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Surgical repair of aortic aneurysms and reduced incidence of dementia

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ABSTRACT

Background: Dementia and aortic aneurysms share clinical risk factors and molecular signaling pathways. However, the association between dementia and aortic aneurysms has not been examined. The potential effects of open surgical repair (OSR) of aortic aneurysms on future dementia events are unknown.
Methods: We conducted this nationwide population-based, retrospective cohort study using the Taiwanese National Health Insurance Research Database (NHIRD). The cumulative incidence of dementia over a 13-year follow-up period was compared among 1) aortic aneurysms and non-aortic aneurysm patients and 2) aortic aneurysm patients who underwent OSR, endovascular aneurysm repair (EVAR) or nonsurgical treatment (NST).
Results: This study enrolled 19,921 aortic aneurysms patients and 19,921 matched controls. The aortic aneurysm cohort exhibited a significantly increased incidence of dementia compared with the controls (adjusted hazard ratio (HR) = 3.559, $p < 0.001$). Furthermore, 5409 aortic aneurysm patients were treated with surgical intervention, whereas 5409 matched aortic aneurysm patients were not. Aortic aneurysm patients who underwent OSR had a significantly lower incidence of dementia than those who underwent NST (adjusted HR = 0.638, 95% confidence interval (CI) = 0.411–0.764, $p < 0.001$). Patients who underwent EVAR did not have a lower incidence of dementia than those who underwent NST.
Conclusion: OSR was associated with a reduced incidence of dementia in patients with aortic aneurysms compared to NST.

1. Introduction

Dementia is a progressive, incurable neuropsychiatric disease that progresses to advanced stages with severe disability [1]. The pooled prevalence of dementia was 48.62 per 1000 in 23 communities [2]. Alzheimer's disease, the most common type of dementia, is a chronic neurodegenerative disease with an insidious onset and a progressive but slow decline. Vascular dementia (VaD) symptoms may be most obvious when they occur suddenly following a stroke [3]. The risk of dementia and aortic aneurysms increases with age. Dementia and aortic aneurysms share several clinical risk factors and molecular signaling pathways [4–7]. Several atherosclerotic risk factors, including hypertension, smoking, and hyperlipidemia, are shared between dementia and aortic aneurysms [8,9]. No cure is currently available for dementia [10], and no approved medications to slow or stop abdominal aortic aneurysm (AAA) growth exist [11]. Currently, several drugs have been evaluated for their potential to limit AAA. Beta-blockers, anti-inflammatory agents, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and statins have been examined, but none of these drugs have been shown to provide a benefit [12]. The usual threshold for elective AAA repair is an aortic diameter of 5.5 cm in men and 5.0 cm in women. Repair should be considered for an AAA with a growth rate exceeding 0.5 cm in diameter over a period of 6 months, regardless of its absolute size [9,13]. In elderly men with aortic aneurysms, dementia was an independent factor of mortality [14]. Aortic aneurysms are associated with systemic vascular inflammation and elevated circulation of inflammatory biomarkers

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[15,16]. In addition, individuals with peripheral inflammation are prone to Alzheimer's disease and Lewy body dementia [17]. However, the association between dementia and aortic aneurysms has not been thoroughly evaluated in large-scale studies. In addition, the potential effect of surgical treatments with open surgical repair (OSR) and endovascular aneurysm repair (EVAR) of aortic aneurysms in future dementia events is unknown.

In this regard, we used the National Health Insurance Research Database (NHIRD) to evaluate whether associations existed between aortic aneurysms and dementia and to determine the possible effects of surgical repair of aortic aneurysms on the incidence of dementia.

2. Methods

2.1. Data source

The National Health Insurance (NHI) Program was launched in Taiwan in 1995. It includes >99% of the Taiwanese population (>23 million people). The NHIRD contains encrypted patient identification numbers, birthdays, genders, dates of admission and discharge, ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic and procedure codes (up to five each) and outcomes. In this study, we used data from the Longitudinal Health Insurance Database 2005 (LHID 2005), a subset of the NHIRD in Taiwan. LHID 2005 contains information on the medical service utilization of approximately one million randomly selected beneficiaries, representing approximately 5% of the population in Taiwan in 2005. Information from 2000 to 2013 was extracted from the NHIRD. The accuracy of the diagnoses of major diseases, such as acute coronary syndrome and stroke, as described in the NHIRD has been validated in previous studies [18]. This study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Institutional Review Board of Tri-Service General Hospital at the National Defense Medical Center in Taipei, Taiwan (TSGH IRB No. 2-105-05-082).

