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Complete List of Authors:	Liao, Kuang-Ming CHEN, CHUNG-YU;
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Outcomes in Patients with Chronic Obstructive Pulmonary Disease and Aortic Aneurysms

Kuang-Ming Liao[1], Chung-Yu Chen[2,3]

1. Department of Internal Medicine, Chi Mei Medical Center, Chiali, Taiwan
2. Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
3. School of Pharmacy, Master Program in Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan

Corresponding author

Chung-Yu Chen, School of Pharmacy, Kaohsiung Medical University. No. 100, Shih-Chuan 1st Rd., Sanmin District, Kaohsiung City 80708, Taiwan (R.O.C.)

E-mail: jk2975525@hotmail.com

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Abbreviations:

AA	Aortic Aneurysm
AAA	Abdominal Aortic Aneurysm
ACEI	Angiotensin-Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
BB	Beta-Blocker
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
OAD	Oral Anti-Diabetic Agent
PAD	Peripheral Artery Disease
PSM	Propensity Score Matching
TAA	Thoracic Aortic Aneurysm
TAAA	Thoracoabdominal Aortic Aneurysm
VHD	Valvular Heart Disease

Abstract

Objectives: Aortic aneurysms (AAs), including abdominal AAs (AAAs), thoracic AAs (TAAs) and thoracoabdominal AAs (TAAAs), are a leading cause of death worldwide, and AA rupture is associated with a high mortality rate. Chronic obstructive pulmonary disease (COPD) is a risk factor for AA, and the prognosis of COPD patients with AA regardless of whether they underwent surgery needs to be investigated.

Methods: We included patients with AA who were over 18 years and presented at either an ambulatory visit or an inpatient hospitalization with a first-time AA diagnosis between 2005 and 2011 in Taiwan. The date of the ambulatory visit or inpatient hospitalization when AA was first diagnosed was considered the index date. Patients who were diagnosed with COPD before the index date served as the case groups, while AA patients without COPD served as the control groups. We also matched propensity scores according to age group, demographic characteristics, comorbidities, and co-medications at a 1:1 ratio. The patients were separated into the TAA, AAA, and TAAA groups. The outcomes, including death from any cause and admission to the hospital for AA or surgical repair, were evaluated.

Results: There were 3,263 patients with COPD and AA before propensity score matching and 2,127 patients with COPD and AA after propensity score matching enrolled in this study. Among the patients with AA, patients with COPD had higher mortality and re-hospitalization rate than did patients without COPD with adjusted hazard ratios (HRs) of 1.118 (95% CI=1.028-1.217) and 1.114 (95% CI=1.007-1.2327), respectively, after propensity score matching. Within the operation group, there was no significant difference in mortality between the COPD and non-COPD groups. Within the non-operation group, the COPD group had higher

mortality than did the non-COPD group with an adjusted HR of 1.105 (95% CI=1.004-1.216).

Conclusions: COPD patients with AA who underwent surgery had improved outcomes; however, their mortality rates were still high compared with those of AA patients without COPD. High mortality was also observed in the COPD non-operation group. Further investigation is required to identify effective treatments for reducing the mortality rate in this group.

Strengths and limitations

1. COPD patients with aortic aneurysms had higher mortality and re-hospitalization rates than did non-COPD patients with adjusted HRs of 1.118 (95% CI=1.028-1.217) and 1.114 (95% CI=1.007-1.2327), respectively.
2. Within the operation group, there was no significant difference in mortality between the COPD and non-COPD groups.
3. Within the non-operation group, the COPD group had higher mortality than did the non-COPD group with an adjusted HR of 1.105 (95% CI=1.004-1.216).
4. Some features of COPD and aortic aneurysms, such as lung function, aneurysm size, and the presence of dissection/rupture, may have an impact on mortality but were not analyzed in the present study.
5. The safety and outcomes of patients with COPD undergoing AAA repair have improved, while the overall mortality of these patients remains higher than that of patients without COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is an obstructive airway disease that cannot be fully reversed using medication. Not only is COPD a systemic inflammatory disease that shares the common risk factor of smoking with aortic aneurysms (AAs) but COPD is also an independent risk factor for AA in its various forms.[1] AAs, including abdominal AAs (AAAs), thoracic AAs (TAAs) and thoracoabdominal AAs (TAAAs), are associated with high mortality, particularly following rupture.[2–4]

Previous studies either focused on the prognosis of patients with COPD undergoing operations for AAA[5] or compared the outcomes of patients with COPD and AAA who were undergoing open or endovascular repair.[6] However, these studies only considered the effect of COPD in patients with AAA who underwent surgery, and some of these studies were performed more than 10 years ago. In addition, patients with AAs may receive either surgical or medical treatment, but few studies have investigated the effect of COPD on patients with AAs who receive medication. In a previous study of patients with AAA, the risk of death was significantly greater when COPD was present.[7] Another study showed that severe COPD, for which patients were dependent on home oxygen, was not a contraindication for AAA repair and did not increase mortality.[8] Unfortunately, generalization of these observational studies was limited by their small sample sizes, short follow-up periods, lack of medication records, and conflicting results. Moreover, improvements in intraoperative and postoperative care for vascular surgery have resulted in significant reductions in morbidity and mortality that may have affected the outcomes of AAs in patients with COPD, indicating that further investigation is required.

To investigate the outcomes of patients with AAs (including AAAs, TAAAs, and

AAAs) and COPD, we used data available in the Taiwanese National Health Insurance Research Database (NHIRD) from patients receiving either surgical or medical treatment.

Materials and Methods

Study design

This was a population-based observational study using information from the NHIRD in Taiwan. Data regarding hospital visits, emergency care, and prescriptions were provided by the National Health Insurance Research Institutes. The diagnosis of AA in the NHIRD has previously been evaluated.[9] This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT-20130199).

Participants

We included patients from the NHIRD aged ≥18 years presenting with a first-time diagnosis of AA (ICD-9: 441.1–441.9) between 2005 and 2011. The date of the first ambulatory visit or inpatient hospitalization at which AA was diagnosed was designated the index date. We excluded patients who died at first presentation and those who had fewer than 30 days of follow-up after discharge.

Only participants who had a diagnosis of COPD (ICD-9: 490–492, 496) before the index date were included as cases. Patients were not excluded for taking the following medications: long-acting inhaled anticholinergics, long-acting inhaled β2-adrenergic receptor agonists, inhaled corticosteroids, short-acting anticholinergics, short-acting β2-agonists, or xanthines. Patients were excluded if COPD was diagnosed or if medications for COPD were prescribed after the index date.

The control group consisted of patients with AA who had no comorbid diagnosis of

COPD. To decrease selection bias due to baseline differences, we also conducted propensity score matching (PSM) at a 1:1 ratio by age group, demographic characteristics, comorbidities, and co-medications. Depending on which occurred first, patients in this study were followed until readmission or operation for AA, death, withdrawal from the national health insurance, or December 31, 2012.

Variables

The patients were divided into the TAA (ICD-9 codes 441.1–441.2), AAA (ICD-9 codes 441.3–441.4), and TAAA (ICD-9 codes 441.6–441.7) groups based on the diagnosis site at the index date. We also evaluated whether patients underwent surgery and, if so, whether that was by open or endovascular repair.

Patient comorbidities were identified by diagnostic code as inpatient or outpatient diagnoses within 180 days of the index date. The following comorbidities were included in the assessment: hypertension, diabetes, dyslipidemia, congestive heart failure (CHF), atrial fibrillation, valvular heart disease (VHD), peripheral artery disease (PAD), coronary artery disease (CAD), stroke (ischemic and hemorrhagic), malignancy, chronic kidney disease (CKD), thyroid disease, liver disease, gout, peptic ulcer disease, and sleep apnea. Prescribed drugs were also evaluated within 180 days of the index date. The following medications were also included as variables: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), diuretics, alpha-blockers, statins, fibrates, antiplatelet drugs, and oral anti-diabetic agents (OADs).

We also evaluated the demographic characteristics of patients with AAs and with or without COPD. Potential confounders included gender, age group (<50, 50–59, 60–69, 70–79, and >80 years), urbanization (urban or rural), income group, and smoking status. Income groups were defined as low (<NT$24,000), middle (NT$24,000–

NT$42,000), or high (>NT$42,000) based on the individual monthly gross income during a 1-month period before the index date.

Because no information was available regarding smoking status, we used the mean percentage of city/county smoking rates available from the National Health Interview Survey (2005 to 2011). All subjects in this survey were randomly sampled and selected from different cities and counties to be personally interviewed by trained interviewers.[10] Although this smoking rate is not a direct measure of the rate for patients in this database, it can be considered to reflect the likely rate of smoking and passive smoking (stratified by age, gender, and living area) if we assume a normally distributed cohort that reflects the broader population.

Outcome

The main outcomes of interest were death from any cause and hospital admission for AA or surgical repair. Moreover, all patient deaths were confirmed by withdrawal from the NHIRD within 1 month of a major medical event. [11] We considered readmission to be when patients were admitted with AA-related events (ICD-9 codes 441.1–441.9) as the principal or secondary diagnosis after discharge from the index event. Surgical repair was stratified by whether or not patients underwent surgery at the time of the index event. If patients underwent surgical repair for AA at the index event and were readmitted to the hospital for surgical repair more than 30 days after discharge, they were classified as undergoing repeat surgical repair. The surgical repair group consisted of patients who did not undergo surgical repair at the index event and who were admitted to the hospital more than 30 days after discharge.

Statistics

All data are expressed as the frequency (percentage) and mean ± standard deviation (SD). Categorical and continuous variables were compared between the COPD and non-COPD groups using chi-square tests and Student t-tests, as appropriate. The

outcomes in the COPD and non-COPD groups were examined by Cox proportional hazards models for the 8-year follow-up period. Analyses and calculations were performed using SAS ver. 9.4 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was inferred at a two-sided p-value <0.05.

Univariate and multivariate analyses (including age group, comorbidities, co-medications, and demographic characteristics) were used to assess the risk of outcome by the presence or absence of COPD during follow-up. We used PSM for patients in the COPD and non-COPD groups. Because the outcomes may have been influenced by the presence of disease (diabetes mellitus, dyslipidemia, and hypertension) or medication (OADs, statins, fibrates, and antihypertensives), we examined these factors in a multivariate model. The difference in the cumulative probability of mortality between the COPD and non-COPD patients was calculated using Kaplan–Meier estimates with the log-rank test; we also divided patients by surgical repair type and site of diagnosis for these analyses.

To assess the robustness of the outcomes, a subgroup analysis was performed including age (≥70 and <70 years), AA site (TAA, AAA, and TAAA), high-risk patients (hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, stroke, and CKD), concomitant drug use (ACEIs, BBs, CCBs, statins, and antiplatelet agents), and type of surgery.

Results

Descriptive data

We identified 6,117 patients with AAs, of which 3,263 also had COPD. After PSM, 2,127 patients with COPD were enrolled in the study. Figure 1 shows the study flow diagram for patients with AAs with and without comorbid COPD.

Table 1 summarizes the characteristics of patients with AAs by COPD diagnosis before and after PSM. Before matching, one-third of the patients with AAs were aged 70–80 years and more than half were >70 years of age. There was a notable preponderance of males in both COPD groups, at approximately 74% in the non-COPD group and 81% in the COPD group. In addition, most participants had low incomes, with approximately 90% and 96% of patients in the non-COPD and COPD groups, respectively, having incomes below NT$24,000.

In both groups, AAA was the most common type, followed by TAA and TAAA. Most patients (58%) received open repair in the non-COPD group, while most patients (55%) received endovascular repair in the COPD group. The most common comorbidity was hypertension, which was present in more than 96% of patients. CAD and dyslipidemia, the next most common comorbidities, were much less frequent (approximately 50% or less). The three most common medications used by patients in the non-COPD group were CCBs, diuretics, and BBs, while CCBs, diuretics, and antiplatelet agents were most commonly used by patients in the COPD group.

Outcome of AAs based on the presence or absence of COPD

Table 2 shows the outcomes of patients with AAs in the COPD and non-COPD groups. Table 3 shows the HRs and 95% confidence intervals (CIs) for death and re-hospitalization with and without PSM. These tables show that patients with COPD had higher mortality rates than patients without COPD, with respective adjusted HRs before and after PSM of 1.104 (95% CI 1.022–1.192) and 1.118 (95% CI 1.028–1.217) (Tables 2 and 3). The AA re-hospitalization rate was also higher in the COPD group than in the non-COPD group, with respective adjusted HRs before and after PSM of 1.100 (95% CI 1.004–1.206) and 1.114 (95% CI 1.007–1.2327) (Tables 2 and 3). In contrast, there was no significance difference in the number of patients receiving operations between the groups.

Outcomes based on the operation and non-operation groups

Patients with AAs were separated into the operation and non-operation groups for comparison, but we found no significant differences in mortality and reoperation rate before PSM (Table 3). However, after PSM, the reoperation rate for AA was higher in the COPD group than in the non-COPD group, with an adjusted HR of 3.314 (95% CI 1.394–7.043), although there was no significant effect on mortality or re-hospitalization rate in the operation group. In the non-operation group, the mortality rate was higher in the COPD group than in the non-COPD group both before and after PSM, with respective adjusted HRs of 1.233 (95% CI 1.130–1.344) and 1.105 (95% CI 1.004–1.216); however, there was no significant difference in re-hospitalization or operation rate 30 days after the index date, either before or after PSM.

Other factors affecting outcomes

COPD and age ≥80 years were associated with higher mortality rates after PSM, with respective HRs of 1.118 (95% CI 1.028–1.217) and 2.970 (95% CI 1.533–5.755). In addition, not only were AAA and TAAA associated with a higher risk of re-hospitalization than TAA after PSM but AAA was also associated with a lower risk of mortality than TAAA.

