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Increased depression risk in patients with abdominal aortic aneurysm: a nationwide cohort study

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Purpose: Abdominal aortic aneurysm (AAA) is a critical disease. Most studies of AAA consider reoperation rate, complications, or mortality, but do not consider a patient's mental state. However, there is a possibility of interaction between AAA and depression in disease development and prognosis. We investigated the incidence and risk ratio of depression in patients with AAA using nationwide data.
Methods: We selected subjects from National Health Insurance System database who were diagnosed with AAA between 2009 and 2015 and survived at least 1 year after diagnosis or AAA surgery (n = 10,373). We determined the control group using propensity score matching by age and sex. The control group had about 3 times the number of subjects as the AAA cohort (n = 31,119).
Results: The incidence of depression was 1.4 times higher in the AAA group than the control group. We further analyzed the incidence of depression in the AAA group according to treatment modalities (nonsurgical *vs*. surgical or nonsurgical *vs*. open surgical aneurysm repair *vs*. endovascular aneurysm repair) but found no significant difference among them. The incidence of depression was significantly higher in patients aged <65 years than in patients aged ≥65 years (hazard ratio, 1.539 *vs*. 1.270; P < 0.001).
Conclusion: The incidence of depression was higher in the AAA group, with an especially high risk for depression in patients aged <65 years. The psychiatric status of patients with AAA should be carefully monitored for clinicians to intervene when appropriate.
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Key Words: Aortic aneurysm, Depression, Incidence, Mental disorders, Psychiatry

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a very serious disease that is frequently associated with severe disability or death. Even after successful treatment, various sequelae or impairment can occur. Most studies of AAA have considered 30-day

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mortality, reoperation rate, reintervention rate, complications, and mortality as their end-points. Additionally, clinicians in practice generally concentrate on a patient's physical problems, not psychiatric problems. Furthermore, Asian cultures generally associate depression with negative sentiments, such as considering it a "weakness of will," so patients hesitate to express their feelings or difficulties. In these contexts, previous studies that consider AAA and depression are rare.

In contrast, the relationship between heart disease and depression has been widely investigated. The incidence of depression is reportedly 14%–47% after coronary bypass surgery and 19%–66% after myocardial infarction, which is 3 times higher than the general population [1-5]. Patients diagnosed with depression have double the risk of developing coronary artery disease [6,7]. Depression and heart disease each affect the development of the other and have a bidirectional interaction in their prognosis. Patients who have both depression and heart disease have more complications, lower life expectancy, and higher mortality, which are related to poor compliance to treatment or lifestyle corrections [1,8,9]. These effects are also associated with pathophysiologic interactions between depression and heart disease, with one of the most well-known mechanisms being neuroendocrine theory. In pathologic conditions, the hypothalamic-pituitary-adrenal axis is stimulated, which increases cortisol excretion, affects neurons, and contributes to depression development. In another pathway, increased cortisol induces atherosclerosis and sustains low-activity chronic inflammation, which eventually leads to heart disease [1,10,11]. Other mechanisms under investigation involve proinflammatory cytokines, depletion of folate or homocysteine, and continuous stimulation of the autonomic nervous system [1,8,12-15].

Both AAA and coronary artery disease are caused by atherosclerosis and inflammatory reactions, and both share risk factors such as smoking, male sex, hypertension, or dyslipidemia. Because of these similarities, we hypothesized that AAA and depression may interact [16,17]. In addition, depression can be caused in AAA patients after surgery by posttraumatic stress disorder (PTSD) caused by fear of aneurysm rupture, time spent in an intensive care unit (ICU), or social and functional impairment [18-20]. In this study, we investigated the incidence and risk ratios of depression in patients with AAA using nationwide cohort data.