2.2. Sampled patients

Study and comparison cohorts were included. Patients in the LHID 2005 database aged ≥50 years who were newly diagnosed with aortic aneurysms including thoracic, abdominal, and thoracoabdominal aortic aneurysms (ICD-9-CM 441.1-441.9) after 2005 and were followed up between 2000 and 2013 were enrolled. We excluded patients who had been diagnosed with VaD (ICD-9-CM 290.4), nonvascular dementia (non-VaD, ICD-9-CM 290 expect 290.4; ICD-9-CM code 331.0) and aortic aneurysms prior to the index date. Alzheimer's disease (ICD-9-CM 331.0) was classified as non-VD in this study. We also excluded patients who had a follow-up duration of <6 months. The date of dementia diagnosis was used as the index date. Control patients were selected from individuals in the LHID 2005 who had no history of aortic aneurysm or dementia. The patient and control cohorts were selected by 1:1 matching according to baseline variables, namely, age; gender; comorbidities, including hypertension (ICD-9-CM 401-405), diabetes mellitus (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272.0-272.4), heart failure (ICD-9-CM 428), chronic obstructive pulmonary disease (COPD, ICD-9-CM 490-496), alcoholism (ICD-9-CM 303), obesity (ICD-9-CM 278), cancer (ICD-9-CM 140-208), chronic kidney disease (CKD, ICD-9-CM 580–589); and annual medical visits. Patients with aortic aneurysms were further divided into the OSR group, in which the aneurysm was removed and a graft was attached to the aorta; the EVAR group, in which a stent graft was placed within the aorta; and the nonsurgical treatment (NST) group. Medication history, including information related to β-blockers, calcium channel blockers (CCB), ACEi, ARB, diuretics, statins, steroids, digoxin and warfarin, and the number of medical follow-up visits were also obtained. A flow diagram of patient enrollment in this study is presented in Supplemental Fig. 1.

2.3. Outcome measures

The outcomes that were evaluated in this study were 1) the cumulative incidence of dementia, which was compared between aortic aneurysm and non-aortic aneurysm patients; and 2) the cumulative incidence of dementia, which was compared between patients with aortic aneurysms who underwent OSR or NST during the 13-year follow-up period.

2.4. Statistical analysis

All data analyses were conducted using SPSS software, version 22 (SPSS Inc., Chicago, IL, USA). The clinical characteristics of the patients enrolled in the study are expressed in numerical form. Categorical variables, which are presented as percentages, were compared using Fisher's exact test and chi-squared tests. Continuous variables were presented as the mean and standard deviation and were compared using *t*-tests. The primary goal of the study was to determine whether the clinical characteristics of patients were associated with dementia formation. Fine and Gray's competing risk analysis was used to determine the risk of dementia, as death can act as a competing risk factor for dementia. Associations between time-to-event outcomes (prognoses) and clinical characteristics were examined using Kaplan-Meier survival analysis and multivariate Cox regression analysis with forward stepwise selection. The results are presented as adjusted HRs with corresponding 95% confidence intervals (CIs). Statistical significance was indicated by $p < 0.05$.

3. Results

Among a total of 989,753 patients in the LHID 2005 from the NHIRD, 19,921 patients diagnosed with aortic aneurysms were identified. Another 19,921 age-, gender-, comorbidity- and medication-matched patients were used as controls. Furthermore, 5409 patients with aortic aneurysms were treated with surgical intervention, and another 5409 age-, gender-, comorbidity- and medication-matched patients with aortic aneurysms were not treated with surgical intervention. In the surgical intervention group, 4975 patients received OSR and 434 received EVAR (Supplemental Fig. 1). There were no significant differences in gender, age, comorbidities or the number of medical follow-up visits between the groups with and without aortic aneurysms after matching. There were no significant differences between the groups in regard to medication use. There was also no significant difference between aortic aneurysm patients with and without surgical intervention (Supplemental Table 1).