Other comorbidities associated with a higher risk of mortality after PSM included diabetes, dyslipidemia, CHF, atrial fibrillation, VHD, stroke, malignancy, CKD, and peptic ulcer disease. Among the patients with multiple comorbidities, only CAD and CKD were associated with a significantly higher risk of re-hospitalization.

Medications that showed an apparent protective effect on mortality after PSM were ARBs, BBs, and CCBs. Patients prescribed CCBs had a lower risk of re-hospitalization, and those prescribed α blockers had a higher risk of re-hospitalization. After PSM, patients with AAs had a lower risk of mortality if they

were receiving ARBs than if they were receiving ACEIs, with HRs of 0.846 (95% CI 0.766–0.934) and 1.170 (95% CI 1.058–1.293), respectively. However, there was no significant difference in re-hospitalization rates among patients receiving either ACEIs or ARBs after PSM.

Mortality analysis in patients with AAs and COPD

Table 4 shows the results of a subgroup analysis for mortality in patients with AAs based on the presence or absence of COPD. Patients with AAs and COPD had higher mortality rates than did those without COPD. Patients ≥70 years old (HR 1.117, 95% CI, 1.021–1.223) or with TAAs (HR 1.262, 95% CI 1.075–1.482) also had higher risks of mortality. The HR for mortality in patients with AAs, COPD, and hypertension was also significant (HR 1.111, 95% CI 1.019–1.211). Other comorbidities, including diabetes, dyslipidemia, atrial fibrillation, stroke, and CKD, were not associated with increased risks of mortality in patients with AAs and COPD. There was also no significant difference in the mortality rates between the operation procedures for patients with COPD and AA.

Figure 2 shows the cumulative risk of AA mortality in patients with and without COPD, stratified by patients who underwent surgery and by the AA site. There was no significant difference in mortality between the COPD and non-COPD groups (p=0.6516) for patients with TAAAs who underwent surgery. However, for all other subgroups, there were significant differences in mortality based on the presence or absence of COPD in patients with AAs.

Discussion

This nationwide population-based study showed that patients with AAs and COPD had higher risks of all-cause death and re-hospitalization than did those without

COPD. In patients with AAs who underwent surgery, those with COPD had the greatest risk of reoperation for AAs. However, there was no difference in mortality between procedures for AAs in patients with COPD.

Prognosis in patients with COPD and AAs

A previous study showed that the increased prevalence of COPD in patients with AAAs was independent of smoking.[1] Other studies have found that COPD is associated with a high prevalence of AAAs, with rates from 7.7% to 9.9% and with the prevalence increased in the case of severe emphysema and when the forced expiratory volume/vital capacity ratio decreased.[12,13] Aneurysm rupture rates also correlate with COPD risk factors, initial aneurysm size, and diastolic hypertension,[14] but surgeons are hesitant to repair AAAs electively because of the associated high morbidity and mortality.[15] In a database review of 1,053 patients undergoing surgery for intact or ruptured AAAs in a hospital between 1997 and 1998, David et al.[16] showed that mortality was no higher in patients with COPD than in patients without COPD; however, they also showed that patients with COPD required longer hospital stays, longer intensive care unit stays, and more days of ventilation. However, their study was performed more than 15 years ago and only focused on patients with AAAs receiving surgical repair.

Our study included patients with a first-time AA diagnosis between 2005 and 2011 who were followed until December 31, 2012. The final cohort of patients with AAs comprised 2,854 controls without COPD and 3,263 cases with COPD, and these were further divided into those who did and did not undergo surgery. Our study indicated that patients with COPD and AAs had a higher rate of readmission to the hospital and higher mortality compared with patients without COPD. In patients undergoing surgery for AAs, we found that the mortality and re-hospitalization rates were not significantly different between those with and without COPD, although the

reoperation rate was higher in those with COPD. Among those not undergoing surgery for AA, the all-cause mortality rate was also higher for patients with COPD than for those without COPD.

Surgical procedure and mortality in patients with COPD and AAs

Christopher et al.[17] retrospectively reviewed 44 patients with oxygen-dependent COPD undergoing AAA repair, of which 24 underwent endovascular aneurysm repair and 20 underwent open procedures. They showed that type of repair, comorbidities, and lung function test results did not significantly affect survival. Many other studies have also shown that endovascular AAA repair offers long-term survival similar to open AAA repair in patients with COPD.[18–20] Moqueet et al.[21] performed a prospective study of high-risk patients undergoing endovascular repair of AAAs or TAAAs between 1998 and 2009 and showed that mortality was no different between patients with and without COPD when endovascular techniques were used. In our study comparing all types of AAs in COPD and non-COPD groups, we found no significant difference in mortality rates for either procedure between the two groups.

Patient characteristics

In our study, patients with COPD had higher rates of AAs than did those without COPD. Most patients with AAs were males, regardless of whether or not they had COPD. The most common comorbidities in patients with AAs and COPD were hypertension, CAD, stroke, dyslipidemia, and CHF. These results are similar to those reported by Flessenkaemper et al.,[22] who suggested that risk factors such as male gender and CAD could be used to increase the efficiency of screening for AAAs. We suggest that other risk factors, such as hypertension, stroke, dyslipidemia, and CHF, may be useful in future screening for AAs in patients with COPD.

In a survey of 231 patients with COPD, Katsutoshi et al.[23] reported that only 27 (11.7%) had AAs and 20 (8.7%) had AAAs. This contrasts with the results of our

nationwide study, in which 2,089 (64%) patients with AAAs also had comorbid COPD. To our knowledge, except for two studies with conflicting results,[24,25] there have been no major reports on the prevalence or incidence of AAs in the Asian population. Poon et al.[26] reported that the prevalence of AAAs in Chinese patients was low and that their results did not support routine screening for AAAs. However, another study showed that AAAs were not uncommon and that the incidence of AAAs was comparable to that in the West.[25] A larger population study including more Asian countries is needed to clarify these issues.

Prescription patterns

Medical management is important in the control of AAs, with the main goal of therapy being to decrease shear stress by reducing blood pressure and contractility.[27] In a small retrospective study, BBs decreased AAA growth effectively.[28] In another study, prophylactic BBs were associated with a decrease in the rate of aortic dilatation.[29] Indeed, BBs can not only reduce left ventricular contractility but also reduce shear stress in the aorta. However, a prospective randomized double-blind study has shown that patients with AAAs do not tolerate BBs and that these medications have no significant effect on the growth rates of small AAAs.[30]

In our study, before PSM, the most common medications for AAs were CCBs, followed by diuretics and then BBs. Although there was a significant difference in the prescribing rate of BBs between the COPD and non-COPD groups, this difference did not persist after PSM. BBs are often prescribed for AA, but physicians may be concerned about contraindications and may fear inducing adverse reactions or bronchospasms, especially in patients with obstructive airway disease. In our analysis, BBs were well tolerated by patients with AAs and COPD. Moreover, BBs had the clear protective effect of reducing mortality. This is consistent with their recommended use. In fact, the safety of BBs has long been proven in patients with

COPD, and there is a growing body of evidence from clinical trials showing that BBs should not be withheld from this patient group.[31]

ACEI and ARB in AA

In our analysis, ARBs, BBs, CCBs, and diuretics, but not ACEIs, were associated with reduced mortality in patients with AAs and COPD. In an animal model, AAs have been associated with increased transforming growth factor-β signaling, and the ARB losartan has been shown to block transforming growth factor-β.[32] Losartan can, therefore, prevent elastic fiber fragmentation and blunt transforming growth factor-β signaling in the aorta, reducing the growth rates of AAs.[33] However, ACEIs prevented aortic dissection and apoptosis of vascular smooth muscle cells in another animal model.[34] Meanwhile, Hackam et al. reported that ACEIs were protective against aortic expansion and rupture, whereas ARBs did not protect against AAA rupture.[35] Other experimental evidence showed that ACEIs increase collagen synthesis, improve plaque stabilization, and diminish aortic stiffness.[36] To further complicate matters, in a prospective cohort study of 1,701 patients in the UK, Sweeting et al.[37] showed that aneurysm growth was faster in patients receiving ACEIs. This conflicts with previous research and observational data from Canada showing that ACEIs have protective benefits.[36]

Taken together, the inconsistent results regarding the efficacies of ARBs and ACEIs in reducing AA growth limit any meaningful conclusion. Undoubtedly, these problems result from differences in the models used, selection bias, unaccounted confounding factors, and the fact that there are multiple possible pathways of AA development. Therefore, a prospective, double-blind, randomized study may be needed to delineate the true effects of ACEIs and ARBs on AAs.

Limitations

There were some important limitations in this study. We did not have access to data on

vital signs (i.e., blood pressure and heart rate) or to imaging results (i.e., we could not estimate the size or progression of AAs). We also did not include data on pulmonary function tests or the severity of COPD, and we were unable to determine a clear relationship between the size of AAs and the severity of COPD. However, we focused on all-cause mortality, re-hospitalization rates, and reoperation rates, and we used subgroup analysis (operation vs. non-operation) to reduce bias. This was also a large nationwide study of all registered patients with AAs in Taiwan, which should allow for generalization to other COPD populations. Finally, we also performed PSM, which reduced the bias in estimating treatment effects and reduced the likelihood of confounding data.

Conclusions

Improvements in the pre- and postoperative management of patients with COPD undergoing major surgery have resulted in reduced mortality and morbidity rates. However, although we showed that the safety and outcomes of patients with COPD undergoing AAA repair have improved, we also showed that the overall mortality remains higher than that in patients without COPD. In addition, we observed high mortality rates among patients with COPD who did not undergo surgery. Further research is clearly needed to identify the most appropriate therapy for reducing mortality in patients with AAs and COPD.

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Table 1.

Variable	Non-COPD (n=2854) No	%	COPD (n=3263) No	%	p	PS-matching Non-COPD (n=2127) No	%	PS-matching COPD (n=2127)	p
Age group (yr)					<0.001				0.436
<50	273 (9.6)		61 (1.9)			64 (3.0)		61 (2.9)	
50-60	356 (12.5)		113 (3.5)			134 (6.4)		112 (5.3)	
60-70	508 (17.8)		388 (11.9)			327 (15.4)		354 (16.6)	
70-80	932 (32.6)		1183 (36.2)			837 (39.4)		853 (40.1)	
>80	785 (27.5)		1515 (46.5)			763 (35.9)		747 (35.1)	
Gender					<0.001				0.971
Female	745 (26.1)		631 (19.3)			509 (23.9)		508 (23.9)	
Male	2109 (73.9)		2632 (80.7)			1618 (76.1)		1648 (76.1)	
Urbanicity					<0.001				0.733
Urban	724 (25.4)		1011 (31.0)			592 (27.8)		602 (28.3)	
Rural	2130 (74.6)		2252 (69.0)			1535 (72.2)		1525 (71.7)	
Income (NT)					<0.001				0.831
Low (<24,000)	2564 (89.8)		3136 (96.1)			2002 (94.1)		2011 (94.6)	
Middle (24,000-42,000)	149 (5.2)		74 (2.3)			71 (3.3)		65 (3.1)	
High (>42,000)	141 (5.0)		53 (1.6)			54 (2.5)		51 (2.4)	
Aortic aneurysm site					<0.001				0.918
TAA	965 (33.8)		1018 (31.2)			664 (31.2)		662 (31.1)	
AAA	1689 (59.2)		2089 (64.0)			1355 (63.7)		1351 (63.5)	
TAAA	200 (7.0)		156 (4.8)			108 (5.1)		114 (5.4)	
Operation	1181 (41.4)		1018 (31.2)		<0.001	823 (38.7)		753 (35.4)	0.026
Open repair	689 (58.3)		455 (44.7)			425 (51.6)		340 (45.2)	
Endovascular repair	492 (41.7)		563 (55.3)			399 (48.4)		413 (54.7)	
Smoking rate	26.3 (±13.4)		28.6 (±12.3)		<0.001	27.0 (±13.1)		27.0 (±13.1)	0.921
Co-morbidities									
Diabetes	414 (14.5)		450 (13.8)		0.423	310 (14.6)		307 (14.4)	0.896
Hypertension	2766 (96.9)		3138 (96.2)		0.112	2055 (96.6)		2051 (96.4)	0.738
Dyslipidemia	944 (33.1)		1032 (31.6)		0.227	727 (34.2)		725 (34.1)	0.948
CHF	561 (19.7)		1019 (31.2)		<0.001	488 (22.9)		482 (22.7)	0.826
Atrial fibrillation	230 (8.1)		384 (11.8)		<0.001	196 (9.2)		189 (8.9)	0.708
VHD	594 (20.8)		556 (17.0)		<0.001	377 (17.7)		368 (17.3)	0.717
PAD	152 (5.3)		222 (6.8)		0.016	128 (6.0)		139 (6.5)	0.487
CAD	1135 (39.8)		1685 (51.6)		<0.001	965 (45.4)		974 (45.8)	0.782
Stroke	736 (25.8)		1127 (34.5)		<0.001	642 (30.2)		646 (30.4)	0.894
Malignance	479 (16.8)		645 (19.8)		0.003	402 (18.9)		407 (19.6)	0.560
CKD	453 (15.9)		597 (18.7)		0.012	374 (17.6)		378 (17.8)	0.872
Thyroid disease	87 (3.1)		97 (3.0)		0.863	59 (2.8)		64 (3.0)	0.647
Liver disease	343 (12.0)		441 (13.5)		0.081	267 (12.6)		254 (11.9)	0.543
Sleep apnea	317 (11.1)		533 (16.3)		<0.001	271 (12.7)		268 (12.6)	0.890
Peptic ulcer disease	257 (9.0)		361 (11.1)		0.007	215 (10.1)		218 (10.3)	0.879
Gout	520 (18.2)		628 (19.5)		0.305	414 (19.5)		411 (19.3)	0.974
Prescribed Drugs									
ACEI	691 (24.2)		857 (26.3)		0.066	521 (24.5)		507 (23.8)	0.616
ARB	948 (33.2)		1058 (32.4)		0.510	695 (32.7)		679 (31.9)	0.600
BB	1737 (60.9)		1583 (48.5)		<0.001	1174 (55.2)		1178 (55.4)	0.902
CCB	2187 (76.6)		2419 (74.13)		0.024	1607 (75.4)		1616 (76.7)	0.747
Diuretics	1874 (65.7)		2158 (66.1)		0.697	1371 (64.5)		1388 (65.3)	0.585
Alpha-blocker	457 (16.0)		541 (16.6)		0.549	344 (16.2)		346 (16.2)	0.934
Statin	480 (16.8)		535 (16.4)		0.658	373 (17.5)		378 (17.8)	0.841
Fibrate drugs	68 (2.4)		61 (1.9)		0.163	41 (1.9)		42 (1.9)	0.912
Antiplatelet drugs	1349 (47.3)		1742 (53.4)		<0.001	1083 (50.9)		1084 (50.9)	0.976
OADs	236 (8.3)		293 (8.9)		0.324	192 (9.0)		186 (8.7)	0.747

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OADs, oral anti-diabetic agents; VHD, valvular heart disease; PAD, peripheral artery disease; CAD, coronary artery disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

Table 2.