METHODS

Data source and study population

The National Health Insurance Service (NHIS) is a single-payer universal coverage health insurance system for the entire Korean population managed by Korean government. The system has 2 health care programs: national health insurance and medical aid. About 97% of the population is under national health insurance and the remaining 3% is under medical aid [21]. NHIS contains all information claimed by medical service providers in Korea about diagnosis, prescription, and consultation. Statements in the NHIS database are defined by the Korean Classification of Disease, 6th edition, and a modified version of the International Classification of Diseases, 10th edition. All NHIS subscribers are requested to have a general health checkup biannually. General health checkups include questionnaires (e.g., smoking, alcohol consumption, regular exercise, sleeping), physical examination (height, weight, waist circumference, blood pressure, eye test, and hearing tests), laboratory tests (blood, urine, and tumor biomarkers), imaging tests (simple chest or mammogram), and esophagogastroduodenoscopy.

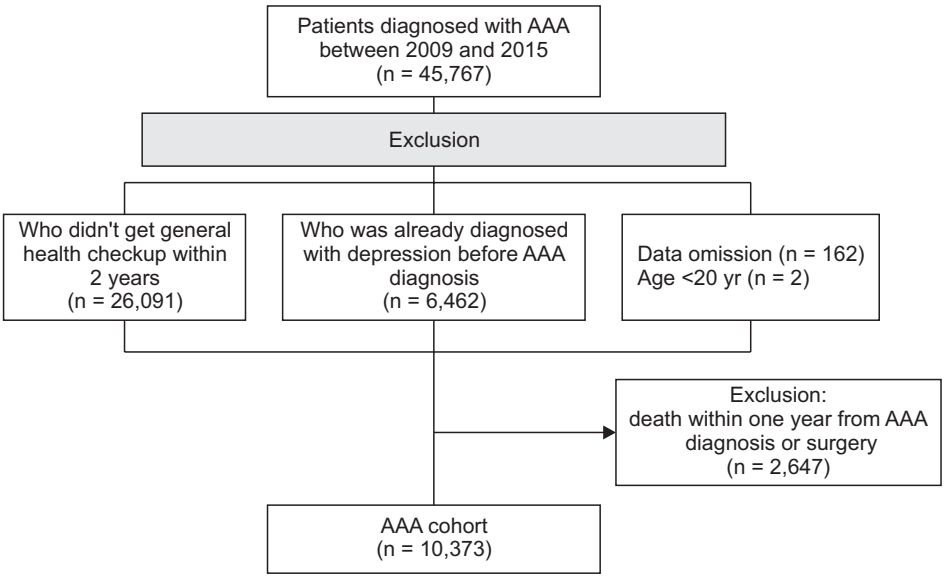

Fig. 1. Flowchart of the study population. AAA, abdominal aortic aneurysm.

Table 1. Definitions for data collection

	Definition
AAA	At least 2 claims per year under ICD-10 codes I71, I713-716, I718, or I719, or at least one claim for hospitalization under the same ICD-10 codes, or at least one claim for surgery under the same ICD-10 codes
OSAR	Open surgical aneurysm repair, codes O0223, O0224, or O0234
EVAR	Endovascular aneurysm repair, codes M6603, M6611, or M6612
Depression	At least 1 claim under ICD-10 codes F32 or F33
Diabetes	At least 1 claim for the prescription of antidiabetic medication or insulin under ICD-10 codes E11-14
Hypertension	At least 1 claim for the prescription of antihypertension medication under ICD-10 codes I10-13 or I15
Dyslipidemia	At least 1 claim for the prescription of antidyslipidemic medication under ICD-10 code E78
Stroke	At least 1 claim under ICD-10 codes I60-64 or stated history of stroke by patient
Coronary disease	At least 1 claim under ICD-10 codes I20-25 or stated history of myocardiac infarction or angina by patient

AAA, abdominal aortic aneurysm; ICD-10, a modified version of the International Classification of Diseases, 10th edition; OSAR, open surgical aneurysm repair; EVAR, endovascular aneurysm repair.

We selected subjects from the NHIS database who were diagnosed with AAA between 2009 and 2015 (n = 45,767). We excluded subjects who did not get a general health checkup in the previous 2 years (n = 26,091), who were diagnosed with depression before their AAA diagnosis (n = 6,462), who were less than 20 years old (n = 2), or who had missing data (n = 162). We included subjects who survived more than 1 year after AAA diagnosis or AAA surgery (n = 10,373). We set the control group using propensity score matching by age and sex and included 3 times as many subjects as the AAA cohort (n = 31,119) (Fig. 1).

