scientific reports

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Association between preventive treatment for unruptured intracranial aneurysms and incident dementia: a nationwide population-based cohort study

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Preventive treatments for unruptured intracranial aneurysms (UIAs) are used worldwide. However, the long-term effects to cognition have been underestimated. Using representative sample data from the National Health Insurance Service-Senior Cohort database, we compared cumulative risk of incident dementia between two groups: (1) treatment versus observation group, and (2) within the treatment group (surgical versus endovascular treatment). Cox proportional hazard ratios were estimated after applying one-to-one propensity score matching. Subgroup analyses were conducted to investigate interactions between treatment effects and sex, age and history of stroke, respectively. After matching, 3,763 participants were included in each group. The 10-year incidence rates of dementia were 9.82 and 8.68 per 1,000 person-years in the treatment and observation groups, respectively (HR: 1.11, 95% CI: 0.90–1.38, *P* = 0.33). Furthermore, the risk of incident dementia was not different between the surgical and endovascular treatment groups (HR: 0.98, 95% CI: 0.70–1.37, *P* = 0.91). In the subgroup analysis, surgical treatment was associated with an increased risk of developing dementia, particularly among male patient (HR: 2.34, 95% CI: 1.04–5.28). Preventive treatment of UIAs appears acceptable in terms of long-term effects to cognition. However, further researches are strongly required to identify the high risk patients of development of dementia.

Keywords Intracranial aneurysm, Surgical, Endovascular, Dementia, Incidence

Unruptured intracranial aneurysms (UIAs) have a prevalence of 3–5%, and which are the second most common intracranial pathology on magnetic resonance[1,2]. Up to date, selective prevention strategy has been established. However, the treatment options, either open surgical or endovascular treatment, has distinct pros and cons, which make the decision-making process for treatment selection complex. Notably, as a treatment decision is based on the future rupture risk and functional outcomes[3–5], the long-term cognitive results have not adequately explained.

Several observational studies have attempted to elucidate this relationship in cognitive outcomes[6–9]. Recent reports show that procedures under general anesthesia has a potential effect on the development of dementia[10,11]. However, most of studies for UIAs treatment included a small cohort (< 100 patients), focused on short-term cognitive assessment (< 1 year), and combined two distinct treatment modalities. Thus, the association between long-term cognitive outcome and preventive treatment of UIAs remains unclear, and the current decision-making process for treating UIAs fails to include the crucial points.

Therefore, we designed a retrospective nationwide population-based cohort study using the National Health Insurance Service-Senior Cohort (NHIS-SC) database in South Korea. We aimed to present the effect of UIAs

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treatment on incident dementia over a long-term follow-up period (10 years) and compare the risk of incident dementia between surgical and endovascular treatments.

Methods

Ethics declarations

Research ethics approval was obtained from the Institutional Review Board of Severance hospital, Yonsei university college of medicine (number: 4-2023-0514). Due to retrospective nature of the study, need for informed consent of patients was waived by the same ethics committee, and the study was conducted in accordance with the Declaration of Helsinki.

Data sources

In the present population-based study, we used representative sample cohort data from the NHIS National Health Claims Database. The National Health Insurance Service-Senior Cohort (NHIS-SC) database is provided for research in elderly patients. This database is constructed of older adults and these people were selected by 8% stratified random sampling (stratification variables: sex, age, region, and insurance contribution) from about 6.4 million population aged 60–80 years in 2008. To maintain the sample proportion of the population, an additional 8% of new participants (aged 60) is selected each year by NHIS, thus, a total of 1,057,784 patients were identified. The senior cohort was followed from 2002 to 2019. Especially, the NHIS-SC database contains the data collected using the Prescreening Korean Dementia Screening Questionnaires (KDSQ-P), which quantifies cognitive functions. Medical information was recorded using the International Classification of Diseases 10th Revision code (ICD-10) and electronic data interchange [EDI] codes). The main information extracted from the NHIS-SC database is presented in Supplementary Table 1.

