs as a result of a single exposure within a year. Our data are consistent with a prior case-control study showing that neither exposure to six or more episodes of GA, nor cumulative exposure to 600 min or more of GA, was associated with an increased risk of AD.[28] In contrast, cell culture and animal studies have suggested that inhaled anesthetics induce neuronal apoptosis in dose- and time-dependent manners. And in an epidemiological study, Bohnen et al. found that age of onset of AD was inversely related to cumulative exposure to anesthesia in earlier life.[21] The inconsistency between previous studies and our findings may be due to different study designs and different methods of statistical analysis.

With the exception of studies related to cardiac surgery, the literature lacks research reports providing information about the possible relationship between surgery type and dementia development. In our analysis, cardiovascular surgery was not associated with an increased risk of AD. However, it should be noted that our cohort included only 17 patients who were subjected to this type of surgery, which limits interpretations of this result. The small number of patients in our study in this surgery type subgroup was most likely due to our exclusion of patients with a diagnosis of stroke. A study on

noncardiac surgeries reported that the incidence of cognitive dysfunction 1–2 y following major abdominal, thoracic, or orthopedic surgery was similar to the control group.[29] However, the number of subjects in the control group may have been inadequate. Another group did not detect long-term cognitive decline attributable to noncardiac surgery, but their analysis did not consider surgery type.[30] In our study, patients undergoing digestive, genitourinary, or musculoskeletal surgery showed an increased risk for dementia. Eye and dermatological surgery were also associated with increased risk of dementia, but the case numbers in these surgery type subgroups were small. The effect of the surgery itself on cognitive decline remains unclear. Indeed, in animals, surgery combined with anesthesia produced greater cognitive dysfunction than anesthesia alone.[31] In addition, inflammatory cascades and microglial activation, which are strongly implicated in neurodegeneration, are triggered by surgery. Thus, surgery may initiate a pro-inflammatory event in the brain in both humans[32] and other animals.[33] Moreover, enhanced neuro-inflammation is hypothesized to accelerate AD neuropathology.[32]

Several caveats merit attention in the interpretation of our results. Because we pulled our source data from the NHIRD claims database of Taiwan, we were unable to investigate nonmodifiable (Apo-E genotype) and modifiable risk factors (alcohol, smoking, level of education, etc.) Additionally, age, prevalence of comorbidity, and Charlson index values were higher in the anesthetized group than in the control group. Although we adjusted the Cox regression model for these factors, solely adjusting for these confounding factors may not have fully controlled for group differences. It is also possible that patients who underwent surgery were followed-up more frequently than subjects in the control group, which could have allowed for more opportunities for dementia diagnosis. Additionally, despite the large size of our sample, the number of cases in some of the subgroups was relatively small following stratification based on surgery type, which could have affected our statistical results.

In conclusion, this nationwide population-based study showed a significant association between anesthesia with surgery and dementia. The present findings support the view that anesthesia and surgery may accelerate the onset and progression of AD. Although anesthesia and surgery have provided immeasurable health and social benefits, our observations highlight the need for further studies to understand the association and causality between anesthesia with surgery and subsequent dementia.

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Table 1. Comparison of subjects exposed to anesthesia with nonanesthetized subjects*

Characteristics	**Subjects with anesthesia (n = 24,901)**		**Subjects without anesthesia (n = 110,972)**		***P* Value+**
Age, median (IQR), y	63	(55-71)	61	(54-69)	<.001
50-65	14,248	(57.2)	70,957	(63.9)	
>65	10,653	(42.8)	40,015	(36.1)	
Gender					<.001
Male	12,332	(49.5)	53,528	(48.2)	
Comorbidities					

Hypertension	10,501	(42.2)	37,955	(34.2)	<.001
Hyperlipidemia	7084	(28.4)	26,289	(23.7)	<.001
Depression	1046	(4.2)	3044	(2.7)	<.001
Charlson index, mean	2.15		1.49		<.001
< 3	16,080	(64.6)	86,892	(78.3)	
>= 3	8821	(35.4)	24,080	(21.7)	

Abbreviation: IQR, interquartile range.
*Data are number (percentage) except where indicated.
+Group comparisons by the chi-square test.

Table 2. Characteristics of anesthetized patients in terms of mode of anesthesia, number of anesthesia within one year, and type of surgery

Group	No. (%) of anesthetized patients (n = 24,901)	
Mode of anesthesia*		
IV or IM anesthesia	1686	(6.8)
Regional anesthesia	8777	(35.2)
General anesthesia	13,715	(55.1)
Number of anesthesia within one year		
Once	14,212	(57.1)
Twice or more	10,689	(42.9)
Type of surgery+		
Eye surgery	1206	(4.8)
Ear-nose-throat surgery	1182	(4.7)
Respiratory surgery	425	(1.7)
Cardiovascular surgery	950	(3.8)
Digestive surgery	5108	(20.5)
Genitourinary surgery	4062	(16.3)
Musculoskeletal surgery	9825	(39.5)
Dermatologic surgery	762	(3.1)

Abbreviations: IM, intramuscular; IV, intravenous.

*Some modes of anesthesia, e.g., nitrous oxide-oxygen sedation, hypothermia anesthesia, etc. are not shown due to small number.