Data collection

We collected data from the NHIS database, including baseline data (age, sex, and medical aid), lifestyle data (smoking, alcohol consumption, and regular exercise), physical examination data (body mass index [BMI], waist circumference, and blood pressure), laboratory test data (fasting glucose and cholesterol), and comorbidities (diabetes, hypertension, dyslipidemia, stroke, and coronary disease). Among lifestyle data, alcohol consumption was classified into 3 grades according to the amount of daily use: none, mild to moderate (1–30 g/day), and heavy (over 30 g/day). Regular exercise was exercising more than 5 times per week with slight sweating (mild intensity) or more than 3 times per week with heavy sweating or increased heartbeat (high intensity). We determined AAA, depression, and comorbidities from claim data in the NHIS database (Table 1).

The present study was approved by the Institutional Review Board of the Catholic University of Korea (No. PC20ZISI0145). This study was performed in accordance with the Declaration of Helsinki and written informed consent was exempted.

Statistical analysis

Continuous variables are presented as means ± standard deviation and categorical variables are presented as number and percentages. To compare cohort characteristics, we used analysis of variance for continuous variables and chi-square test for binary or categorical variables. We calculated the incidence rate of depression by dividing the event number by 1,000 person-years. To evaluate the hazard ratio (HR) for depression development, we used the Cox proportional hazards model. Model 1 analyzed HR without adjustment. Model 2 was adjusted for age, sex, smoking, alcohol, regular exercise, BMI, medical aid, diabetes, hypertension, and dyslipidemia. Model 3 was based on model 2, and we also adjusted for stroke and coronary disease. We analyzed HRs according to the absence or presence of AAA and performed subgroup analysis after dividing the AAA group into non-surgery and surgery groups (subgroup 1) or into non-surgery, open surgical aneurysm repair (OSAR), and endovascular aneurysm repair (EVAR) groups (subgroup 2). We used a Kaplan-Meier plot to analyze the incidence of depression according to the absence or presence of AAA and treatment modalities (subgroups 1 and 2). We performed subgroup analysis for HRs of depression according to each variable after adjustment for model 3. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) and the R Project for Statistical Computing ver. 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic characteristics of abdominal aortic aneurysm patients

We compared demographic characteristics of AAA and control groups (Table 2, Supplementary Table 1). Patients with a history of smoking, especially current smokers, were more common in the AAA group ($P < 0.001$). Patients in the AAA group exercised less and drank less alcohol ($P < 0.001$ and $P < 0.001$, respectively). Diabetes ($P = 0.017$), hypertension ($P < 0.001$), dyslipidemia ($P < 0.001$), stroke ($P < 0.001$), and coronary artery disease ($P < 0.001$) were more common in the AAA group. BMI

Table 2. Demographic characteristics of AAA cohort (n = 10,373)

Characteristic	AAA		P-value
	No	Yes	
No. of patients	31,119	10,373	
Male sex	21,966 (70.6)	7,322 (70.6)	>0.999
Age (yr)	64.74 ± 11.80	64.74 ± 11.80	>0.999
Smoking			<0.001
Non	16,979 (54.6)	4,823 (46.5)	
Ex-smoker	7,922 (25.5)	2,615 (25.2)	
Current smoker	6,218 (20.0)	2,935 (28.3)	
Alcohol consumption (g/day)			<0.001
None	18,159 (58.4)	6,553 (63.2)	
Mild (≤30)	10,678 (34.3)	3,080 (29.7)	
Heavy (>30)	2,282 (7.3)	740 (7.1)	
Regular exercise[a]	7,177 (23.1)	2,191 (21.1)	<0.001
Diabetes	5,960 (19.2)	2,097 (20.2)	0.017
Hypertension	16,006 (51.4)	8,055 (77.7)	<0.001
Dyslipidemia	9,389 (30.2)	5,726 (55.2)	<0.001
Stroke	1,359 (4.4)	1,406 (13.6)	<0.001
Coronary disease	3,397 (10.9)	4,985 (48.1)	<0.001
Medical aid[b]	5,901 (19.0)	1,874 (18.1)	0.042
Body mass index (kg/m^2)	23.91 ± 3.06	24.06 ± 3.20	<0.001
Waist circumstance (cm)	83.21 ± 8.47	84.31 ± 8.83	<0.001
SBP (mmHg)	127.41 ± 15.37	128.71 ± 16.86	<0.001
DBP (mmHg)	77.52 ± 9.80	78.63 ± 11.03	<0.001
Fasting glucose (mg/dL)	104.01 ± 27.66	102.1 ± 25.05	<0.001
Cholesterol (mg/dL)	192.54 ± 38.56	193.13 ± 44.59	0.194