Study design and study population

We defined the patients with UIAs (ICD-10 code: I67.1). The patients were then dichotomized into treatment and observation groups. The treatment group was further classified into surgical or endovascular treatment groups in the same manner. The index dates were defined as the first date of UIA diagnosis in the observation group and first date of surgical or endovascular treatment in the treatment group. We excluded patients who met at least one of the following criteria: (i) undergoing multiple, staged, or concurrent treatments for UIAs; (ii) history of subarachnoid hemorrhage; (iii) history of any procedure for intracranial lesions during the study period (brain tumor or arteriovenous malformation); and (iv) history of traumatic brain injury (TBI). Finally, we included 3,764 patients in the treatment group and 15,383 patients in the observation group (Fig. 1).

Outcome definitions

We determined the incidence of all types of dementia in the observation and treatment group for a period of 10 years. We set a wash-out period of 1 year before the index date. As the index dates differed between the observation and treatment groups, we further analyzed the days between the date of diagnosis and treatment in 604 patients who underwent UIAs treatment at a tertiary hospital. The mean difference was 70.98 days, which was insufficient to affect the development of dementia. The follow-up period began 90 days after the index date

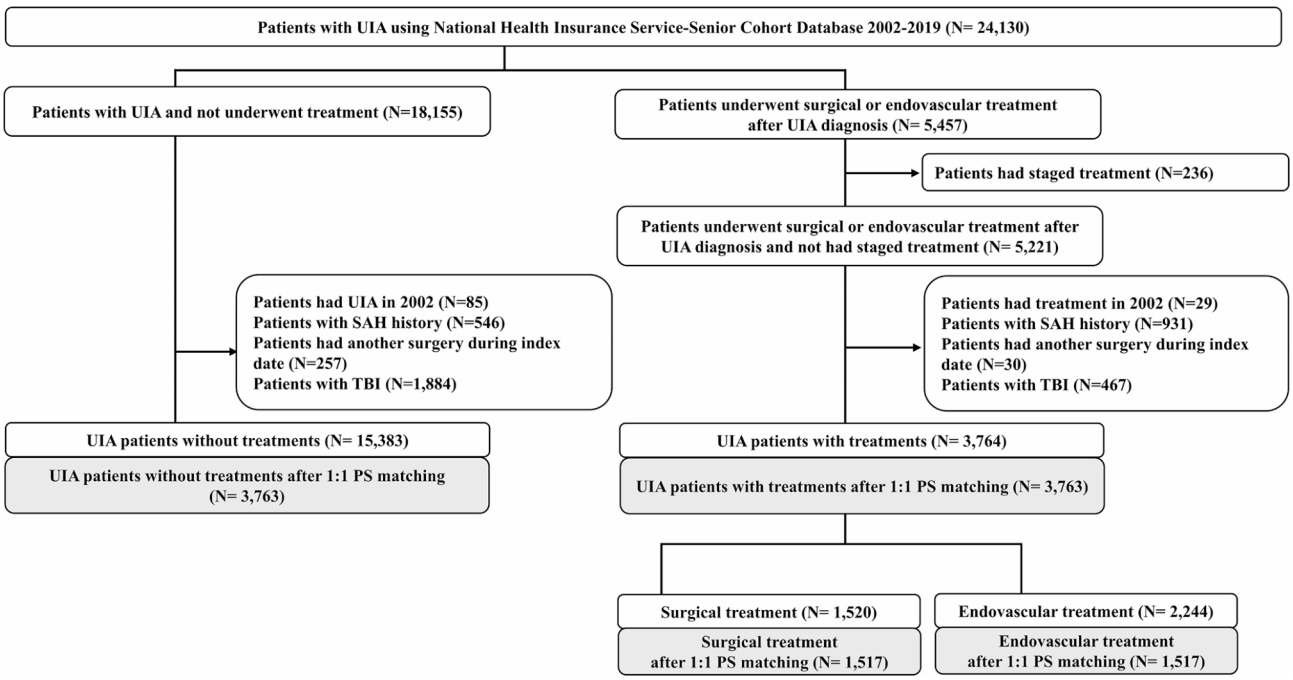

Fig. 1. Flow chart.

to minimize misdiagnosis of temporal cognitive decline as dementia. The follow-up period was defined as the period from the index date until the first occurrence of the outcome of interest, death, or the last date of the study (December 31, 2019), whichever occurred first.