Outcome	No. of person-yr	Events after discharge: COPD (n=3263)	Events after discharge: Non-COPD (n=2854)	Cox regression unadjusted HR	p	Cox regression Adjusted HR [a]	p	PS-matching Cox regression Adjusted HR [a]	p
Total population									
All-cause death	15403	1795/3263 (55.0)	1198/2854 (41.9)	1.503 (1.397-1.617)	<0.001	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009
AA re-hospitalization	11958	1159/3263 (35.5)	941/2854 (33.0)	1.241 (1.138-1.353)	<0.001	1.100 (1.004-1.206)	0.042	1.114 (1.007-1.232)	0.036
Operation	8262	384/3263 (11.8)	367/2854 (12.9)	0.897 (0.777-1.036)	0.897	0.909 (0.779-1.061)	0.227	0.972 (0.8221.149)	0.738
Operation									
All-cause death	6104	324/1018 (31.8)	308/1181 (26.1)	1.373 (1.174-1.605)	<0.001	1.092 (0.925-1.288)	0.299	0.985 (0.819-1.185)	0.873
AA re-hospitalization	5286	252/1018 (24.8)	238/1181 (20.2)	1.376 (1.152-1.643)	<0.001	1.242 (1.031-1.496)	0.022	1.172 (0.950-1.446)	0.138
Re-operation	188	38/1018 (3.7)	68/1181 (5.8)	1.182 (0.789-1.772)	0.417	1.214 (0.665-2.218)	0.527	3.134 (1.394-7.043)	0.006
Non-Operation									
All-cause death	9299	1471/2245 (65.5)	890/1673 (53.2)	1.401 (1.289-1.523)	<0.001	1.233 (1.130-1.344)	<0.001	1.105 (1.004-1.216)	0.042
AA re-hospitalization	6672	907/2245 (40.4)	703/1673 (42.0)	1.085 (0.983-1.198)	0.106	1.070 (0.966-1.186)	0.963	1.022 (0.910-1.148)	0.713
Operation	8074	346/2245 (15.4)	299/1673 (17.8)	0.971 (0.831-1.134)	0.971	0.980 (0.829-1.158)	0.808	1.045 (0.872-1.252)	0.633

[a] Adjusted for age, gender, geographical region, comorbidity and prescribed drugs

Table 3.

	Death				AA re-hospitalization			
	No matching		PS-matching		No matching		PS-matching	
Variable	HR	p	HR	p	HR	p	HR	p
COPD	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009	1.100 (1.004-1.206)	0.042	1.114 (1.007-1.232)	0.036
Age group (yr)								
<50	1		1		1			
50-60	0.981 (0.582-1.652)	0.943	0.825 (0.340-2.002)	0.671	1.160 (0.772-1.743)	0.475	1.033 (0.907-1.177)	0.623
60-70	0.873 (0.564-1.350)	0.542	0.798 (0.389-1.637)	0.538	0.866 (0.605-1.239)	0.430	0.920 (0.465-1.820)	0.811
70-80	1.435 (0.963-2.139)	0.076	1.256 (0.642-2.460)	0.506	1.057 (0.752-1.485)	0.751	0.586 (0.326-1.052)	0.074
>80	3.392 (2.306-4.989)	<0.001	2.970 (1.533-5.755)	0.001	1.374 (0.988-1.912)	0.059	0.760 (0.438-1.319)	0.330
Gender								
Female	1		1		1			
Male	0.798 (0.579-1.099)	0.167	0.73 (0.502-1.062)	0.099	0.806 (0.553-1.175)	0.263	0.992 (0.638-1.542)	0.970
Urbanicity								
Urban	1		1		1			
Rural	0.969 (0.896-1.049)	0.441	1.006 (0.914-1.107)	0.902	0.984 (0.894-1.083)	0.741	0.995 (0.887-1.116)	0.931
Income (NT)								
Low (<24,000)	1		1		1			
Middle (24,000-42,000)	0.671 (0.488-0.923)	0.014	0.603 (0.389-0.936)	0.024	0.893 (0.686-1.163)	0.402	0.711 (0.496-0.019)	0.063
High (>42,000)	0.558 (0.389-0.801)	0.002	0.525 (0.336-0.821)	0.005	0.792 (0.591-1.063)	0.121	0.787 (0.55-1.127)	0.191
Aortic aneurysm site								
TAA	1		1		1		1	
AAA	0.876 (0.805-0.954)	0.002	0.870 (0.785-0.964)	0.008	1.235 (1.110-1.373)	<0.001	1.418 (1.248-1.611)	<0.001
TAAA	1.312 (1.122-1.535)	<0.001	1.385 (1.157-1.657)	<0.001	1.294 (1.064-1.573)	0.010	1.66 (1.325-2.081)	<0.001
Smoking rate	1.005 (0.995-1.016)	0.322	1.008 (0.995-1.020)	0.222	1.009 (0.997-1.021)	0.141	0.999 (0.985-1.014)	0.910
Co-morbidities								
Diabetes	1.142 (0.992-1.314)	0.064	1.169 (0.993-1.377)	0.061	0.960 (0.801-1.151)	0.662	0.976 (0.794-1.201)	0.821
Hypertension	0.937 (0.764-1.148)	0.529	0.894 (0.702-1.138)	0.362	0.866 (0.678-1.107)	0.250	0.863 (0.644-1.157)	0.325
Dyslipidemia	0.686 (0.612-0.768)	<0.001	0.675 (0.591-0.770)	<0.001	0.938 (0.827-1.064)	0.320	0.913 (0.79-1.055)	0.218
CHF	1.434 (1.316-1.563)	<0.001	1.406 (1.268-1.558)	<0.001	0.976 (0.874-1.090)	0.666	0.955 (0.555-1.644)	0.868
Atrial fibrillation	1.304 (1.166-1.457)	<0.001	1.320 (1.149-1.517)	<0.001	1.053 (0.906-1.225)	0.500	1.017 (0.843-1.226)	0.863
VHD	0.801 (0.720-0.891)	<0.001	0.801 (0.707-0.908)	<0.001	0.967 (0.854-1.095)	0.601	0.935 (0.808-1.081)	0.363
PAD	1.092 (0.944-1.264)	0.237	1.030 (0.863-1.229)	0.745	1.061 (0.893-1.261)	0.501	1.065 (0.869-1.306)	0.543
CAD	0.920 (0.851-0.994)	0.035	0.954 (0.870-1.045)	0.310	1.124 (1.022-1.235)	0.016	1.201 (1.077-1.34)	0.001
Stroke	1.344 (1.245-1.451)	<0.001	1.347 (1.229-1.475)	<0.001	1.016 (0.922-1.119)	0.746	1.004 (0.895-1.126)	0.948
Malignance	1.538 (1.411-1.675)	<0.001	1.557 (1.408-1.721)	<0.001	0.978 (0.869-1.100)	0.709	0.961 (0.836-1.103)	0.570
CKD	1.732 (1.585-1.894)	<0.001	1.788 (1.610-1.986)	<0.001	1.309 (1.168-1.468)	<0.001	1.327 (1.161-1.516)	<0.001
Thyroid disease	0.861 (0.696-1.064)	0.166	0.807 (0.625-1.042)	0.100	1.060 (0.828-1.357)	0.642	1.134 (0.85-1.513)	0.392
Liver disease	1.037 (0.932-1.154)	0.503	1.054 (0.928-1.196)	0.422	1.010 (0.888-1.148)	0.884	1.016 (0.874-1.181)	0.839
Sleep apnea	0.927 (0.836-1.027	0.145	0.921 (0.810-1.047)	0.210	1.079 (0.956-1.217)	0.217	1.073 (0.927-1.242)	0.348
Peptic ulcer	1.233 (1.106-1.375)	<0.001	1.149 (1.009-1.310)	0.037	1.132 (0.985-1.302)	0.081	1.118 (0.95-1.317)	0.180
Gout	1.011 (0.921-1.111	0.816	1.002 (0.898-1.119)	0.965	0.992 (0.887-1.109)	0.883	0.973 (0.854-1.109)	0.685
Prescribed Drugs								
ACEI	1.171 (1.077-1.273)	<0.001	1.170 (1.058-1.293)	0.002	1.109 (1.002-1.227)	0.045	1.082 (0.958-1.222)	0.204
ARB	0.893 (0.822-0.971)	0.007	0.846 (0.766-0.934)	<0.001	1.055 (0.958-1.162)	0.275	1.016 (0.906-1.139)	0.786
BB	0.875 (0.808-0.948)	0.011	0.852 (0.776-0.937)	<0.001	1.103 (1.003-1.214)	0.044	1.100 (0.982-1.231)	0.099
CCB	0.812 (0.742-0.889)	<0.001	0.832 (0.748-0.926)	<0.001	0.999 (0.892-1.118)	0.980	0.975 (0.854-1.112)	0.704
Diuretics	1.372 (1.259-1.495)	<0.001	1.358 (1.229-1.501)	<0.001	0.916 (0.830-1.011)	0.082	0.856 (0.764-0.96)	0.008
Alpha-blocker	0.924 (0.836-1.022)	0.125	0.928 (0.824-1.045)	0.220	1.112 (0.990-1.249)	0.074	1.173 (1.023-1.345)	0.022
Statin	1.098 (0.952-1.267)	0.200	1.112 (0.941-1.315)	0.212	1.099 (0.942-1.282)	0.230	1.039 (0.868-1.242)	0.679
Fibrate drugs	1.095 (0.822-1.459)	0.536	1.018 (0.714-1.451)	0.923	0.919 (0.669-1.261)	0.599	0.840 (0.568-1.242)	0.382
Antiplatelet drugs	1.224 (1.085-1.381)	0.001	1.058 (0.961-1.165)	0.249	1.114 (1.010-1.228)	0.031	1.092 (0.973-1.225)	0.135
OADs	1.106 (1.020-1.200)	0.015	1.135 (0.986-1.307)	0.077	1.001 (0.862-1.162)	0.993	0.996 (0.839-1.183)	0.966

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OADs, oral anti-diabetic agents; VHD, valvular heart disease; PAD, peripheral artery disease; CAD, coronary artery disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

Table 4.

	COPD			
	No matching		PS-matching	
Variable	HR	p	HR	p
COPD	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009
Age group (yr)				
<70	1.161 (0.933-1.444)	0.181	1.184 (0.926-1.514)	0.179
≥70	1.103 (1.016-1.198)	0.020	1.117 (1.021-1.223)	0.016
Aortic aneurysm site				
TAA	1.205 (1.042-1.392)	0.012	1.262 (1.075-1.482)	0.004
AAA	1.048 (0.952-1.154)	0.340	1.055 (0.949-1.173)	0.318
TAAA	1.074 (0.775-1.488)	0.670	0.986 (0.687-1.414)	0.939
Co-morbidities				
Diabetes (Yes)	0.911 (0.711-1.166)	0.458	0.826 (0.624-1.093)	0.181
Diabetes (No)	1.137 (1.048-1.234)	0.002	1.164 (1.064-1.272)	<0.001
Hypertension (Yes)	1.103 (1.020-1.193)	0.014	1.111 (1.019-1.211)	0.017
Hypertension (No)	1.467 (0.923-2.331)	0.105	1.173 (0.710-1.939)	0.532
Dyslipidemia (Yes)	1.100 (0.949-1.275)	0.206	1.141 (0.969-1.344)	0.113
Dyslipidemia (No)	1.105 (1.009-1.210)	0.031	1.116 (1.011-1.233)	0.030
Atrial fibrillation (Yes)	1.141 (0.900-1.446)	0.276	1.182 (0.902-1.548)	0.226
Atrial fibrillation (No)	1.099 (1.012- 1.193)	0.024	1.111 (1.016-1.216)	0.022
Stroke (Yes)	1.085 (0.954-1.234)	0.212	1.089 (0.942-1.259)	0.248
Stroke (No)	1.118 (1.014- 1.231)	0.025	1.140 (1.026-1.267)	0.015
CKD (Yes)	1.021 (0.869-1.199)	0.805	0.998 (0.834-1.194)	0.982
CKD (No)	1.131 (1.036-1.235)	0.006	1.153 (1.046-1.270)	0.004
Prescribed Drugs				
ACEI (Yes)	1.199 (1.032-1.393)	0.018	1.198 (1.017-1.412)	0.030
ACEI (No)	1.068 (0.976-1.169)	0.151	1.087 (0.984-1.200)	0.099
BB (Yes)	1.130 (1.015-1.259)	0.025	1.167 (1.030-1.323)	0.015
BB (No)	1.080 (0.965-1.207)	0.179	1.080 (0.961-1.214)	0.194
CCB (Yes)	1.133 (1.034-1.241)	0.007	1.141 (1.032-1.261)	0.009
CCB (No)	1.005 (0.868-1.165)	0.945	1.034 (0.879-1.217)	0.684
Statin (Yes)	1.114 (0.904-1.373)	0.313	1.140 (0.904-1.438)	0.2681
Statin (No)	1.103 (1.015-1.199)	0.021	1.117 (1.019-1.223)	0.018
Antiplatelet drugs (Yes)	1.080 (0.971-1.202)	0.156	1.082 (0.960-1.219)	0.196
Antiplatelet drugs (No)	1.132 (1.012-1.267)	0.029	1.163 (1.030-1.312)	0.015
Operation type				
Open repair (Yes)	1.069 (0.855-1.338)	0.558	1.009 (0.830-1.226)	0.930
Endovascular repair (Yes)	0.911 (0.705-1.179)	0.479	1.029 (0.793-1.334)	0.832