Patients who had aortic aneurysms had a significantly higher cumulative risk of developing dementia in subsequent years than patients without aortic aneurysms (log rank test < 0.001, Fig. 1A). Moreover, patients with aortic aneurysms who underwent OSR had a lower cumulative risk of developing dementia than patients who underwent NST (log rank test < 0.001, Fig. 1B). At the end of the thirteen-year follow-up period, significantly higher incidences of dementia (4.44% vs. 3.70%, $p < 0.001$) and several comorbidities were observed in patients with aortic aneurysms than in patients without aortic aneurysms (Table 1). Moreover, patients with aortic aneurysms who received surgery had lower incidences of VaD and non-VaD than those without surgery (VaD: 0.38% vs. 0.58%, $p = 0.046$; non-VaD: 2.85% vs. 4.23%, $p < 0.001$), and the incidence of non-VaD was lower in patients with aortic aneurysms than in those without aortic aneurysms (3.97% vs. 3.34%, $p = 0.001$). Furthermore, patients with aortic aneurysms also exhibited a significantly increased incidence of dementia than patients without aortic aneurysms according to Cox regression analysis and Fine & Gray's competing risk model (adjusted HR = 3.559, 95% CI = 2.950–4.295, $p < 0.001$). Other association for developing dementia included older age, hyperlipidemia, cancer, CKD, and heart failure (HF) (Table 2). The sensitivity test revealed that aortic aneurysms were associated with an increased incidence of overall dementia for both VaD and non-VaD, whereas dementia diagnoses were excluded in the first year or first 5 years after aortic aneurysm occurrence (Supplemental Table 2).

Aortic aneurysm patients who underwent OSR had a significantly lower incidence of dementia than those who did not receive surgery (adjusted HR = 0.638, 95% CI = 0.411–0.764, $p < 0.001$). In addition, patients who underwent EVAR did not have a significantly different rate of developing dementia than patients who did not undergo a surgical intervention (adjusted HR = 1.309, 95% CI = 0.980–1.631, $p = 0.172$) (Table 3).

4. Discussion

In this population-based study in a nationwide data set, we revealed that aortic aneurysms were associated with an increased incidence of overall dementia, even after adjusting for several comorbidities and medications. For a representative sample of enrollees aged ≥50 years, 4.44% of the subjects and 3.70% of the control group developed dementia. This finding was similar to the reported 2%–5% prevalence in a population aged ≥65 years in the community studies [19], even though Taiwan's Ministry of Health and Welfare reported that the vast majority of dementia patients were underdiagnosed in Taiwan [20]. The sensitivity test revealed that aortic aneurysms were associated with an increased incidence of overall dementia, both VaD and non-VaD, even after dementia

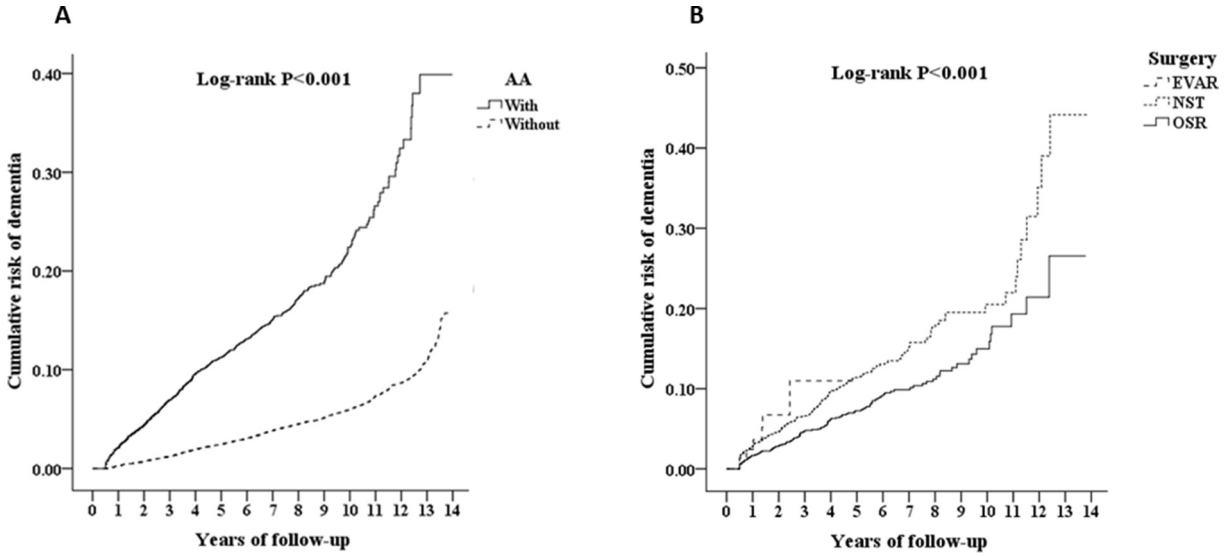

Fig. 1. Cumulative incidence of dementia *p < 0.05 was considered statistically significant. A: Comparison between patients with and without aortic aneurysms; B: comparison among aortic aneurysm patients who underwent OSR, EVAR or nonsurgical interventions.

diagnoses were excluded in the first year or first 5 years after aortic aneurysm occurrence. Notably, we also found that OSR of aortic aneurysms is associated with a lower incidence of newly diagnosed dementia. Therefore, this study provides the first evidence that aortic aneurysms are associated with an increased incidence of dementia and that OSR was associated with a reduced incidence of dementia in patients with aortic aneurysms.