To define incident dementia, we included prescription data because the NHIS approved only four medications (donepezil, rivastigmine, galantamine, and memantine) for the treatment of dementia. Finally, incident dementia was defined as the concurrent receipt of a prescription for dementia medication and a new diagnosis of dementia (ICD-10 codes: F00 or G30 for Alzheimer's disease, F01 for vascular dementia, and F02 and F03 for others). The positive predictive value of dementia was 94.7%.[12]

Propensity score matching and covariates

We used propensity score matching (PSM) to reduce the effect of potential confounders. The propensity score was calculated using a logistic regression model for baseline characteristics. We then conducted one-to-one matching using nearest-neighbor analyses. The following covariates were included as matching variables: age, sex, diabetes mellitus, hypertension, dyslipidemia, cardiac arrhythmia, congestive heart failure, valvular disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease, ischemic stroke, and hemorrhagic stroke. Comorbidities were defined as the presence of ICD-10 codes during the 1-year timeframe prior to the index date. The ICD-10 codes and related information on the study covariates are presented in Supplementary Table 2. The balance of covariates was determined when the standardized difference between all covariates was < 0.1.

Statistical analysis

For the main analysis, the baseline characteristics and comorbidities were presented descriptively. Categorical variables were reported as frequencies, whereas continuous variables were presented as mean and standard deviation (SD). The incidence rate (IR) of dementia was calculated per 1,000 person-years. Kaplan–Meier analysis was used for time-sensitivity analysis, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards regression model.

We conducted subgroup analysis stratifying the study group by sex, age (reference age, 65 years), and history of stroke and conducted an interaction analysis, including the interaction term. Statistical significance was set at $P < 0.05$, and all statistical analyses were conducted using the SAS Enterprise Guide, version 8.3 (SAS Institute, Cary, NC, USA).

Sensitivity analysis

To validate the robustness of this study, we conducted a sensitivity analysis. First, dementia was defined using only the diagnosis without the condition of antidementia drugs during the study period. The "others" definition of dementia was defined as a score ≥ 4 on the KDSQ-P (Supplementary Table 3)[12]. We also set multiple endpoints using different timeframes for the risk of dementia: 1, 5, and 10 years. Lastly, as dementia has several subtypes, the IR and HR for each subtype (Alzheimer's disease, vascular dementia, and others) were calculated.

Furthermore, stabilized inverse probability treatment weighting (IPTW) analysis was performed to reduce large variances, and overlap weighting was performed using the propensity score. The IPTW analysis weighted the reciprocal of the propensity score. The overlap weight was calculated as 1 minus the propensity score and as the propensity score for both groups to balance population average treatment effects[13]. Finally, we performed additional analysis excluding patients with a history of hemorrhagic stroke.

Results

Population characteristics before matching

The baseline characteristics of the population before and after PSM are presented in Tables 1 and 2, respectively. Before PSM, the UIAs treatment group included 3,764 patients with mean age of 65.17 years (SD: 7.11) and the UIAs observation group included 15,383 patients with mean age of 68.72 years (SD: 8.76; Table 1). Before PSM, approximately two-thirds of both groups consisted of women, and the proportions of patients with hypertension, hyperlipidemia, and ischemic stroke were higher in the UIAs treatment group (standard difference: 0.12, 0.15, and 0.10, respectively) than in the UIAs observation group.

On comparing the surgical and endovascular treatment groups (Table 2), the latter group was found to be older (65.90 vs. 64.09 years, standard difference: 0.26). The underlying medical conditions were comparable, although 2.36% of patients who underwent endovascular treatment had a history of myocardial infarction (0.99% in the surgical treatment group, standard difference: 0.11). All covariate variables were balanced after one-to-one PSM.