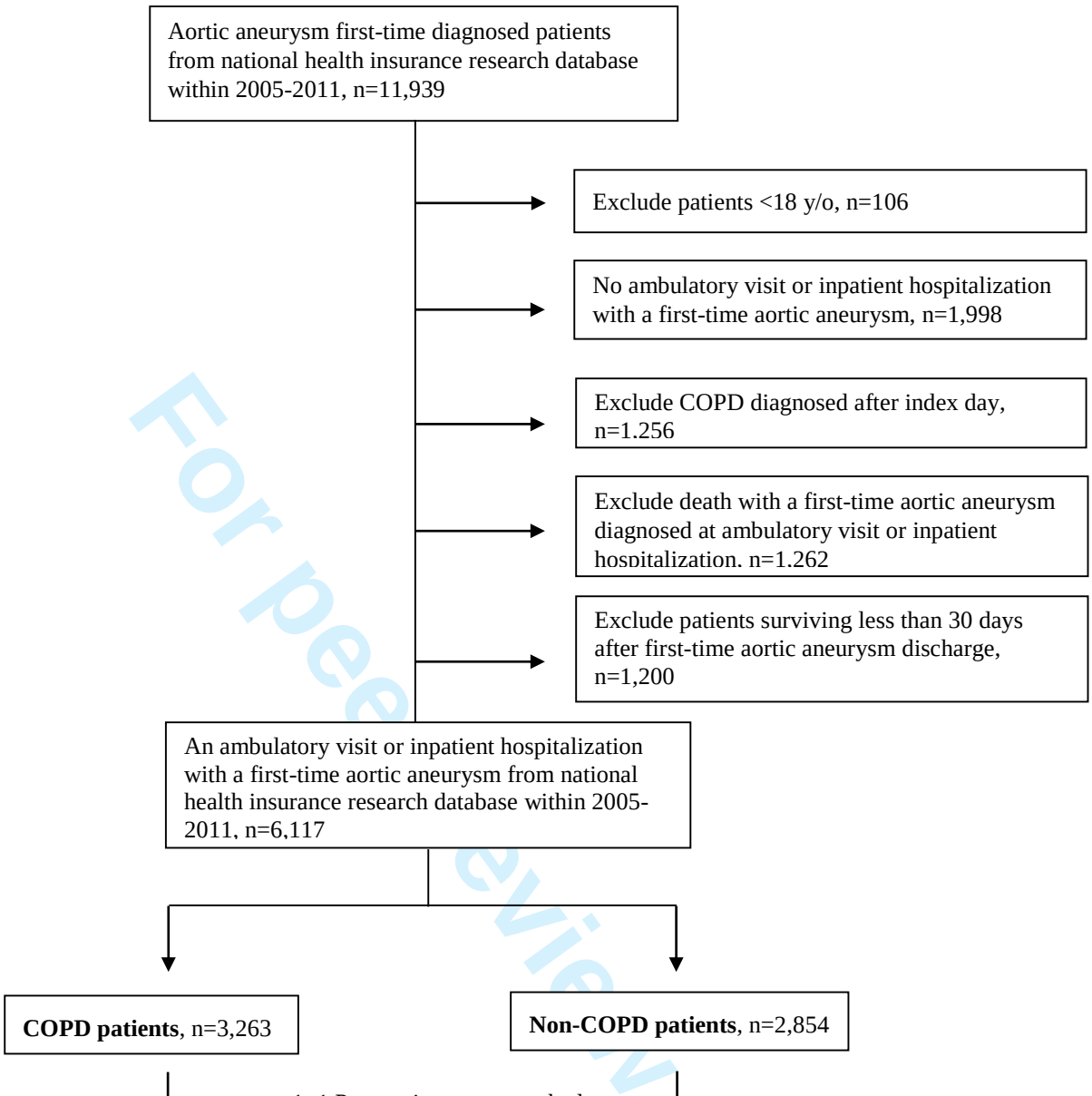
ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

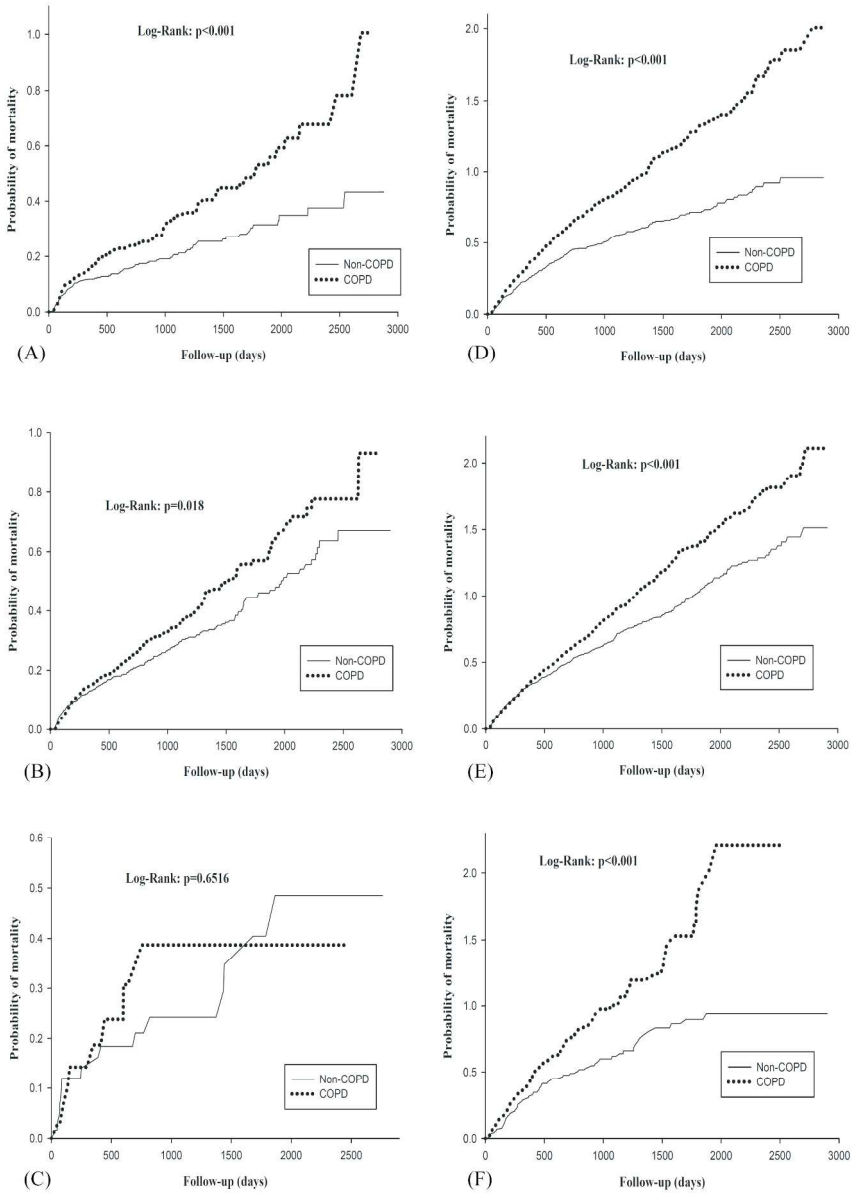
Figure Legends

Figure 1. Study flow diagram.

Figure 2. Cumulative risk of mortality between the COPD and non-COPD groups

(A) Operation and TAA, (B) operation and AAA, (C) operation and TAAA, (D) non-operation and TAA, (E) non-operation and AAA, and (F) non-operation and TAAA. *Abbreviations:* AAA, abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm.





Cumulative risk of mortality between the COPD and non-COPD groups
(A) Operation and TAA, (B) operation and AAA, (C) operation and TAAA, (D) non-operation and TAA, (E) non-operation and AAA, and (F) non-operation and TAAA. Abbreviations: AAA, abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm.

206x288mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10-12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NP

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Chronic Obstructive Pulmonary Disease is Associated with Poor Outcomes in Patients with Aortic Aneurysms: A Nationwide Retrospective Study in Taiwan.

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Chronic Obstructive Pulmonary Disease is Associated with Poor Outcomes in Patients with Aortic Aneurysms: A Nationwide Retrospective Study in Taiwan

Kuang-Ming Liao[1], Chung-Yu Chen[2,3]

1. Department of Internal Medicine, Chi Mei Medical Center, Chiali, Taiwan
2. Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.
3. School of Pharmacy, Master Program in Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan.

Corresponding author

Chung-Yu Chen, School of Pharmacy, Kaohsiung Medical University. No. 100, Shih-Chuan 1st Rd., Sanmin District, Kaohsiung City 80708, Taiwan (R.O.C.)

E-mail: jk2975525@hotmail.com

Keywords: chronic obstructive pulmonary disease, aortic aneurysms

Abbreviations:

AA	Aortic Aneurysm
AAA	Abdominal Aortic Aneurysm
ACEI	Angiotensin-Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
BB	Beta-Blocker
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
OAD	Oral Anti-Diabetic Agent
PAD	Peripheral Artery Disease
PSM	Propensity Score Matching
TAA	Thoracic Aortic Aneurysm
TAAA	Thoracoabdominal Aortic Aneurysm
VHD	Valvular Heart Disease

Abstract

Objectives: Aortic aneurysm (AA) was a leading cause of death in the world. Chronic obstructive pulmonary disease (COPD) is a risk factor for AA and the prognosis of COPD patients with AA received operation or not need to be investigated.

Methods: We included AA older than 18 years as those having a first-time AA diagnosis between 2005 and 2011 in Taiwan. The date of the first-time ambulatory visit or an inpatient hospitalization of AA diagnosis was assigned as the index date. The patients who were diagnosed once COPD before the index date as case group. Control groups were selected from AA patients without COPD. We also conducted propensity score matched according to age group, demographic characteristics, comorbidities, co-medication at a 1:1 ratio. Patient comorbidities and prescribed drugs were identified within 180 days of the index date. The main outcomes were all-cause mortality and re-hospitalization for AA or operation. The outcomes in the COPD and non-COPD patients were examined by Cox proportional hazards models for the 8-year follow-up period.

Results: There are 3,263 patients with COPD and AA before propensity score matching and 2,127 patients with COPD and AA after propensity score matching enrolled in the study. In AA population, COPD patients had higher mortality and re-hospitalization than non-COPD patients with adjusted HR was 1.12 (95% CI=1.03-1.22) and 1.11 (95% CI=1.01-1.23), respectively after propensity score matching. In operation group, the mortality was no significant difference between COPD and non-COPD patients. In non-operation group, the mortality was higher in COPD patients than non-COPD patients with adjusted HR=1.11 (95% CI=1.0-1.22).

Conclusions: The outcomes of COPD patients with AA undergo operation was

improved but their mortality rate still high compared with AA patients without COPD. Effective treatment to reduce mortality in this group need to be further investigated.

Strengths and limitations

1. Our study was to analyze the outcome, included all-cause mortality, re-hospitalization and operation between aortic aneurysm and COPD.
2. Our study also analyzed the impact of comorbidities and prescribed drugs on outcome in AA patients.
3. This is a comprehensive national study with large population to be representative for AA patients with and without COPD in clinical scenario.
4. The study relies on diagnosed COPD but according to the previous study that a large proportion of the cases may be missed.
5. Some details regarding COPD and aortic aneurysm, such as lung function, size of aneurysm, presence of dissection/rupture may have an impact on mortality, but were not obtained in our analyses.

Introduction

Chronic obstructive pulmonary disease (COPD) is an obstructive airway disease that is not fully reversible by medication. Not only is COPD a systemic disease that shares smoking as a common risk factor with aortic aneurysms (AAs), but also has it been shown to be an independent risk factor for abdominal aortic aneurysm (AAA).[1] AAs include those of the abdominal aorta (AAA), thoracic aorta (TAA), and thoracoabdominal aorta (TAAA), and they are associated with high mortality, particularly following rupture.[2–4]

Previous studies have focused on the prognosis of patients with COPD undergoing operation for AAA[5] or have compared the outcomes of patients with COPD and AAA undergoing open or endovascular repair.[6] However, these studies only considered effect of COPD in AAA patients receiving operation, and some studies were performed more than 10 years ago. In addition, AA patients may receive either surgical or medical treatment, but few studies have mentioned the effect of COPD on AA patients who receive medication. In a previous study among AAA patients, it was found that the risk of death was significantly greater when COPD was present.[7] Another study showed that severe COPD, for which patients were dependent on home oxygen, was not a contraindication to AAA repair and mortality did not increase.[8] Unfortunately, generalization of these observational studies was limited by their small sample sizes, short follow-up periods, lack of medication records, and conflicting results. Moreover, improvements in intraoperative and postoperative care for vascular operation have resulted in significant reductions in morbidity and mortality that may have affected the outcomes of AA in patients with COPD, justifying further investigation.

To investigate the outcomes of AA patients (including AAA, TAAA, and AAA) and

COPD, we used data from the Taiwanese National Health Insurance Research Database (NHIRD) for patients receiving either surgical or medical treatment. The aim of our study was to analyze the association between aortic aneurysm and COPD, regardless of the risk factors of aortic aneurysm. The hypothesis was that COPD have a large influence on the outcome of aortic aneurysms.