+Some types of surgery, e.g., endocrine surgery, etc. are not shown due to small number.

Table 3. The distribution of the three types of anesthesia among different types of surgical procedures

Type of surgery	IV or IM anesthesia	Regional anesthesia	General anesthesia
Eye surgery	2%	73.5%	24.5%
Ear-nose-throat surgery	0.9%	0%	99.1%
Respiratory surgery	5.4%	0.2%	94.4%
Cardiovascular surgery	8.7%	9.7%	81.6%
Digestive surgery	7.7%	37.0%	55.3%
Genitourinary surgery	6.9%	51.5%	41.6%
Musculoskeletal surgery	5.3%	36.8%	57.9%
Dermatologic surgery	19.7%	33.5%	46.8%

Abbreviations: IM, intramuscular; IV, intravenous.

Table 4. Hazard ratios of dementia in patients receiving anesthesia with nonanesthetized patients stratified by age and gender

Group	Anesthetized patients with dementia diagnosis, No. (%)		Nonanesthetized patients with dementia diagnosis, No. (%)		HR	(95% CI)	Adjusted HR	(95% CI)	*P* Value
All	661	(2.65)	1539	(1.39)	1.99	(1.81-2.17)	1.75	(1.59-1.92)	<.001
Gender									
Male	296	(2.40)	583	(1.09)	2.30	(2.00-2.65)	2.01	(1.78-2.37)	<.001
Female	365	(2.90)	956	(1.66)	1.80	(1.60-2.03)	1.58	(1.40-1.78)	<.001
Age									
50-65	91	(0.64)	239	(0.34)	1.90	(1.49-2.42)	1.65	(1.30-2.11)	<.001
>65	570	(5.35)	1300	(3.25)	1.79	(1.62-1.97)	1.70	(1.53-1.87)	<.001
Charlson index									
< 3	91	(0.57)	293	(0.34)	1.90	(1.68-2.16)	1.85	(1.63-2.09)	<.001
>= 3	570	(6.46)	1246	(5.17)	1.67	(1.45-1.91)	1.63	(1.43-1.87)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

All models are analysed by Cox regressions adjusted for hypertension, hyperlipidemia, depression, and Charlson index.

Table 5. Hazard ratios of dementia in patients receiving anesthesia in terms of mode of anesthesia and number of anesthesia within one year

Group	Anesthetized patients with dementia diagnosis, No. (%)		Nonanesthetized patients with dementia diagnosis, No. (%)		Adjusted HR	(95% CI)	*P* Value	Adjusted HR	(95% CI)	*P* Value
Mode of anesthesia§										
IV or IM anesthesia	45	(2.67)	97	(1.27)	1.60	(1.11-2.30)	.011	1.07	(0.78-1.47)*	.664
Regional anesthesia	299	(3.41)	643	(1.69)	1.80	(1.57-2.07)	<.001	1.42	(1.20-1.66)*	<.001
General anesthesia	301	(2.19)	778	(1.26)	1.46	(1.28-1.68)	<.001	1*		
Number of anesthesia within 1 year										
Once	357	(2.51)	863	(1.36)	1.73	(1.53-1.96)	<.001	1+		
Twice or more	304	(2.84)	676	(1.43)	1.75	(1.53-2.01)	<.001	1.09	(0.93-1.27)+	.290

Abbreviations: CI, confidence interval; IM, intramuscular; IV, intravenous; HR, hazard ratio.
All models are analysed by Cox regressions adjusted for hypertension, hyperlipidemia, depression, and Charlson index.
*Group comparison with general anesthesia as baseline.
+Group comparison with anesthesia exposure once within 1 year as baseline.

§Some modes of anesthesia, e.g., nitrous oxide-oxygen sedation, hypothermia anesthesia, etc. are not shown due to small number .

Table 6. Hazard ratios of dementia in patients receiving anesthesia stratified by type of surgery

Type of surgery§	Anesthetized patients with dementia diagnosis, No. (%)		Nonanesthetized patients with dementia diagnosis, No. (%)		Adjusted HR	(95% CI)	*P* Value
Eye surgery	36	(2.99)	90	(1.70)	1.55	(1.05-2.31)	.029
Ear-nose-throat surgery	16	(1.35)	45	(0.80)	1.46	(0.82-2.61)	.198
Respiratory surgery	5	(1.18)	35	(2.08)	0.49	(0.19-1.27)	.141
Cardiovascular surgery	17	(1.79)	66	(1.62)	0.92	(0.53-1.61)	.771
Digestive surgery	122	(2.39)	284	(1.26)	1.75	(1.41-2.17)	<.001
Genitourinary surgery	89	(2.19)	189	(1.03)	1.93	(1.50-2.49)	<.001
Musculoskeletal surgery	330	(3.36)	728	(1.68)	1.88	(1.65-2.15)	<.001
Dermatologic surgery	27	(3.54)	50	(1.45)	2.36	(1.46-3.80)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
All models are analysed by Cox regressions adjusted for hypertension, hyperlipidemia, depression, and Charlson index.

§Some types of surgery, e.g., endocrine surgery, etc. are not shown due to small number.