UIAs treatment versus observation groups after matching

After matching, 3,763 participants were included in each group, the median follow-up duration was 4.79 years (interquartile range: 2.09–8.23) in the UIAs treatment group and 3.92 years (interquartile range: 1.76–7.73) in the observation group. At 10-year follow-up, the incidence of dementia was similar between the treatment and observation groups (IR: 9.82 versus 8.68 per 1,000 person-years; Table 3). In addition, the cumulative incidence of dementia did not differ between the groups (log-rank $P = 0.32$; Fig. 2A). The hazard ratio (HR) of UIAs treatment group versus observation group was 1.11 without statistical significance (95% CI: 0.90–1.38, $P = 0.33$; Table 3).

For the various definitions of dementia, the results did not differ from those of the main analysis (Supplementary Tables 4 and Supplementary Fig. 1A). Also, the risk of dementia was similar when the definition of dementia was based on the KDSQ-P score (51.42 versus 51.26 per 1,000 person-years, HR: 1.03, 95% CI: 0.78–1.36). Furthermore, the 1-year and 5-year IRs with diverse time windows were not significantly different ($P = 0.12$ and

	Before propensity score matching			After propensity score matching		
	UIAs treatments (*N* = 3,764)	UIAs observation (*N* = 15,383)	Standardized Difference	UIAs treatments (*N* = 3,763)	UIAs observation (*N* = 3,763)	Standardized Difference
Age (Mean ± SD)	65.17 ± 7.11	68.72 ± 8.76	0.45	65.17 ± 7.11	65.07 ± 7.39	0.01
Sex			0.14			0.01
Male	1,031 (27.39)	5,229 (33.99)		1,031 (27.40)	1,022 (27.16)	
Female	2,733 (72.61)	10,154 (66.01)		2,732 (72.60)	2,741 (72.84)	
Duration of FU(Median (Q1, Q3))	4.79 (2.09, 8.23)	3.95 (1.69, 7.57)	-	4.79 (2.09, 8.23)	3.92 (1.76, 7.73)	-
Comorbidities						
Diabetes mellitus	1,169 (31.06)	5,263 (34.21)	0.07	1,169 (31.07)	1,172 (31.15)	0.00
Hypertension	2,614 (69.45)	9,822 (63.85)	0.12	2,613 (69.44)	2,596 (68.99)	0.01
Hyperlipidemia	1,577 (41.90)	5,337 (34.69)	0.15	1,576 (41.88)	1,565 (41.59)	0.01
Cardiac arrhythmia	304 (8.08)	1,249 (8.12)	0.00	304 (8.08)	257 (6.83)	0.05
Congestive heart failure	271 (7.20)	1,360 (8.84)	0.06	271 (7.20)	240 (6.38)	0.03
Valvular disease	50 (1.33)	202 (1.31)	0.00	50 (1.33)	39 (1.04)	0.03
Myocardial infarction	68 (1.81)	266 (1.73)	0.01	68 (1.81)	45 (1.20)	0.05
Renal failure	90 (2.39)	463 (3.01)	0.04	90 (2.39)	68 (1.81)	0.04
COPD	1,361 (36.16)	5,433 (35.32)	0.02	1,361 (36.17)	1,360 (36.14)	0.00
Ischemic stroke	816 (21.68)	2,701 (17.56)	0.10	815 (21.66)	785 (20.86)	0.02
Hemorrhagic stroke	111 (2.95)	241 (1.57)	0.09	110 (2.92)	94 (2.50)	0.03

Table 1. Baseline characteristics of patients with unruptured intracranial aneurysms, with regard to treatment status. Values are presented as number and proportion (%) of the patients not otherwise specified. UIAs, unruptured intracranial aneurysms; SD, standard deviation; FU, follow up; COPD, Chronic obstructive pulmonary disease.