Materials and Methods

Study design

This was a population-based, observational study using information from the NHIRD in Taiwan. Data for hospital visits, emergency care, and prescriptions were provided by the National Health Insurance Research Institutes for this study. The diagnosis of AA in the NHIRD has previously been described.[9] This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT-20130199).

Participants

We included patients from the NHIRD aged ≥18 years presenting with a first-time diagnosis of AA (ICD-9: 441.1–441.9) between 2005 and 2011. The date of the first ambulatory visit or inpatient hospitalization at which AA was diagnosed was designated the index date. We excluded patients who died at first presentation and those who had fewer than 30 days' follow-up after discharge.

Participants included as cases were required to have a diagnosis of COPD (ICD-9: 490–492, 496) before the index date and treated on COPD medications with the following: long-acting inhaled anticholinergics, long-acting inhaled β2-adrenergic receptor agonists, inhaled corticosteroids, short-acting anticholinergics, short-acting β2-agonists, or xanthines. Patients were excluded if COPD was diagnosed or

medications for COPD were prescribed after the index date.

The control group was selected from among AA patients who had no comorbid diagnosis of COPD. To decrease selection bias from baseline differences, we also conducted propensity score matching (PSM) at a 1:1 ratio by age group, demographic characteristics, comorbidities, and co-medications. Patients in this study were followed until re-admission or operation for AA, death, withdrawal from the national health insurance, or December 31, 2012, whichever was the soonest.

Variables

All patients were divided into TAA (ICD-9 codes 441.1–441.2), AAA (ICD-9 codes 441.3–441.4), and TAAA (ICD-9 codes 441.6–441.7) groups according to the diagnosis site at the index date. We also identified whether patients underwent operation, and if so, whether that was by open or endovascular repair.

Patient comorbidities were identified by diagnostic code as inpatient or outpatient diagnoses within 180 days of the index date. The following comorbidities were included in the assessment: hypertension, diabetes, dyslipidemia, congestive heart failure (CHF), atrial fibrillation, valvular heart disease (VHD), peripheral artery disease (PAD), coronary artery disease (CAD), stroke (ischemic and hemorrhagic), malignancy, chronic kidney disease (CKD), thyroid disease, liver disease, gout, peptic ulcer disease, and sleep apnea. Prescribed drugs were also identified within 180 days of the index date. The following medications were also included as variables: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), diuretics, alpha-blockers, statins, fibrates, antiplatelet drugs, and oral anti-diabetic agents (OADs).

We also described the demographic characteristics of AA patients by the presence or absence of a COPD diagnosis. Potential confounders included gender, age group

(<50, 50–59, 60–69, 70–79, and over 80 years), urbanization (urban or rural), income group, and smoking status. Income group was defined as low (<NT$24,000), middle (NT$24,000– NT$42,000), or high (>NT$42,000) according to the individual monthly gross income during a 1-month period before the index date.

Because no information was available regarding smoking status, we used the mean percentage of city/county smoking rates available from the National Health Interview Survey (2005 to 2011). All subjects in this survey were randomly sampled and selected from different cities and counties to be interviewed by trained interviewers.[10] Although this smoking rate is not a direct measure of the rate for patients in this database, it can be considered to reflect the likely rate of smoking and passive smoking (stratified by age, gender, and living area) if we assume a normally distributed cohort that reflects the broader population.

Outcome

The main outcomes of interest were all-cause mortality and re-hospitalization for AA or operation. Moreover, all-cause mortality confirmed by withdrawn from NHI within 1 month of a major medical event. [11] We considered re-hospitalization to be when patients were admitted with AA-related events (ICD-9 codes 441.1–441.9) as the principal or secondary diagnosis after discharge from the index event. Operation was stratified by whether or not patients underwent operation at the time of the index event. Then, if patients underwent operation for AA at the index event, and were re-hospitalization for operation more than 30 days after discharge, they were classified as undergoing repeat operation. Patients who did not undergo operation at the index event, and who were re-hospitalization more than 30 days after discharge, were classified into the operation group. Furthermore, patients received operation less than 30 days after discharge at the index event, were classified as operation group at the index event.

Statistics

All data are expressed as the frequency (percentage). Categorical and continuous variables were compared between the COPD and non-COPD patients using chi-square tests and Student t-tests, as appropriate. The outcomes in the COPD and non-COPD patients were examined by Cox proportional hazards models for the 8-year follow-up period.

Simple and multiple analyses (including age group, comorbidities, co-medications, and demographic characteristics) were used to assess the risk of outcome by the presence or absence of COPD during follow-up. We used PSM for patients in the COPD and non-COPD patients. Because the outcomes may have been influenced by the presence of disease (diabetes mellitus, dyslipidemia, and hypertension) or medication (OAD, statins, fibrates, and antihypertensives), we examined these in a multiple model. The difference in the cumulative probability of mortality between the COPD and non-COPD patients was calculated using Kaplan–Meier estimates with the log-rank test; we also divided patients by operation type and site of diagnosis for these analyses.

To assess the robustness of the outcomes, a subgroup analysis was performed including age (≥70 and <70 years), aortic aneurysm site (TAA, AAA, and TAAA) high-risk patients (hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, stroke, and CKD), concomitant drug use (ACEIs, BBs, CCBs, statins, and antiplatelet agents), and type of operation. Analyses and calculations were performed using SAS ver. 9.4 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was inferred at a two-sided p-value <0.05.

Results

Descriptive data

We identified 6,117 AA patients, of which 3,263 also had COPD. After PSM, 2,127 COPD patients were eligible for enrollment in the study. Figure 1 shows the study flow diagram for AA patients with and without COPD.

Table 1 summarizes the characteristics of AA patients. Before matching, one-third of the AA patients were aged 70–80 years. There was a notable male preponderance in COPD and non-COPD patients.

In both groups, AAA was the most common type, followed by TAA and TAAA. Most patients (58%) received open repair in the non-COPD patients, while most (55%) received endovascular repair in the COPD patients. The most common comorbidity was hypertension, which was present in more than 96% of patients. The two most common medications were CCBs, diuretics in the COPD and non-COPD patients.

Outcomes based on the operation and non-operation groups

In Table 2, among AA Patients received operation, there is no significant differences in all-cause mortality between COPD and non-COPD patients. Among non-operation group, the all-cause mortality was higher in COPD patients compared with non-COPD patients both before and after PSM, with respective adjusted HRs of 1.233 (95% CI 1.130–1.344) and 1.105 (95% CI 1.004–1.216). The re-operation rate for AA was higher in the non-COPD patients than in the COPD patients, with an adjusted HR of 3.134 (95% CI 1.394–7.043) after PSM.

Outcome of AAs by the presence or absence of COPD

In table 2, COPD patients had higher all-cause mortality than patients without COPD in total population. The AA re-hospitalization rate was also higher in the COPD patients than in the non-COPD patients, with respective adjusted HRs before

and after PSM of 1.100 (95% CI 1.004–1.206) and 1.114 (95% CI 1.007–1.2327). In total population, there was no significance difference in the numbers receiving operation between the COPD and non-COPD patients.

Other factors affecting outcomes

Table 3 shows the hazard ratios (HRs) and 95% confidence intervals (CI) for all-cause mortality and re-hospitalization before and after PSM.

Table 3, COPD and age ≥80 years were associated with higher mortality rates after PSM, with respective HRs of 1.118 (95% CI 1.028–1.217) and 2.970 (95% CI 1.533–5.755). In addition, not only were AAA and TAAA associated with a higher risk of re-hospitalization than TAA after PSM, but AAA was also shown to be associated with a lower risk of mortality than TAAA.

Other comorbidities associated with a higher risk of mortality after PSM included diabetes, dyslipidemia, CHF, atrial fibrillation, VHD, stroke, malignancy, CKD, and peptic ulcer disease. Among the patients with multiple comorbidities, only CAD and CKD were associated with a significantly higher risk of re-hospitalization. Medications that showed an apparent protective effect on mortality after PSM were ARBs, BBs, and CCBs. Patients prescribed CCBs had a lower risk of re-hospitalization, and those prescribed α blockers had a higher risk of re-hospitalization. After PSM, AA patients had lower risk of mortality if they were receiving ARBs than if they were receiving ACEIs, with HRs of 0.846 (95% CI 0.766–0.934) and 1.170 (95% CI 1.058–1.293). However, there was no significant difference in re-hospitalization rates among patients receiving either ACEIs or ARBs after PSM.

Mortality analysis in patients with AA and COPD

Table 4 shows the results of a subgroup analysis for mortality in AA patients by the

presence or absence of COPD. AA Patients and COPD had higher mortality rates than those without COPD. Patients ≥70 years old (HR 1.117, 95% CI, 1.021–1.223) or with TAA (HR 1.262, 95% CI 1.075–1.482) also had higher risks of mortality. The HR for mortality in the patients with AA, COPD, and hypertension was also significant (HR 1.111, 95% CI 1.019–1.211). Other comorbidities, including diabetes, dyslipidemia, atrial fibrillation, stroke, and CKD, were not associated with increased risks of mortality in patients with AA and COPD. There was also no significant difference in mortality rates between the operation procedures for patients with COPD and AA.

Figure 2 shows the cumulative risk of AA mortality in patients with and without COPD, stratified by patients who received operation and by the AA site. There no significant difference in mortality between the COPD and non-COPD patients (p = 0.6516) for patients with TAAA who underwent operation. However, for all other subgroups, there were significant differences in mortality based on the presence or absence of COPD in AA patients.

Discussion

This nationwide population-based study showed that patients with AA and COPD had higher risk of all-cause death and re-hospitalization than those without COPD. In AA patients who underwent operation, those with COPD had the greatest risk of re-operation for AAs. However, there was no difference in mortality between procedures for AA in patients with COPD.

Prognosis in patients with COPD and AA

A previous study showed that the increased prevalence of COPD in AAA patients was independent of smoking.[1] Other studies have found that COPD is associated with

a high prevalence of AAA, and rates being from 7.7% to 9.9%, with the prevalence increased in severe emphysema and when the forced expiratory volume/vital capacity ratio was decreased.[12,13] The aneurysm rupture rates have also been shown to correlate with COPD risk factors, initial aneurysm size, and diastolic hypertension,[14] but surgeons are hesitant to repair AAAs electively because of the associated high morbidity and mortality.[15] In a database review of 1053 patients undergoing surgery for intact or ruptured AAAs in a hospital between 1997 and 1998, David et al.[5] showed that mortality was no higher in patients with COPD than in patients without COPD; but, they also showed that patients with COPD required longer hospital stays, longer intensive care unit stays, and more days of ventilation. However, their study was performed more than 15 years ago, and only focused on AAAs patients receiving operation. David et al.[5] did not find an increased risk in patients undergoing surgery and this may be due to adequate patient selection in an era of open repair.

Our study included patients with a first-time AA diagnosis between 2005 and 2011, and who were followed to December 31st, 2012. The final cohort of AA patients comprised 2,854 controls without COPD and 3,263 cases with COPD, and these were further divided into those who did and did not undergo operation. Our study indicated that patients with COPD and AA had a higher rate of re-hospitalization and higher mortality when compared with patients without COPD. In patients undergoing operation for AAs, we found that the mortality and re-hospitalization rates were not significantly different between those with and without COPD, though the re-operation rate was higher in those with COPD. Among those not undergoing operation for AA, the all-cause mortality rate was also higher among COPD patients than those without COPD.

Surgical procedure and mortality in patients with COPD and AA

Christopher et al.[16] retrospectively reviewed 44 patients with oxygen-dependent

COPD undergoing AAA repair, of which 24 underwent endovascular aneurysm repair and 20 underwent open procedures. They showed that type of repair, comorbidities, and lung function test results did not significantly affect survival. Many other studies have also shown that endovascular AAA repair offers long-term survival similar to open AAA repair in patients with COPD.[17-19] Moqueet et al.[20] performed a prospective study of high-risk patients undergoing endovascular repair of AAAs or TAAAs between 1998 and 2009, and showed that mortality was no different between patients with and without COPD when endovascular techniques were used. In our study comparing all types of AA in COPD and non-COPD patients, we found no significant difference in mortality rates for either procedure between the two groups.

Patient characteristics

In our study, patients with COPD had higher rates of AA than those without COPD. Most AA patients were males, regardless of whether or not they had COPD. The most common comorbidities in patients with AA and COPD were hypertension, CAD, stroke, dyslipidemia, and CHF. These results are similar to those reported by Flessenkaemper et al.,[21] who suggested that risk factors such as male gender and CAD could be used to increase the efficiency of screening for AAA. We suggest that other risk factors, such as hypertension, stroke, dyslipidemia, and CHF, may be useful in future screening for AA in patients with COPD.

In a survey of 231 patients with COPD by Katsutoshi et al.,[22] it was reported that only 27 (11.7%) had AA and 20 (8.7%) had AAA. This contrasts with the results of our nationwide study, in which 2089 (64%) AAA patients also had comorbid COPD. To our knowledge, except for two studies with conflicting results,[23,24] there have been no major reports on the prevalence or incidence of AA in the Asian population. Poon et al.[25] reported that the prevalence of AAA in Chinese patients was low, and that their results did not support routine screening for AAA; however, another study showed

that AAA was not uncommon and had a comparable incidence to that in the West.[24] To clarify these issues, a study is needed that includes more Asian countries and a larger population.