Values are presented as number only, number (%), or mean ± standard deviation.
AAA, abdominal aortic aneurysm; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]More than 5 times per week with mild intensity or more than 3 times per week with high intensity (sweating, increased heartbeat); [b]Socioeconomic state in the lowest 20% and whose medical costs were supported by the government.

Table 3. Incidence of depression and hazard ratio according to AAA diagnosis and type of management

Variable	No. of patients	Depression	Incidence per 1,000 person-years	Model		
				1	2	3
AAA						
No	31,119	4,906	35.8193	1 (Reference)	1 (Reference)	1 (Reference)
Yes	10,373	2,003	50.1666	1.402 (1.331–1.477)	1.387 (1.313–1.465)	1.287 (1.213–1.366)
AAA_subgroup1						
No	31,119	4,906	35.8193	1 (Reference)	1 (Reference)	1 (Reference)
Non-surgery	7,403	1,482	50.2589	1.404 (1.325–1.488)	1.41 (1.328–1.498)	1.305 (1.223–1.392)
Surgery	2,970	521	49.906	1.395 (1.275–1.528)	1.32 (1.201–1.451)	1.237 (1.124–1.363)
AAA_subgroup2						
No	31,119	4,906	35.8193	0.712 (0.672–0.755)	0.709 (0.668–0.753)	0.766 (0.719–0.817)
Non-surgery	7,403	1,482	50.2589	1 (Reference)	1 (Reference)	1 (Reference)
OSAR	903	163	47.4453	0.943 (0.803–1.109)	0.943 (0.801–1.11)	0.964 (0.819–1.135)
EVAR	2,067	358	51.1131	1.019 (0.907–1.143)	0.933 (0.830–1.048)	0.941 (0.837–1.058)

Values are presented as number or hazard ratio (95% confidence interval).
AAA, abdominal aortic aneurysm; OSAR, open surgical aneurysm repair; EVAR, endovascular aneurysm repair.
Model 1: unadjusted; model 2: adjusted for age, sex, smoking, alcohol, regular exercise, body mass index (BMI), medical aid, diabetes, hypertension, and dyslipidemia; model 3: adjusted for age, sex, smoking, alcohol, regular exercise, BMI, medical aid, diabetes, hypertension, dyslipidemia, stroke, and coronary disease.

and waist circumference were higher in the AAA group ($P < 0.001$ and $P < 0.001$, respectively) and systolic and diastolic blood pressure were also higher ($P < 0.001$ and $P < 0.001$, respectively).

Risk of depression development in abdominal aortic aneurysm patients

The AAA group had a higher incidence of depression (Table 3). In the adjusted model, we found that patients with AAA had 1.28–1.40 times higher risk of developing depression than patients in the control group. We analyzed the incidence of depression in the AAA group according to treatment modalities (non-surgery *vs.* surgery or non-surgery *vs.* OSAR *vs.* EVAR) but did not find significant differences in depression incidence among them.

We performed subgroup analysis to evaluate how individual variables related to risk of developing depression (Table 4). The incidence of depression was higher in patients aged <65 years (HR, 1.539). Risk of depression was higher in patients with no previous diagnosis of dyslipidemia or coronary artery disease. We found that sex or other comorbidities, such as diabetes, hypertension, or stroke, had no effect on depression development.