	Before propensity score matching			After propensity score matching		
	Surgical treatment (*N* = 1,520)	Endovascular treatment (*N* = 2,244)	Standardized Difference	Surgical treatment (*N* = 1,517)	Endovascular treatment (*N* = 1,517)	Standardized Difference
Age (Mean ± SD)	64.09 ± 6.52	65.90 ± 7.39	0.26	64.11 ± 6.51	64.07 ± 6.79	0.01
Sex			0.02			0.00
Male	423 (27.83)	608 (27.09)		422 (27.82)	420 (27.69)	
Female	1,097 (72.17)	1,636 (72.91)		1,095 (72.18)	1,097 (72.31)	
Duration of FU (Year, median ([Q1, Q3])	5.42 (2.61, 8.76)	4.24 (1.76, 7.80)	-	5.41 (2.61, 8.76)	4.57 (1.94, 7.98)	-
Comorbidities						
Diabetes mellitus	459 (30.20)	710 (31.64)	0.03	459 (30.26)	455 (29.99)	0.01
Hypertension	1,079 (70.99)	1,535 (68.40)	0.06	1,076 (70.93)	1,057 (69.68)	0.03
Hyperlipidemia	622 (40.92)	955 (42.56)	0.03	621 (40.94)	602 (39.68)	0.03
Cardiac arrhythmia	105 (6.91)	199 (8.87)	0.07	105 (6.92)	110 (7.25)	0.01
Congestive heart failure	109 (7.17)	162 (7.22)	0.00	108 (7.12)	92 (6.06)	0.04
Valvular disease	19 (1.25)	31 (1.38)	0.01	19 (1.25)	15 (0.99)	0.02
Myocardial infarction	15 (0.99)	53 (2.36)	0.11	15 (0.99)	13 (0.86)	0.01
Renal failure	32 (2.11)	58 (2.58)	0.03	32 (2.11)	27 (1.78)	0.02
COPD	534 (35.13)	827 (36.85)	0.04	533 (35.14)	532 (35.07)	0.00
Ischemic stroke	297 (19.54)	519 (23.13)	0.09	297 (19.58)	289 (19.05)	0.01
Hemorrhagic stroke	54 (3.55)	57 (2.54)	0.06	51 (3.36)	47 (3.10)	0.02

Table 2. Baseline characteristics of patients with unruptured intracranial aneurysm by treatment modalities. Values are presented as number and proportion (%) of the patients not otherwise specified. SD, standard deviation; FU, follow up; COPD, Chronic obstructive pulmonary disease.

	N (Event/Patients)		IR (per 1,000 person-year, 95% CI)			
	Target group	Comparator group	Target group	Comparator group	Hazard ratio (95% CI)	*P* value
UIAs treatment vs. Observation	189 / 3,763	153 /3,763	9.82 (8.49–11.30)	8.68 (7.38–10.13)	1.11 (0.90–1.38)	0.33
Surgical treatment vs. Endovascular treatment	74 /1,517	65 / 1,517	8.79 (6.95–10.97)	8.65 (6.74–10.95)	0.98 (0.70–1.37)	0.91

Table 3. Risk of incident dementia at 10-year follow-up in patients with unruptured intracranial aneurysm. The former defined as target group and the latter as comparator group. IR, incidence rate; UIAs, unruptured intracranial aneurysms; CI, confidence interval.

0.49, respectively; Supplementary Table 5). We further analyzed the risk of dementia after excluding patients with hemorrhagic stroke at the baseline. As a result, the risk of dementia was not significant (Supplementary Table 12).

The baseline characteristics for each IPTW analysis and propensity overlap weighting are described in Supplementary Table 6. The 10-year IR using IPTW was 11.40 and 11.75 per 1,000 person-years in the UIAs treatment and observation groups, respectively; UIAs treatment was not associated with dementia risk (HR: 0.98, 95% CI: 0.84–1.14). The result from the overlap weighting analysis was consistent (Supplementary Table 7).

In the subgroup analysis, we found a no significant interaction effects of age, sex and history of stroke for UIAs treatment compared with observation groups (P for interaction 0.19, 0.24, 0.22, respectively, Supplementary Table 8).

Surgical versus endovascular treatment groups after matching

Following PSM, 1,517 patients in each group were matched (Table 2). In the main analysis, the 10-year IRs of dementia in the surgical and endovascular treatment groups were 8.79 and 8.65 per 1,000 person-years, respectively (Table 3). Furthermore, there was no time-dependent difference in the IRs between the groups (log-rank $P = 0.91$, HR: 0.98 [95% CI: 0.70–1.37]; Fig. 2B).