Prescription patterns

Medical management is important in the control of AAs, with the main goal of therapy being to decrease shear stress by reducing blood pressure and contractility.[26] In a small retrospective study, BBs were shown to decrease AAA growth effectively.[27] In another study, prophylactic BBs were associated with a slowing in the rate of aortic dilatation.[28] Indeed, BBs can not only reduce left ventricular contractility but also reduce shear stress in the aorta. However, a prospective randomized double-blind study has shown that AAA patients do not tolerate BBs, and that these medications have no significant effect on the growth rates of small AAAs.[29]

In our study, before PSM, the most common medications for AA were CCBs, then diuretics, and then BBs. Although the prescribing rates of BBs was associated with significant differences between the COPD and non-COPD patients, this difference did not persist after PSM. BBs are often prescribed for AA, but physicians may be concerned about contraindications, and may fear inducing adverse reactions or bronchospasm, especially in patients with obstructive airway disease. In our analysis, BBs were well tolerated in patients with AA and COPD, moreover, they had a clear protective effect on reducing mortality. This is consistent with their use being recommended. In fact, the safety of BBs has long been proven in COPD patients, and there is a growing body of evidence from clinical trials showing that BBs should not be withheld in this patient group.[30]

ACEI and ARB in AA

In our analysis, ARBs, BBs, CCBs, and diuretics, but not ACEIs, were associated with reduced mortality in patients with AA and COPD. In an animal model, AAs have been

associated with increased transforming growth factor-β signaling, and the ARB losartan has been shown to be able to block transforming growth factor-β.[31] Losartan can, therefore, prevent elastic fiber fragmentation and blunt transforming growth factor-β signaling in the aorta, reducing the growth rates of AAs.[32] However, ACEIs were shown to be able to prevent aortic dissection and apoptosis of vascular smooth muscle cells in another animal model,[33] while Hackam et al. have reported that ACEIs were protective against aortic expansion and rupture, whereas ARBs did not protective against AAA rupture.[34] Other experimental evidence shows that ACEIs increase collagen synthesis, improve plaque stabilization, and diminish aortic stiffness.[35] To further complicate matters, in a prospective cohort study of 1701 patients in the UK, Sweeting et al.[36] showed that aneurysm growth was faster in patients receiving ACEIs. This conflicts with previous research and observational data from Canada showing that ACEIs have protective benefits.[35]

On balance, the inconsistent results regarding the efficacies of ARBs and ACEIs in reducing AA growth limit any meaningful conclusion. Undoubtedly, these problems result from differences in the models used, selection bias, unaccounted confounding factors, and the fact that there are multiple possible pathways of AA development.

A recently systematic review of the current data on pharmaceutical therapies for AAA shown that pharmaceutical therapies cannot halt AAA growth.[37] Small AAA growth rates were lower than anticipated and ACEI was no significant impact to reduce small AAA growth rate.[38]

Limitations

There were some important limitations in this study. Our study relies on diagnosed COPD but according to the previous study[1] that a large proportion of the cases may be missed. We did not have access to data on vital signs (i.e., blood pressure and heart rate) or to imaging results (i.e., we could not estimate the size or progression of AAs).

We also did not include data on pulmonary function tests or severity of COPD and it was unable to find a clear relation of the size of AA and the severity of COPD. However, we focused on all-cause mortality, re-hospitalization rates, and re-operation rates, and used subgroup analysis (operation vs non-operation) to reduce bias. This was also a large nationwide study of all registered AA patients in Taiwan, which should allow generalization to other COPD populations. Finally, we also performed PSM, which reduced the bias in estimating treatment effects and reduced the likelihood of confounding data.

Conclusions

Improvements in the pre- and postoperative management of COPD patients undergoing major operation have resulted in reduced mortality and morbidity rates. However, although we showed that the safety and outcomes of COPD patients undergoing AAA repair have improved, we also showed that the overall mortality remains higher than that in patients without COPD. In addition, we also observed high mortality rates among COPD patients who did not undergo operation. Further research is clearly needed to identify the most appropriate therapy for reducing mortality in patients with AA and COPD.

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Table 1. Characteristics of patients with aortic aneurysms in Taiwan

Variable	No-COPD (n=2854) No	%	COPD (n=3263) No	%	p	PS-matching No-COPD (n=2127) No	%	PS-matching COPD (n=2127)	p
Age group (yr)					<0.001				0.436
<50	273	(9.6)	61	(1.9)		64	(3.0)	61 (2.9)	
50-60	356	(12.5)	113	(3.5)		134	(6.4)	112 (5.3)	
60-70	508	(17.8)	388	(11.9)		327	(15.4)	354 (16.6)	
70-80	932	(32.6)	1183	(36.2)		837	(39.4)	853(40.1)	
>80	785	(27.5)	1515	(46.5)		763	(35.9)	747 (35.1)	
Gender					<0.001				0.971
Female	745	(26.1)	631	(19.3)		509	(23.9)	508 (23.9)	
Male	2109	(73.9)	2632	(80.7)		1618	(76.1)	1648 (76.1)	
Rubanicity					<0.001				0.733
Urban	724	(25.4)	1011	(31.0)		592	(27.8)	602 (28.3)	
Rural	2130	(74.6)	2252	(69.0)		1535	(72.2)	1525 (71.7)	
Income (NT)					<0.001				0.831
Low (<24,000)	2564	(89.8)	3136	(96.1)		2002	(94.1)	2011 (94.6)	
Middle (24,000-42,000)	149	(5.2)	74	(2.3)		71	(3.3)	65 (3.1)	
High (>42,000)	141	(5.0)	53	(1.6)		54	(2.5)	51 (2.4)	
Aortic aneurysm site					<0.001				0.918
TAA	965	(33.8)	1018	(31.2)		664	(31.2)	662 (31.1)	
AAA	1689	(59.2)	2089	(64.0)		1355	(63.7)	1351 (63.5)	
TAAA	200	(7.0)	156	(4.8)		108	(5.1)	114 (5.4)	
Operation	1181	(41.4)	1018	(31.2)	<0.001	823	(38.7)	753 (35.4)	0.026
Open repair	689	(58.3)	455	(44.7)		425	(51.6)	340 (45.2)	
Endovascular repair	492	(41.7)	563	(55.3)		399	(48.4)	413 (54.7)	
Smoking rate	26.3 (±13.4)		28.6 (±12.3)		<0.001	27.0 (±13.1)		27.0 (±13.1)	0.921
Co-morbidities									
Diabetes	414	(14.5)	450	(13.8)	0.423	310	(14.6)	307 (14.4)	0.896
Hypertension	2766	(96.9)	3138	(96.2)	0.112	2055	(96.6)	2051 (96.4)	0.738
Dyslipidemia	944	(33.1)	1032	(31.6)	0.227	727	(34.2)	725 (34.1)	0.948
CHF	561	(19.7)	1019	(31.2)	<0.001	488	(22.9)	482 (22.7)	0.826
Atrial fibrillation	230	(8.1)	384	(11.8)	<0.001	196	(9.2)	189 (8.9)	0.708
VHD	594	(20.8)	556	(17.0)	<0.001	377	(17.7)	368 (17.3)	0.717
PAD	152	(5.3)	222	(6.8)	0.016	128	(6.0)	139 (6.5)	0.487
CAD	1135	(39.8)	1685	(51.6)	<0.001	965	(45.4)	974 (45.8)	0.782
Stroke	736	(25.8)	1127	(34.5)	<0.001	642	(30.2)	646 (30.4)	0.894
Malignance	479	(16.8)	645	(19.8)	0.003	402	(18.9)	407 (19.6)	0.560
CKD	453	(15.9)	597	(18.7)	0.012	374	(17.6)	378 (17.8)	0.872
Thyroid disease	87	(3.1)	97	(3.0)	0.863	59	(2.8)	64 (3.0)	0.647
Liver disease	343	(12.0)	441	(13.5)	0.081	267	(12.6)	254 (11.9)	0.543
Sleep apenea	317	(11.1)	533	(16.3)	<0.001	271	(12.7)	268 (12.6)	0.890
Peptic ulcer disease	257	(9.0)	361	(11.1)	0.007	215	(10.1)	218 (10.3)	0.879
Gout	520	(18.2)	628	(19.5)	0.305	414	(19.5)	411 (19.3)	0.974
Prescribed Drugs									
ACEI	691	(24.2)	857	(26.3)	0.066	521	(24.5)	507 (23.8)	0.616
ARB	948	(33.2)	1058	(32.4)	0.510	695	(32.7)	679 (31.9)	0.600
BB	1737	(60.9)	1583	(48.5)	<0.001	1174	(55.2)	1178 (55.4)	0.902
CCB	2187	(76.6)	2419	(74.13)	0.024	1607	(75.4)	1616 (76.7)	0.747
Diuretics	1874	(65.7)	2158	(66.1)	0.697	1371	(64.5)	1388 (65.3)	0.585
Alpha-blocker	457	(16.0)	541	(16.6)	0.549	344	(16.2)	346 (16.2)	0.934
Statin	480	(16.8)	535	(16.4)	0.658	373	(17.5)	378 (17.8)	0.841
Fibrate drugs	68	(2.4)	61	(1.9)	0.163	41	(1.9)	42 (1.9)	0.912
Antiplatelet drugs	1349	(47.3)	1742	(53.4)	<0.001	1083	(50.9)	1084 (50.9)	0.976
OAD	236	(8.3)	293	(8.9)	0.324	192	(9.0)	186 (8.7)	0.747

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CCB, calcium channel blockers; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OAD, oral Anti-diabetic agent; VHD, valvular heart disease; PAD, peripheral artery disease; CAD, coronary artery disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

Table 2 Outcome of aortic aneurysms by the presence or absence of chronic obstructive pulmonary disease

Outcome	No. of person-yr	Events after discharge: COPD (n=3263)	Events after discharge: Non-COPD (n=2854)	Cox regression unadjusted HR	p	Cox regression Adjusted HR [a]	p	PS-matching Cox regression Adjusted HR [a]	p
Total population									
All caused mortality	15403	1795/3263 (55.0)	1198/2854 (41.9)	1.503 (1.397-1.617)	<0.001	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009
AA re-hospitalization	11958	1159/3263 (35.5)	941/2854 (33.0)	1.241 (1.138-1.353)	<0.001	1.100 (1.004-1.206)	0.042	1.114 (1.007-1.232)	0.036
Operation (operation and re-operation)	8262	384/3263 (11.8)	367/2854 (12.9)	0.897 (0.777-1.036)	0.897	0.909 (0.779-1.061)	0.227	0.972 (0.822-1.149)	0.738
Operation									
All caused mortality	6104	324/1018 (31.8)	308/1181 (26.1)	1.373 (1.174-1.605)	<0.001	1.092 (0.925-1.288)	0.299	0.985 (0.819-1.185)	0.873
AA re-hospitalization	5286	252/1018 (24.8)	238/1181 (20.2)	1.376 (1.152-1.643)	<0.001	1.242 (1.031-1.496)	0.022	1.172 (0.950-1.446)	0.138
Re-operation	188	38/1018 (3.7)	68/1181(5.8)	1.182 (0.789-1.772)	0.417	1.214 (0.665-2.218)	0.527	3.134 (1.394-7.043)	0.006
Non-Operation									
All caused mortality	9299	1471/2245 (65.5)	890/1673 (53.2)	1.401 (1.289-1.523)	<0.001	1.233 (1.130-1.344)	<0.001	1.105 (1.004-1.216)	0.042
AA re-hospitalization	6672	907/2245 (40.4)	703/1673 (42.0)	1.085 (0.983-1.198)	0.106	1.070 (0.966-1.186)	0.963	1.022 (0.910-1.148)	0.713
Operation	8074	346/2245 (15.4)	299/1673 (17.8)	0.971 (0.831-1.134)	0.971	0.980 (0.829-1.158)	0.808	1.045(0.872-1.252)	0.633

[a] Adjusted for age, gender, geographical region, comorbidity and prescribed drugs

Table 3. The hazard ratios for all-cause mortality and re-hospitalization in patients with aortic aneurysms