Results from the Kaplan-Meier curve and log-rank tests were similar. The incidence of depression was significantly higher in the AAA group ($P < 0.001$), but there were no significant differences among types of treatment for AAA (Fig. 2).

Table 4. Subanalysis of incidence and hazard ratio of depression according to the variables

Variable	AAA	Incidence per 1,000 person-years	Model[a]	P for interaction
Age (yr)				
<65	No	23.5632	1 (Reference)	<0.001
	Yes	37.3741	1.539 (1.383–1.712)	
≥65	No	48.6449	1 (Reference)	
	Yes	63.2319	1.27 (1.171–1.378)	
Dyslipidemia				
No	No	33.7532	1 (Reference)	0.045
	Yes	47.5365	1.316 (1.213–1.429)	
Yes	No	40.8705	1 (Reference)	
	Yes	52.4987	1.253 (1.150–1.364)	
Coronary disease				
No	No	33.9773	1 (Reference)	0.035
	Yes	46.1553	1.342 (1.247–1.445)	
Yes	No	51.9582	1 (Reference)	
	Yes	54.5002	1.171 (1.061–1.293)	

Values are presented as number or hazard ratio (95% confidence interval).
AAA, abdominal aortic aneurysm.
[a]Adjusted for age, sex, smoking, alcohol, regular exercise, body mass index, medical aid, diabetes, hypertension, dyslipidemia, stroke, and coronary disease.

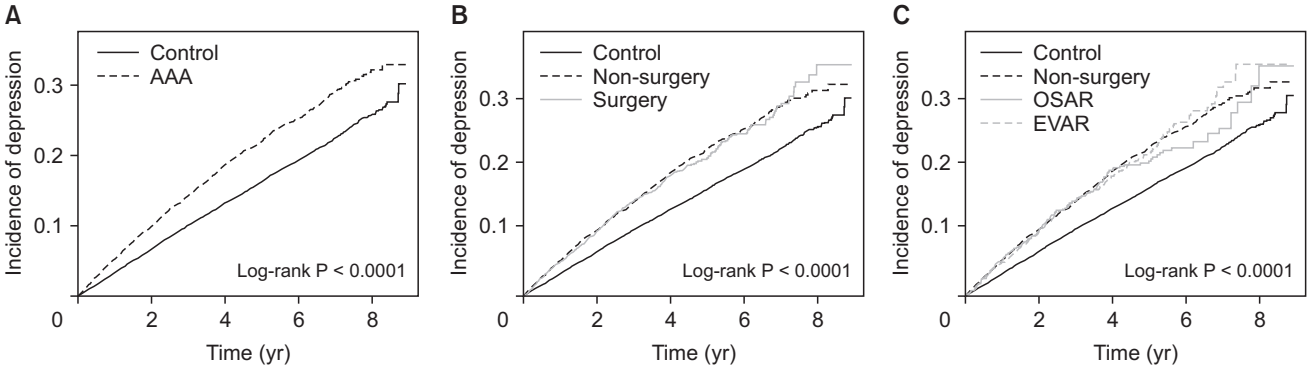

Fig. 2. Kaplan-Meier plot of the incidence of depression. (A) The incidence of depression is increased in the abdominal aortic aneurysm (AAA) cohort with statistical significance. (B, C) There is no definite difference between non-surgery and surgery groups and among non-surgery, open surgical aneurysm repair (OSAR), and endovascular aneurysm repair (EVAR) groups.

DISCUSSION

This study analyzed the incidence of depression in a nationwide cohort of patients with AAA. Depression has been rarely studied in this cohort, and we found that the incidence of depression in patients with AAA was 50.1 per 1,000 person-years, which was 1.4 times higher than in the control group. There were no differences between non-surgery and surgery groups.