Alzheimer's disease was associated with 70% of all dementia cases, whereas VaD accounted for up to 20% of cases [21,22]. Cardiovascular risk factors, such as age, hypertension, HF, coronary heart disease, smoking, and dyslipidemia, are positively associated with non-VaD and VaD [4,5,23–25]. Well-established risk factors for aortic aneurysms include age, hypertension, hyperlipidemia and tobacco use [9]. Cigarette smoking is an important environmental risk factor for Alzheimer's disease [26,27]. Smoking increases the severity of some abnormalities typical of Alzheimer's disease, including amyloidogenesis, neuroinflammation and tau phosphorylation [26].

Several molecular mechanisms are shared between aortic aneurysms and dementia, including mitogen-activated protein kinase (MAPK) and proinflammatory nuclear factor-κB (NF-kB) pathways and matrix metalloproteinases (MMPs) [28–30]. Lacunar strokes and white matter (WM) injury are the consequences of small vessel diseases. MMPs are proteases that degrade the extracellular matrix and tight junctions between endothelial cells, and they have been implicated in blood-brain barrier

Table 1
Incidences of dementia and other characteristics during the thirteen-year follow-up period.

	AA and matched cohort				AA with surgery and matched cohort			
	Total	With AA	Without AA	p	Total	AA with surgery	AA without surgery	p
	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)	
Total	39,842	19,921 (50%)	19,921 (50%)		10,818	5409 (50%)	5409 (50%)	
Dementia	1621 (4.07%)	884 (4.44%)	737 (3.70%)	<0.001*	433 (4.00%)	174 (3.22%)	259 (4.79%)	<0.001*
VaD	170 (0.44%)	96 (0.50%)	74 (0.38%)	0.053	50 (0.48%)	20 (0.38%)	30 (0.58%)	0.046*
Non-VaD	1451 (3.66%)	788 (3.97%)	663 (3.34%)	0.001*	383 (3.54%)	154 (2.85%)	229 (4.23%)	<0.001*
Gender (male)	29,112 (73.07%)	14,556 (73.07%)	14,556 (73.07%)	0.999	8090 (74.78%)	4045 (74.78%)	4045 (74.78%)	0.999
Age (years)	73.77 ± 9.67	72.91 ± 10.06	74.63 ± 9.20	<0.001*	72.32 ± 10.22	72.19 ± 10.01	72.44 ± 10.42	0.203
Hypertension	15,293 (38.38%)	8067 (40.49%)	7226 (36.27%)	<0.001*	4470 (41.32%)	2204 (40.75%)	2266 (41.89%)	0.234
DM	6370 (15.99%)	2594 (13.02%)	3776 (18.95%)	<0.001*	1390 (12.85%)	661 (12.22%)	729 (13.48%)	0.054
Hyperlipidemia	1107 (2.78%)	627 (3.15%)	480 (2.41%)	<0.001*	357 (3.30%)	164 (3.03%)	193 (3.57%)	0.132
COPD	5049 (12.67%)	2199 (11.04%)	2850 (14.31%)	<0.001*	1081 (9.99%)	440 (8.13%)	641 (11.85%)	<0.001*
Cancer	5871 (14.74%)	2234 (11.21%)	3637 (18.26%)	<0.001*	1195 (11.05%)	596 (11.02%)	599 (11.07%)	0.951
CKD	4296 (10.78%)	2044 (10.26%)	2252 (11.30%)	<0.001*	1095 (10.12%)	603 (11.15%)	492 (9.10%)	<0.001*
HF	3238 (8.13%)	1819 (9.13%)	1419 (7.12%)	<0.001*	898 (8.30%)	432 (7.99%)	466 (8.62%)	0.236
Annual medical visits	6.00 ± 6.10	5.97 ± 6.11	6.03 ± 6.09	0.326	5.94 ± 6.34	5.99 ± 6.37	5.89 ± 6.32	0.413
β blockers	8313 (20.86%)	4112 (20.64%)	4201 (21.09%)	0.273	2014 (18.62%)	1015 (18.77%)	999 (18.47%)	0.711
CCB	7114 (17.86%)	3575 (17.95%)	3539 (17.77%)	0.638	1796 (16.60%)	901 (16.66%)	895 (16.55%)	0.897
ACEI	6719 (16.86%)	3412 (17.13%)	3307 (16.60%)	0.160	1656 (15.31%)	825 (15.25%)	831 (15.36%)	0.894
ARB	6830 (17.14%)	3401 (17.07%)	3429 (17.21%)	0.710	1762 (15.73%)	987 (15.65%)	998 (15.82%)	0.811
Diuretic	6326 (15.88%)	3209 (16.11%)	3117 (15.65%)	0.207	1634 (15.10%)	815 (15.07%)	819 (15.14%)	0.936
Statin	1991 (4.91%)	977 (4.82%)	996 (5.00%)	0.620	385 (3.56%)	198 (3.66%)	187 (3.46%)	0.604
Steroid	1652 (4.07%)	814 (4.01%)	838 (4.13%)	0.563	396 (3.66%)	201 (3.72%)	195 (3.61%)	0.798
Digoxin	3657 (9.18%)	1865 (9.36%)	1792 (9.00%)	0.205	968 (8.95%)	485 (8.97%)	483 (8.93%)	0.973
Warfarin	3442 (8.64%)	1687 (8.47%)	1755 (8.81%)	0.225	848 (7.84%)	422 (7.80%)	426 (7.88%)	0.674