	All-cause mortality				AA re-hospitalization			
	No matching		PS-matching		No matching		PS-matching	
Variable	HR	p	HR	p	HR	p	HR	p
COPD	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009	1.100 (1.004-1.206)	0.042	1.114 (1.007-1.232)	0.036
Age group (yr)								
<50	1		1		1			
50-60	0.981 (0.582-1.652)	0.943	0.825 (0.340-2.002)	0.671	1.160 (0.772-1.743)	0.475	1.033 (0.907-1.177)	0.623
60-70	0.873 (0.564-1.350)	0.542	0.798 (0.389-1.637)	0.538	0.866 (0.605-1.239)	0.430	0.920 (0.465-1.820)	0.811
70-80	1.435 (0.963-2.139)	0.076	1.256 (0.642-2.460)	0.506	1.057 (0.752-1.485)	0.751	0.586 (0.326-1.052)	0.074
>80	3.392 (2.306-4.989)	<0.001	2.970 (1.533-5.755)	0.001	1.374 (0.988-1.912)	0.059	0.760 (0.438-1.319)	0.330
Gender								
Female	1		1		1			
Male	0.798 (0.579-1.099)	0.167	0.73 (0.502-1.062)	0.099	0.806 (0.553-1.175)	0.263	0.992 (0.638-1.542)	0.970
Rubanicity								
Urban	1		1		1			
Rural	0.969 (0.896-1.049)	0.441	1.006 (0.914-1.107)	0.902	0.984 (0.894-1.083)	0.741	0.995 (0.887-1.116)	0.931
Income (NT)								
Low (<24,000)	1		1		1			
Middle (24,000-42,000)	0.671 (0.488-0.923)	0.014	0.603 (0.389-0.936)	0.024	0.893 (0.686-1.163)	0.402	0.711 (0.496-0.019)	0.063
High (>42,000)	0.558 (0.389-0.801)	0.002	0.525 (0.336-0.821)	0.005	0.792 (0.591-1.063)	0.121	0.787 (0.55-1.127)	0.191
Aortic aneurysm site								
TAA	1		1		1		1	
AAA	0.876 (0.805-0.954)	0.002	0.870 (0.785-0.964)	0.008	1.235 (1.110-1.373)	<0.001	1.418 (1.248-1.611)	<0.001
TAAA	1.312 (1.122-1.535)	<0.001	1.385 (1.157-1.657)	<0.001	1.294 (1.064-1.573)	0.010	1.66 (1.325-2.081)	<0.001
Smoking rate	1.005 (0.995-1.016)	0.322	1.008 (0.995-1.020)	0.222	1.009 (0.997-1.021)	0.141	0.999 (0.985-1.014)	0.910
Co-morbidities								
Diabetes	1.142 (0.992-1.314)	0.064	1.169 (0.993-1.377)	0.061	0.960 (0.801-1.151)	0.662	0.976(0.794-1.201)	0.821
Hypertension	0.937 (0.764-1.148)	0.529	0.894 (0.702-1.138)	0.362	0.866 (0.678-1.107)	0.250	0.863 (0.644-1.157)	0.325
Dyslipidemia	0.686 (0.612-0.768)	<0.001	0.675 (0.591-0.770)	<0.001	0.938 (0.827-1.064)	0.320	0.913(0.79-1.055)	0.218
CHF	1.434 (1.316-1.563)	<0.001	1.406 (1.268-1.558)	<0.001	0.976 (0.874-1.090)	0.666	0.955 (0.555-1.644)	0.868
Atrial fibrillation	1.304 (1.166-1.457)	<0.001	1.320 (1.149-1.517)	<0.001	1.053 (0.906-1.225)	0.500	1.017 (0.843-1.226)	0.863
VHD	0.801 (0.720-0.891)	<0.001	0.801 (0.707-0.908)	<0.001	0.967 (0.854-1.095)	0.601	0.935 (0.808-1.081)	0.363
PAD	1.092 (0.944-1.264)	0.237	1.030 (0.863-1.229)	0.745	1.061 (0.893-1.261)	0.501	1.065 (0.869-1.306)	0.543
CAD	0.920 (0.851-0.994)	0.035	0.954 (0.870-1.045)	0.310	1.124 (1.022-1.235)	0.016	1.201 (1.077-1.34)	0.001
Stroke	1.344 (1.245-1.451)	<0.001	1.347 (1.229-1.475)	<0.001	1.016 (0.922-1.119)	0.746	1.004(0.895-1.126)	0.948
Malignance	1.538 (1.411-1.675)	<0.001	1.557 (1.408-1.721)	<0.001	0.978 (0.869-1.100)	0.709	0.961 (0.836-1.103)	0.570
CKD	1.732 (1.585-1.894)	<0.001	1.788 (1.610-1.986)	<0.001	1.309 (1.168-1.468)	<0.001	1.327(1.161-1.516)	<0.001
Thyroid disease	0.861 (0.696-1.064)	0.166	0.807 (0.625-1.042)	0.100	1.060(0.828-1.357)	0.642	1.134 (0.85-1.513)	0.392
Liver disease	1.037 (0.932-1.154)	0.503	1.054 (0.928-1.196)	0.422	1.010 (0.888-1.148)	0.884	1.016 (0.874-1.181)	0.839
Sleep apenea	0.927 (0.836-1.027	0.145	0.921 (0.810-1.047)	0.210	1.079 (0.956-1.217)	0.217	1.073 (0.927-1.242)	0.348
Peptic ulcer	1.233 (1.106-1.375)	<0.001	1.149 (1.009-1.310)	0.037	1.132 (0.985-1.302)	0.081	1.118 (0.95-1.317)	0.180
Gout	1.011 (0.921-1.111	0.816	1.002 (0.898-1.119)	0.965	0.992 (0.887-1.109)	0.883	0.973 (0.854-1.109)	0.685
Prescribed Drugs								
ACEI	1.171 (1.077-1.273)	<0.001	1.170 (1.058-1.293)	0.002	1.109 (1.002-1.227)	0.045	1.082 (0.958-1.222)	0.204
ARB	0.893 (0.822-0.971)	0.007	0.846 (0.766-0.934)	<0.001	1.055 (0.958-1.162)	0.275	1.016 (0.906-1.139)	0.786
BB	0.875 (0.808-0.948)	0.011	0.852 (0.776-0.937)	<0.001	1.103 (1.003-1.214)	0.044	1.100 (0.982-1.231)	0.099
CCB	0.812 (0.742-0.889)	<0.001	0.832 (0.748-0.926)	<0.001	0.999 (0.892-1.118)	0.980	0.975 (0.854-1.112)	0.704
Diuretics	1.372 (1.259-1.495)	<0.001	1.358 (1.229-1.501)	<0.001	0.916 (0.830-1.011)	0.082	0.856 (0.764-0.96)	0.008
Alpha-blocker	0.924 (0.836-1.022)	0.125	0.928 (0.824-1.045)	0.220	1.112 (0.990-1.249)	0.074	1.173 (1.023-1.345)	0.022
Statin	1.098 (0.952-1.267)	0.200	1.112 (0.941-1.315)	0.212	1.099 (0.942-1.282)	0.230	1.039 (0.868-1.242)	0.679
Fibrate drugs	1.095 (0.822-1.459)	0.536	1.018 (0.714-1.451)	0.923	0.919 (0.669-1.261)	0.599	0.840 (0.568-1.242)	0.382
Antiplatelet drugs	1.224 (1.085-1.381)	0.001	1.058 (0.961-1.165)	0.249	1.114 (1.010-1.228)	0.031	1.092 (0.973-1.225)	0.135
OAD	1.106 (1.020-1.200)	0.015	1.135 (0.986-1.307)	0.077	1.001 (0.862-1.162)	0.993	0.996 (0.839-1.183)	0.966

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CCB, calcium channel blockers; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OAD, oral Anti-diabetic agent; VHD, valvular heart disease; PAD, peripheral artery disease; CAD, coronary artery disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

Table 4. Subgroup analysis for all-cause mortality in patients with aortic aneurysms and chronic obstructive pulmonary disease

	COPD			
	No matching		PS-matching	
Variable	HR	p	HR	p
COPD	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009
Age group (yr)				
<70	1.161 (0.933-1.444)	0.181	1.184 (0.926-1.514)	0.179
≥70	1.103 (1.016-1.198)	0.020	1.117 (1.021-1.223)	0.016
Aortic aneurysm site				
TAA	1.205 (1.042-1.392)	0.012	1.262 (1.075-1.482)	0.004
AAA	1.048 (0.952-1.154)	0.340	1.055 (0.949-1.173)	0.318
TAAA	1.074 (0.775-1.488)	0.670	0.986 (0.687-1.414)	0.939
Comorbidities				
Diabetes (Yes)	0.911 (0.711-1.166)	0.458	0.826 (0.624-1.093)	0.181
Diabetes (No)	1.137 (1.048-1.234)	0.002	1.164 (1.064-1.272)	<0.001
Hypertension (Yes)	1.103 (1.020-1.193)	0.014	1.111 (1.019-1.211)	0.017
Hypertension (No)	1.467 (0.923-2.331)	0.105	1.173 (0.710-1.939)	0.532
Dyslipidemia (Yes)	1.100 (0.949-1.275)	0.206	1.141 (0.969-1.344)	0.113
Dyslipidemia (No)	1.105 (1.009-1.210)	0.031	1.116 (1.011-1.233)	0.030
Atrial fibrillation (Yes)	1.141 (0.900-1.446)	0.276	1.182 (0.902-1.548)	0.226
Atrial fibrillation (No)	1.099 (1.012- 1.193)	0.024	1.111 (1.016-1.216)	0.022
Stroke (Yes)	1.085 (0.954-1.234)	0.212	1.089 (0.942-1.259)	0.248
Stroke (No)	1.118 (1.014- 1.231)	0.025	1.140 (1.026-1.267)	0.015
CKD (Yes)	1.021 (0.869-1.199)	0.805	0.998 (0.834-1.194)	0.982
CKD (No)	1.131 (1.036-1.235)	0.006	1.153 (1.046-1.270)	0.004
Prescribed Drugs				
ACEI (Yes)	1.199 (1.032-1.393)	0.018	1.198 (1.017-1.412)	0.030
ACEI (No)	1.068 (0.976-1.169)	0.151	1.087 (0.984-1.200)	0.099
BB (Yes)	1.130 (1.015-1.259)	0.025	1.167 (1.030-1.323)	0.015
BB (No)	1.080 (0.965-1.207)	0.179	1.080 (0.961-1.214)	0.194
CCB (Yes)	1.133 (1.034-1.241)	0.007	1.141 (1.032-1.261)	0.009
CCB (No)	1.005 (0.868-1.165)	0.945	1.034 (0.879-1.217)	0.684
Statin (Yes)	1.114 (0.904-1.373)	0.313	1.140 (0.904-1.438)	0.2681
Statin (No)	1.103 (1.015-1.199)	0.021	1.117 (1.019-1.223)	0.018
Antiplatelet drugs (Yes)	1.080 (0.971-1.202)	0.156	1.082 (0.960-1.219)	0.196
Antiplatelet drugs (No)	1.132 (1.012-1.267)	0.029	1.163 (1.030-1.312)	0.015
Operation type				
Open repair (Yes)	1.069 (0.855-1.338)	0.558	1.009 (0.830-1.226)	0.930

Endovascular repair (Yes)	0.911 (0.705-1.179)	0.479	1.029 (0.793-1.334)	0.832

ACEI, angiotensin-converting enzyme inhibitors; BB, beta-blockers; CCB, calcium channel blockers; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

Figure Legends

Figure 1. Study flow diagram.

Figure 2. Cumulative risk of all-cause mortality between the COPD and non-COPD patients

(A) Operation and TAA, (B) operation and AAA, (C) operation and TAAA, (D) non-operation and TAA, (E) non-operation and AAA, and (F) non-operation and TAAA. *Abbreviations:* AAA, abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm.

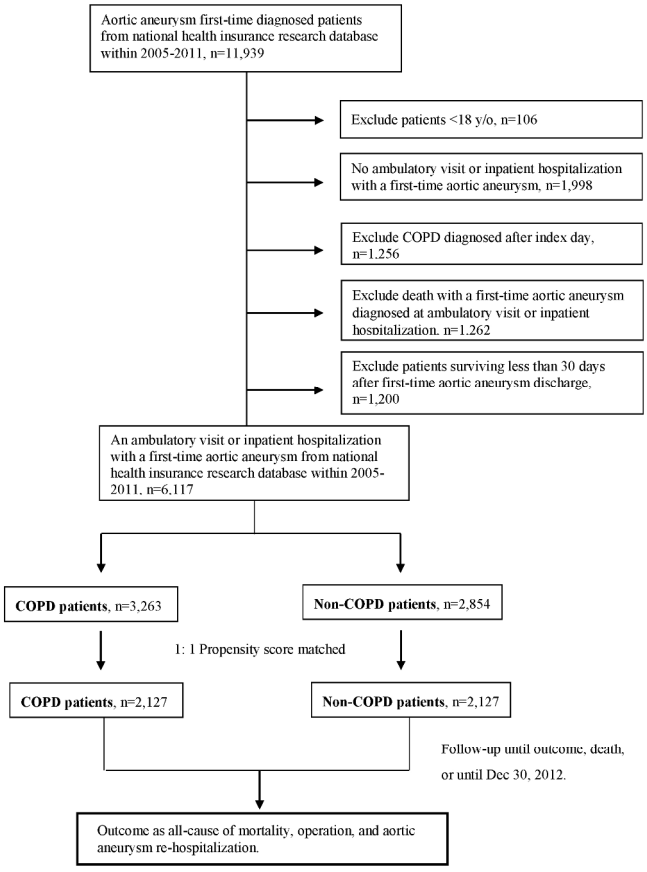

Fig 1

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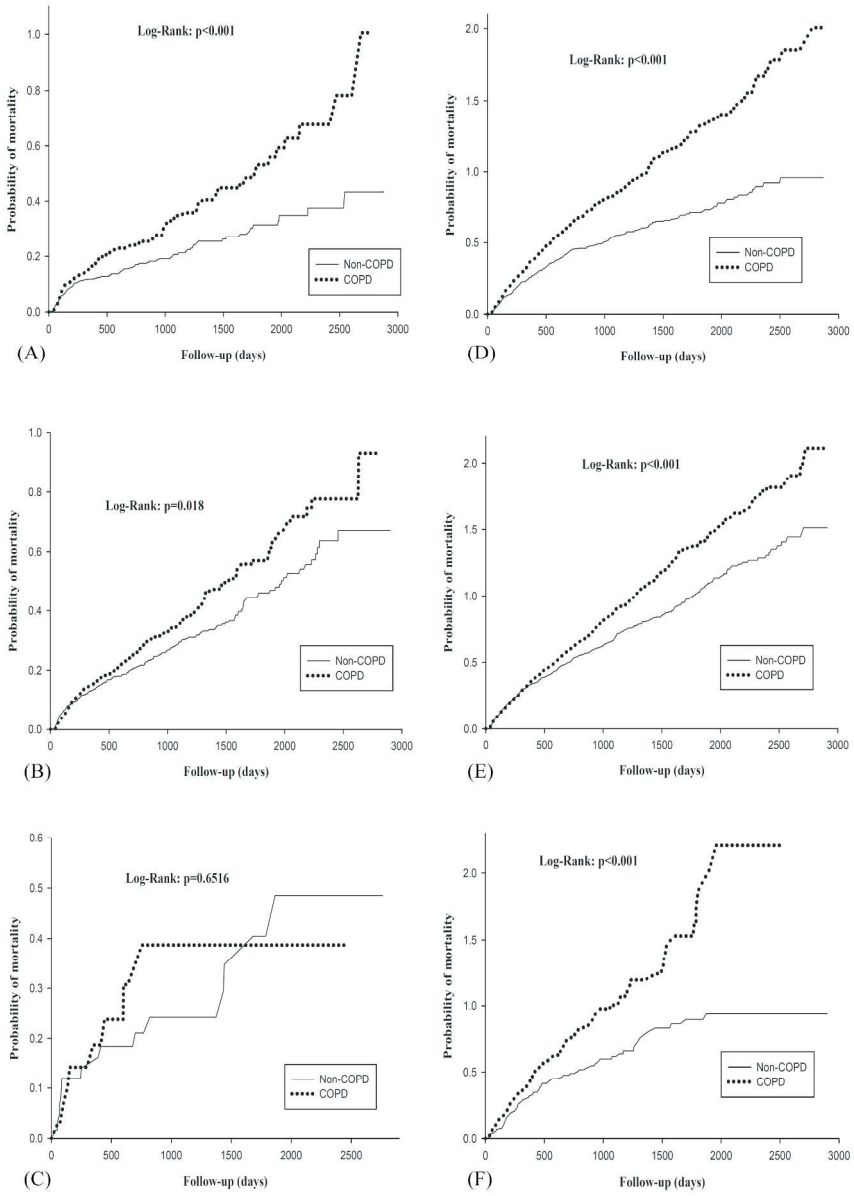

Cumulative risk of mortality between the COPD and non-COPD groups
(A) Operation and TAA, (B) operation and AAA, (C) operation and TAAA, (D) non-operation and TAA, (E) non-operation and AAA, and (F) non-operation and TAAA. Abbreviations: AAA, abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm.