After accounting for dementia definitions, there was no significant difference in incidence of dementia between the surgical and endovascular treatment groups (Supplementary Tables 4 and Supplementary Fig. 1B). Furthermore, the results using time-at-risk windows of 1 and 5 years were similar (Supplementary Table 5). The risk of dementia after excluding patients with hemorrhagic stroke was not significant (Supplementary Table 12). The baseline characteristics after IPTW and overlap weighting are presented in Supplementary Table 9. After matching, the HRs for incident dementia did not differ between the surgical and endovascular treatment groups (Supplementary Table 7).

Age and history of stroke showed no significant interactions with the type of treatment (both P for interaction > 0.05, Supplementary Table 10) for the incidence of dementia. Surgical treatment was associated with increased incident dementia among male patient (HR: 2.34, 95% CI: 1.04–5.28). When we assessed the baseline characteristics of male patient, no significant differences were observed between the treatment groups (Supplementary Table 11).

Discussion

We found that the incidence of dementia was comparable between those who received preventive treatment for UIAs and those in the observation group. Furthermore, there was no difference in the risk of incident dementia between the surgical and endovascular treatment groups. Of note, male patients who underwent open surgical clipping had a higher risk of developing dementia than those who underwent endovascular treatment (HR: 2.34, 95% CI: 1.04–5.28). However, this finding should be interpreted with caution because of the exploratory nature of the subgroup analysis.

Several theories have suggested an increase in incident dementia after the preventive treatment of UIAs. First, surgical and endovascular treatments inevitably were accompanied by a small portion of asymptomatic or symptomatic MRI diffusion restriction spots[14], which could be a potential contributor of incident dementia. In observational studies, surgical clipping was associated with a 9.8% risk of asymptomatic diffusion restriction lesion and a 2.0% risk of symptomatic infarction, whereas endovascular treatment was associated with a 3.7–7.1% risk of symptomatic infarction[15–18]. Additionally, general anesthesia could be another contributor to the incidence of dementia[11,19,20]. In a previous nationwide, population-based observational study, anesthesia and surgery were associated with a two-fold increase in the likelihood of development of dementia (HR: 1.99, 95% CI: 1.81–2.17)[10].

Nevertheless, we did not observe a difference in the incidence of dementia between the preventive treatment group for UIAs and the observation group. We hypothesized the fundamental point of the discrepancy between the present and past studies lies in the lack of a clear definition of dementia, misdiagnosis of postoperative cognitive dysfunction (POCD) as part of dementia. To address these issues, we attempted to reduce the misdiagnosis by including several different definition and endpoints. To enhance the accuracy of dementia diagnosis, a composite of diagnosis codes and medication prescriptions was utilized, and this approach demonstrated a positive predictive value of 94.7% in a previous population-based study[21]. A 3-month lag time was introduced to exclude acute-phase POCD. The lag time could also compensate for confounding effects when patients with preclinical dementia undergo UIAs treatment. Moreover, multiple time endpoints were set to dilute the effects of intermediate and long-term POCD[22].

Previous studies have suggested that asymptomatic ischemic insults by the procedures may be a potential cause of dementia. However, dementia is known to occur as a result of the harmonized effects of