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; HF = congestive heart failure; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.
* p < 0.05 was considered statistically significant.

Table 2
Factors of dementia using Cox regression and Fine & Gray's competing risk model.

Variables	Crude HR	95% CI	p	Adjusted HR	95% CI	p
Aortic aneurysm	3.183	2.646–3.829	<0.001*	3.559	2.950–4.295	<0.001*
Gender (male)	0.984	0.825–1.174	0.858	1.022	0.855–1.222	0.811
Age (≧65 years vs. 50–65 years)	2.436	1.666–3.563	<0.001*	2.742	1.871–1.047	<0.001*
Hypertension	0.974	0.823–1.153	0.757	0.894	0.752–1.062	0.202
DM	0.827	0.677–1.012	0.065	0.879	0.716–1.078	0.216
Hyperlipidemia	1.302	1.143–1.636	0.002*	1.303	1.143–1.641	0.002*
COPD	1.919	1.725–2.165	0.485	1.797	0.972–2.013	0.064
Cancer	1.375	1.262–1.536	<0.001*	1.375	1.261–1.538	<0.001*
CKD	1.927	0.666–2.290	0.653	1.896	0.642–2.251	0.518
HF	1.563	1.385–1.826	0.003*	1.455	1.310–1.666	<0.001
Annual medical visits	1.157	0.897–1.975	0.345	1.111	0.724–1.876	0.411
β blockers	1.842	0.896–3.845	0.533	1.798	0.845–3.780	0.502
CCB	1.798	0.787–3.012	0.709	1.772	0.731–2.987	0.655
ACEI	1.703	0.709–2.944	0.452	1.645	0.682–2.812	0.438
ARB	1.672	0.634–2.786	0.633	1.573	0.603–2.773	0.617
Diuretic	1.405	0.559–3.019	0.494	1.312	0.454–3.018	0.492
Statin	1.509	0.418–2.978	0.518	1.498	0.319–2.945	0.503
Steroid	1.134	0.706–2.705	0.634	1.087	0.608–3.672	0.598
Digoxin	1.348	0.513–2.833	0.511	1.244	0.442–2.803	0.506
Warfarin	1.112	0.504–2.970	0.454	1.096	0.312–2.901	0.452

HR = hazard ratio; CI = confidence interval; Adjusted HR: adjusted variables listed in the table;
DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; HF = heart failure; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.
* $p < 0.05$ was considered statistically significant.

breakdown in neurodegenerative diseases [7]. Aortic aneurysms are caused by intense inflammation accompanied by segmental weakening of the aortic walls and progressive aortic dilation, leading to rupture of the aorta. MMP expression levels were significantly higher in the aortic tissue of patients with aortic aneurysms than in the tissue of patients without aortic aneurysms [6,31]. The degradation of collagen and elastin in the aortic wall is induced by the overexpression of several catabolic MMPs [32]. In the brain, MMPs also cause vasogenic edema in WM and vascular demyelination [33]. The inhibition of c-Jun N-terminal kinase (JNK) activation could reverse Alzheimer's disease by alleviating neuroinflammation, β-amyloid (Aβ) deposition, and tau hyperphosphorylation in ApoE−/− mice fed a high fat diet with Ang II-induced aortic aneurysms [28,34,35]. The risks mentioned above are shared by aortic aneurysms and dementia. These findings suggest the hypothesis that patients with aortic aneurysms have higher incidences of dementia than those without aortic aneurysms. Further prospective and basic studies are warranted to elucidate this hypothesis.