There are some significant differences between previous studies and our study. Liberzon et al. [18,19] performed prospective studies of the incidence of PTSD and depression in patients who underwent aorta surgery due to aneurysm or aortic occlusive disease, found a very high incidence of psychiatric disease (10.5%, or 16 events among 152 patients). In that study, the risk of developing psychiatric disease was higher in the surgery group than in the conservative care group (32% *vs.* 9%), and the risk was especially high in the open surgery group. We posit that these differences are due to differences in the study models. Liberzon et al. [18,19] prospectively evaluated the psychiatric status of patients using various psychosocial measurement tools and recorded patient data immediately postoperative, 3 months after, and 9 months after surgery. They concluded that increased incidence of psychiatric disease was associated with intubation at the end of surgery, time spent in the ICU, and postoperative pain. In contrast, we enrolled patients who survived for more than 1 year after surgery or diagnosis, and we defined depression as when a patient was diagnosed with depression, rather than evaluating emotional status using psychosocial measurement tools. For these reasons, our study found a lower depression incidence and was less influenced by immediate postoperative effects.

Interestingly, we found that the incidence of depression was greatly increased in younger patients with AAA. For further analysis, we divided age into 3 groups and sex into 2 groups (Table 5). In both male and female groups, the youngest group had the highest risk of depression (male 2.029 and female 3.142, respectively) and the risk gradually decreased as patient age increased. Previous studies of heart disease and depression suggest that younger patients with severe illness have a higher risk of depression due to functional or physical impairment, longer treatment duration, and increased stress to support their families [22,23].

We suggest that AAA in younger patients has different pathophysiology than that of aneurysm development in older patients. Typical AAA is an advanced atherosclerotic disease that is common in adults more than 65 years old and is induced by thinning of the media and adventitia in the vasculature due to smooth muscle cell loss [16,17]. However, AAA in younger patients is thought to be caused by proinflammatory cytokines, dysregulation of the immune system, genetics, or rheumatic disease, rather than degenerative changes from aging [16,17,24,25]. We hypothesized that differences in underlying disease could affect vulnerability to depression in younger patients with AAA.

The low incidence of depression in older people may be related to low detection rates. According to Liberzon et al. [18,19], the incidence of psychiatric disease increased by 15%–32%

Table 5. Hazard ratio of depression development according to age and sex

Sex	Age (yr)	AAA	Incidence per 1,000 person-years	Model[a)]
Male	20–39	No	9.4795	1 (Reference)
		Yes	16.3482	2.029 (1.027–4.008)
	40–59	No	15.1876	1 (Reference)
		Yes	27.0242	1.496 (1.214–1.842)
	60–79	No	38.1988	1 (Reference)
		Yes	53.6296	1.277 (1.173–1.391)
	≥80	No	58.9667	1 (Reference)
		Yes	74.3938	1.163 (0.908–1.491)
Female	20–39	No	9.5879	1 (Reference)
		Yes	27.7708	3.142 (1.227–8.047)
	40–59	No	27.7446	1 (Reference)
		Yes	42.1114	1.346 (1.071–1.691)
	60–79	No	51.1931	1 (Reference)
		Yes	68.3820	1.211 (1.073–1.367)
	≥80	No	67.9555	1 (Reference)
		Yes	97.1522	1.352 (1.021–1.79)

Values are presented as number or hazard ratio (95% confidence interval).
AAA, abdominal aortic aneurysm.
[a)]Adjusted for age, sex, smoking, alcohol, regular exercise, body mass index, medical aid, diabetes, hypertension, dyslipidemia, stroke, and coronary disease.

in a group of patients who had aorta surgery. They evaluated patient emotional status before patients expressed difficulties on their own, using various measurement tools [18,19]. Our study did not include any screening and diagnosed depression when patients got worse and needed treatment. Moreover, depression in the elderly can present in various forms, such as cognition impairment, dementia, lack of vigor, or loss of interest in normal activities [26]. Diagnosing depression in older people requires circumspect vigilance and a willingness to take precautions when abnormal behaviors arise.

We found a higher risk for depression in AAA patients, with an especially high risk for depression in younger patients. Clinicians should closely monitor the emotional and psychiatric state of AAA patients and intervene appropriately.

SUPPLEMENTARY MATERIALS

Supplementary Table 1 can be found via https://doi.org/10.4174/astr.2021.101.5.291.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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