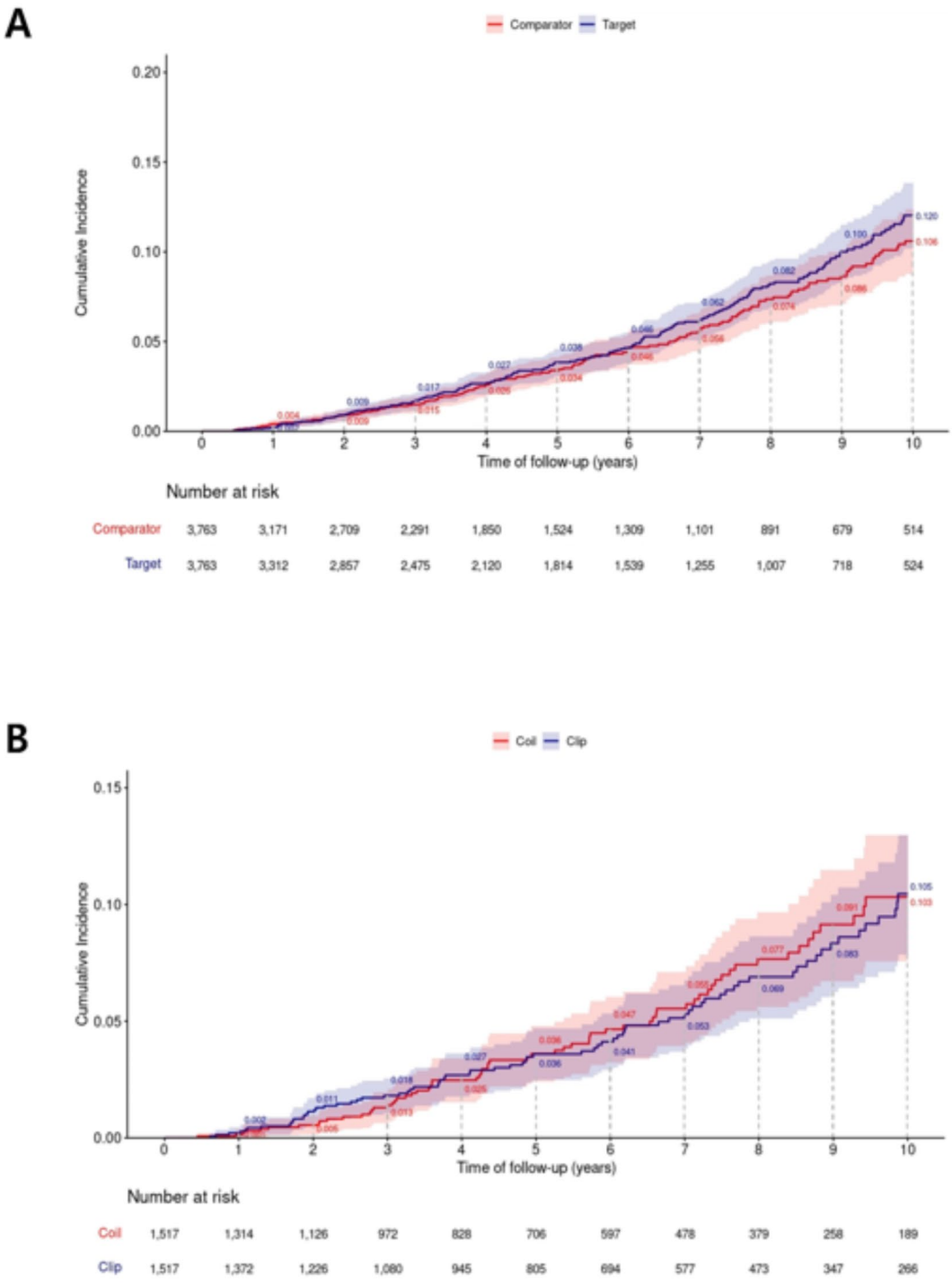

Fig. 2. Kaplan–Meier curves of the incident dementia in the study population. (A) UIAs treatment versus observation; (B) surgical treatment versus endovascular treatment for UIAs.

vascular comorbidity, stroke events, and neurodegeneration[23,24]. This suggestion was concreted by the result that increasing cardiovascular burden is directly correlated with the incidence of vascular dementia (≥3 cardiovascular risk factors, HR: 3.37, 95% CI: 1.49–7.63)[25]. Although loss of brain tissue is detected in both iatrogenic and spontaneous infarction, iatrogenic infarction is a singular incident and not a result of the course of the neurodegenerative conditions. Therefore, iatrogenic infarction had a distinct aspects, which was one of possible explanation of the result of present study.