The use of antidementia drugs, such as acetylcholinesterase inhibitors and memantine, statins, and CCB-antihypertensive medications, were not associated with a reduced risk of dementia. However, the observation that OSR could result in a lower incidence of dementia is a novel finding in our study. EVAR of aortic aneurysms was associated with a substantial early survival advantage that gradually decreased over time compared to OSR of aortic aneurysms. Perioperative complications and health-related quality of life were generally comparable between patients who underwent EVAR and those who underwent OSR [36]. However, the rate of late rupture was significantly higher after EVAR than after OSR [37].

Several inflammatory markers, including c-reactive protein and interleukin-6, are associated with an increased risk of all-cause dementia [15]. In patients with AAAs, systemic vascular inflammation in all phases of atherosclerosis-related disorders could be found in positron emission tomography [16]. Inflammatory factors and MMPs are enriched in the vascular wall of aortic aneurysms and could be disseminated in the systemic circulation and further induce remote effects on distant vessels [38,39]. The presence of inflammatory factors in the aortic wall might cause the aortic aneurysm. We postulate that aortic aneurysm and dementia might share a common etiological pathway, and OSR could provide a benefit by removing this pathway. Based on our findings, we suggest that further research is warranted to investigate the possible therapeutic targets and potential benefits of aortic aneurysm treatment.

4.1. Limitations

Although we extensively adjusted our results by utilizing multivariate logistic regression models, our study nonetheless exhibited several limitations and could not control for certain confounders. The NHIRD registry could not provide detailed information regarding family histories, health-related lifestyle factors, and imaging and laboratory results, which may represent potential confounding factors in this study, e.g., COPD incidence was used as a proxy variable for tobacco use to neutralize the potential confounding effect of tobacco use on our study design [40]. The severity of aortic aneurysms may not be similar between these groups since patients who underwent surgical treatment usually had a greater aortic diameter than patients who underwent NST. In contrast, patients with higher risks for surgery would receive NST rather than a surgical procedure. The medical therapy prescribed after aortic surgery, including blood pressure and cholesterol control, could also impact the risk of VaD. We matched patients for annual medical visits, comorbidities and medications to minimize these cofounding effects. Although

Table 3
Factors of dementia stratified by variables using Cox regression and Fine & Gray's competing risk model.

Subgroups	With surgery		Without surgery		Competing risk		
	Event	Rate (per 10^5 PYs)	Event	Rate (per 10^5 PYs)	Adjusted HR	95% CI	p
Total	174	302.55	259	473.35	0.673	0.555–0.817	<0.001*
OSR	163	292.70	259	473.35	0.638	0.411–0.764	<0.001*
EVAR	11	603.57	259	473.35	1.309	0.980–1.631	0.172

PYs = person-years; HR = hazard ratio; CI = confidence interval; adjusted HR: adjusted variables listed in this figure; OSR = open surgical repair, EVAR = endovascular aneurysm repair.
* $p < 0.05$ was considered statistically significant.

matching was performed at the beginning of follow-up, several comorbidities reached statistically difference after 13 years. These could be the cofounding effects. In addition, EVAR was not financially supported by the health insurance program of Taiwan until 2010; therefore, the EVAR group had a shorter follow-up period and smaller sample size than the OSR and NST groups. Careful interpretation of the results regarding EVAR in our study is required, and additional studies with a larger sample size and longer follow-up period are warranted.

5. Conclusion

We have observed an association between aortic aneurysms and dementia even after adjusting for several comorbidities and medications in a nationwide population database. Notably, the evidence supports that OSR was associated with a reduced incidence of dementia in patients with aortic aneurysms. These findings serve as a reminder to clinicians that monitoring neurocognitive changes in patients with aortic aneurysms is crucial.

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Author contributions

J-CW and S-HT conceived and designed the study. W-CC provided materials for the study. C-HC analyzed the data. N-ST interpreted data and critically revised the manuscript. All the authors collected and interpreted data and wrote and approved the paper.

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