The risk for dementia may differ depending on the type of surgery performed. To the best of our knowledge, there are no comprehensive reports on the association between UIAs treatment modalities and incident dementia. The International Study of Unruptured Intracranial Aneurysms is one of the largest prospective

observational studies, categorizing morbidity by functional dependency and cognitive outcome. Cognitive function remained unchanged in the endovascular treatment group, whereas the incidence in the open surgical group slightly increased from 4.3–5.5%.[9] On the contrary, a meta-analysis of 281 individuals (249 of whom had undergone clipping surgery) demonstrated that cognitive function was spared after treatment of UIAs[6]. We found no difference in incident dementia risk or cognitive decline, as defined by the KDSQ-P, in surgical versus endovascular treatment groups.

One of the notable results was that surgical treatment was associated with an increased risk of incident dementia only among male patient (HR: 2.34, 95% CI: 1.04–5.28). Anatomical investigation identified progressive brain atrophy with advancing age, particularly in the posterior frontal lobe and in men, where a surgical corridor was acquired by displacement or retraction[26]. Another theoretical suggestion is that TBI contributes to a greater increase in the risk of developing dementia in male patient. Two previous meta-analyses indicated that male patient, but not female, had an increased risk of dementia following a TBI[27,28]. Recently, a Danish population-based study of a cohort of 2,794,852 individuals followed up for an average of 9.89 years, revealed that the hazard ratio for the risk of developing dementia with TBI was higher in male patient (HR: 1.30, 95% CI: 1.26–1.35) than in female (HR 1.19, 95% CI: 1.15–1.23)[29]. Nonetheless, there was scant information regarding the relationship between sex and dementia risk, and the subgroup analysis in this study was an exploratory analysis with its limitations. Further investigations are warranted to validate our findings.

Limitations

The present study has some limitations. First, owing to the inherent limitations of the claims-based database, we could not define the location and size of the UIAs. However, the present study aimed to demonstrate the association between real-world treatment and incident dementia. Second, several types of surgical approaches and devices are used for surgical and endovascular treatment, and we could not obtain information regarding these details of the procedures. Third, we tried to minimize confounding or attributing factors by propensity score matching; however, the effect of uncollected or unrevealed attributes could not be controlled. Moreover, it was impossible to obtain modifiable factors that could change during the long-term follow-up period. Fourth, we were unable to capture treatment-related complications from the routinely collected administrative claim data, which limits the ability to fully assess their impact on dementia incidence. Fifth, although the diagnostic accuracy and predictive value for dementia development in the database had a room for consideration, mild cognitive impairment was also a potential confounding factor. Finally, the definitions of dementia and its subtypes were based on the ICD-10 codes, and the accuracy of diagnosis decreased, especially in the case of mixed-type dementia.

Despite these limitations, this study used a retrospective and longitudinal database of the Korean older adult population. As we used data from the national health screening program, the findings are generalizable and reflect the "real-world" UIAs burden on a nationwide scale. Second, we used various definitions of incident dementia, cognitive function based on the KDSQ-P, and different time windows to verify the consistency of the results. Furthermore, we applied various propensity score adjustments.

Conclusion

During the 10-year follow-up period, incident dementia was not associated with the UIAs treatment and its modalities. While the existing strategy for UIAs treatment is considered to be safe, additional investigations are required to identify the vulnerable population at risk of developing dementia following UIAs treatment.

Data availability

Qualified investigators may obtain all the processed data by submitting the appropriate request via email to the corresponding authors.

Received: 23 May 2024; Accepted: 23 September 2024
Published online: 14 October 2024

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Acknowledgements

None.

Author contributions

HJH, SCY and KYP made a study concept and design. HJH, SK, SIK conducted acquisition, analysis, or interpretation of data. HJH wrote the initial draft, and J-JK, YBK, SCY and KYP critically revised the manuscript for important intellectual content. SK and SIK conducted the statistical analysis. All authors reviewed and approved the final manuscript.

Funding

This study was partly supported by a faculty research grant of Yonsei University College of Medicine (6-2020-0221). This work was partly supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT) (No. 2022R1C1C1007191).

Declarations

Competing interests

The authors declare no competing interests except Dr. You reports being CTO of PHI Digital Healthcare.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-74054-8.

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