206x288mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10-12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NP

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The Impact of Chronic Obstructive Pulmonary Disease on Patients with Aortic Aneurysms: A Nationwide Retrospective Cohort Study in Taiwan.

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The Impact of Chronic Obstructive Pulmonary Disease on Patients with Aortic Aneurysms: A Nationwide Retrospective Cohort Study in Taiwan.

Kuang-Ming Liao[1], Chung-Yu Chen[2,3]

1. Department of Internal Medicine, Chi Mei Medical Center, Chiali, Taiwan.
2. Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.
3. School of Pharmacy, Master Program in Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan.

Corresponding author

Chung-Yu Chen, School of Pharmacy, Kaohsiung Medical University. No. 100, Shih-Chuan 1st Rd., Sanmin District, Kaohsiung City 80708, Taiwan (R.O.C.)

E-mail: jk2975525@hotmail.com

Keywords: chronic obstructive pulmonary disease, aortic aneurysms

Abbreviations:

AA	Aortic Aneurysm
AAA	Abdominal Aortic Aneurysm
ACEI	Angiotensin-Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
BB	Beta-Blocker
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
OAD	Oral Anti-Diabetic Agent
PAD	Peripheral Artery Disease
PSM	Propensity Score Matching
TAA	Thoracic Aortic Aneurysm
TAAA	Thoracoabdominal Aortic Aneurysm
VHD	Valvular Heart Disease

Abstract

Objectives: Aortic aneurysm (AA) is a leading cause of death worldwide. Chronic obstructive pulmonary disease (COPD) is a risk factor for AA, and the prognoses of COPD patients with AA who underwent/did not undergo an operation warrant investigation.

Design: A nationwide retrospective cohort study.

Setting: We included AA patients older than 18 years who received their first AA diagnosis between 2005 and 2011 in Taiwan.

Participants: This study enrolled 3,263 COPD patients with AA before propensity score matching and 2,127 COPD patients with AA after propensity score matching.

Outcome measures: The main outcomes were all-cause mortality and re-hospitalization for AA or operation. The outcomes of COPD patients with AA and COPD patients without AA during an 8-year follow-up period were examined using Cox proportional hazards models.

Results: In the AA population, COPD patients showed higher rates of mortality and re-hospitalization than non-COPD patients with adjusted hazard ratios (HRs) of 1.12 (95% CI=1.03-1.22) and 1.11 (95% CI=1.01-1.23), respectively, after propensity score matching. Analysis of the patients who underwent an operation revealed that the rates of mortality of COPD and non-COPD patients were not significantly different. In contrast, among the patients who did not receive an operation, COPD patients showed a higher mortality rate than non-COPD patients with an adjusted HR of 1.11 (95% CI=1.0-1.22).

Conclusions: The outcomes of COPD patients with AA undergoing an operation were improved, but the mortality rate of non-COPD patients with AA remained high. An effective treatment to reduce mortality in this group warrants further investigation.

Strengths and limitations

1. This study is a nationwide cohort study that enrolled most aortic aneurysm patients with long-term follow-up over a period of 8 years.
2. We used propensity score matching to reduce selection bias in aortic aneurysm patients by balancing covariates between patients with and without COPD.
3. This is a comprehensive national study with a large population that intended to be representative of AA patients with and without COPD in a clinical setting.
4. The study relies on diagnosed COPD; however, according to a previous study, a large proportion of cases might be missed.
5. Some details regarding COPD and aortic aneurysm, such as lung function, aneurysm size, and the presence of a dissection/rupture, might impact mortality; however, these were not assessed in our analyses.

Introduction

Chronic obstructive pulmonary disease (COPD) is an obstructive airway disease that is not fully reversible by medication. In fact, COPD is a systemic disease that shares smoking as a common risk factor for inducing aortic aneurysms (AAs); additionally, COPD has been shown to be an independent risk factor for abdominal aortic aneurysm (AAA).[1] AAs include those of the abdominal aorta (AAA), thoracic aorta (TAA), and thoracoabdominal aorta (TAAA) and are associated with high mortality, particularly following rupture.[2–4]

Previous studies have focused on the prognosis of patients with COPD undergoing operation for AAA[5] or have compared the outcomes of COPD patients with AAA undergoing open or endovascular repair.[6] However, these studies only considered the effect of COPD in AAA patients who underwent an operation, and some studies were performed more than 10 years ago. In addition, AA patients may receive either surgical or medical treatment, but few studies have addressed the effect of COPD on AA patients who receive medication. A previous study among AAA patients found that the risk of death was significantly greater in the presence of COPD.[7] Another study showed that severe COPD, for which patients were dependent on home oxygen, was not a contraindication to AAA repair and that the mortality of these patients did not increase.[8] Unfortunately, generalization of these observational studies was limited by their small sample sizes, short follow-up periods, lack of medical records, and conflicting results. Moreover, improvements in intraoperative and postoperative care for vascular operation have resulted in significant reductions in morbidity and mortality that might affect the outcomes of AA in patients with COPD. These factors justify further investigation.

To investigate the outcomes (all-cause mortality, re-hospitalization for AA and

operation) of AA patients (including AAA, TAAA, and AAA) with COPD, we used data from the Taiwanese National Health Insurance Research Database (NHIRD) for patients receiving either surgical or medical treatment. The aim of our study was to analyze the association between aortic aneurysm and COPD regardless of the risk factors of aortic aneurysm. The main outcomes were all-cause mortality and re-hospitalization for AA or operation. The hypothesis was that COPD has a large influence on the outcome of aortic aneurysms.

Materials and Methods

Study design

This was a population-based, observational study using information from the NHIRD in Taiwan. Data regarding hospital visits, emergency care, and prescriptions were provided by the National Health Insurance Research Institutes. The diagnosis of AA in the NHIRD has previously been described.[9] This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT-20130199).

Participants

We included patients from the NHIRD aged ≥18 years who presented with a first-time diagnosis of AA (ICD-9: 441.1–441.9) between 2005 and 2011. The date of the first ambulatory visit or inpatient hospitalization at which AA was diagnosed was designated the index date. We excluded patients who died at first presentation and those who had fewer than 30 days of follow-up after discharge.

Participants included as cases were required to have a diagnosis of COPD (ICD-9: 490–492, 496) before the index date and treated using COPD medications including the following: long-acting inhaled anticholinergics, long-acting inhaled β2-adrenergic

receptor agonists, inhaled corticosteroids, short-acting anticholinergics, short-acting β2-agonists, or xanthines. Patients were excluded if COPD was diagnosed or medications for COPD were prescribed after the index date.

The control group was selected from the group of AA patients who had no comorbid diagnosis of COPD. To decrease selection bias due to baseline differences, we also conducted propensity score matching (PSM) at a 1:1 ratio by age group, demographic characteristics, comorbidities, and co-medications. The patients in this study were followed until re-admission or operation for AA, death, withdrawal from the national health insurance, or December 31, 2012, whichever was soonest.

Variables

All patients were divided into the TAA (ICD-9 codes 441.1–441.2), AAA (ICD-9 codes 441.3–441.4), and TAAA (ICD-9 codes 441.6–441.7) groups according to the diagnosis site at the index date. We also identified whether patients underwent operation and, if so, whether the operation involved open or endovascular repair.

Patient comorbidities were identified by the diagnostic code as inpatient or outpatient diagnoses within 180 days of the index date. The following comorbidities were included in the assessment: hypertension, diabetes, dyslipidemia, congestive heart failure (CHF), atrial fibrillation, valvular heart disease (VHD), peripheral artery disease (PAD), coronary artery disease (CAD), stroke (ischemic and hemorrhagic), malignancy, chronic kidney disease (CKD), thyroid disease, liver disease, gout, peptic ulcer disease, and sleep apnea. The drugs prescribed within 180 days of the index date were also identified. The following medications were also included as variables: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), diuretics, alpha-blockers, statins, fibrates, antiplatelet drugs, and oral anti-diabetic agents (OADs).

We also described the demographic characteristics of AA patients by the presence or absence of a COPD diagnosis. Potential confounders included gender, age group (<50, 50–59, 60–69, 70–79, and over 80 years), urbanization (urban or rural), income group, and smoking status. The income groups were defined as low (<NT$24,000), middle (NT$24,000– NT$42,000), or high (>NT$42,000) according to the individual monthly gross income during a 1-month period before the index date.

Because no information was available regarding smoking status, we used the mean percentage of city/county smoking rates available from the National Health Interview Survey (2005 to 2011). All subjects in this survey were randomly sampled and selected from different cities and counties to be interviewed by trained interviewers.[10] Although this smoking rate is not a direct measure of the rate for patients in this database, it can be considered to reflect the likely rates of smoking and passive smoking (stratified by age, gender, and living area) if we assume a normally distributed cohort that reflects the broader population.

Outcome

The main outcomes of interest were all-cause mortality and re-hospitalization for AA or operation. Moreover, all-cause mortality was confirmed by withdrawal from NHI within 1 month of a major medical event.[11] We considered re-hospitalization to be the time when patients were admitted with AA-related events (ICD-9 codes 441.1–441.9) as the principal or secondary diagnosis after discharge from the index event. Operation was stratified by whether patients underwent an operation at the time of the index event. Then, the patients who underwent an operation for AA at the index event and were re-hospitalized for operation more than 30 days after discharge were classified as undergoing a repeat operation. Patients who did not undergo operation at the index event and who were re-hospitalized more than 30 days after discharge were classified into the operation group. Furthermore, patients who received an operation

less than 30 days after discharge at the index event were classified into the operation group at the index event.

Statistics

All data are expressed as frequencies (percentages). Categorical and continuous variables were compared between the COPD and non-COPD patients using Chi-square tests and Student t-tests, as appropriate. The outcomes of the COPD and non-COPD patients during an 8-year follow-up period were examined by Cox proportional hazards models.

Simple and multiple analyses (including age group, comorbidities, co-medications, and demographic characteristics) were used to assess the risk of outcome by the presence or absence of COPD during follow-up. We used PSM for patients in the COPD and non-COPD groups. Because the outcomes might have been influenced by the presence of disease (diabetes mellitus, dyslipidemia, and hypertension) or medication (OAD, statins, fibrates, and antihypertensives), we examined these in a multiple model. The difference in the cumulative probability of mortality between the COPD and non-COPD patients was calculated using Kaplan–Meier estimates with the log-rank test; we also divided patients by operation type and site of diagnosis for these analyses.

To assess the robustness of the outcomes, a subgroup analysis was performed, and the subgroups were defined by age (≥70 and <70 years), aortic aneurysm site (TAA, AAA, and TAAA), high risk (hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, stroke, and CKD), concomitant drug use (ACEIs, BBs, CCBs, statins, and antiplatelet agents), and type of operation. The analyses and calculations were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was inferred at a two-sided p-value <0.05.

Results

Descriptive data

We identified 6,117 AA patients, and 3,263 of these patients also had COPD. After PSM, 2,127 COPD patients were eligible for enrollment in the study. Figure 1 shows the study flow diagram for AA patients with and without COPD.

Table 1 summarizes the characteristics of AA patients. Before matching, one-third of the AA patients were aged 70–80 years. A notable male preponderance was detected in the COPD and non-COPD patients.

In both groups, AAA was the most common type of AA, followed by TAA and TAAA. Most non-COPD patients (58%) received open repair, whereas most COPD patients (55%) underwent endovascular repair. The most common comorbidity was hypertension, which was present in more than 96% of patients. The two most common medications administered to the COPD and non-COPD patients were CCBs and diuretics, respectively.

Outcomes based on the operation and non-operation groups

As shown in Table 2, among the AA patients who received an operation, there were no significant differences in all-cause mortality between the COPD and non-COPD patients. Among the non-operation group, the all-cause mortality was higher in COPD patients compared with non-COPD patients both before and after PSM, with respective adjusted HRs of 1.233 (95% CI 1.130–1.344) and 1.105 (95% CI 1.004–1.216). The re-operation rate for AA was higher in the non-COPD patients than in the COPD patients with an adjusted HR of 3.134 (95% CI 1.394–7.043) after PSM.

Outcome of AAs by the presence or absence of COPD

As shown in Table 2, an analysis of the total population revealed that COPD patients presented a higher all-cause mortality than patients without COPD. The AA re-hospitalization rate of the COPD patients was also higher than that of the non-COPD patients, with respective adjusted HRs before and after PSM of 1.100 (95% CI 1.004–1.206) and 1.114 (95% CI 1.007–1.2327). Among the total population, no significance difference in the number of patients who underwent an operation was found between the COPD and non-COPD patients.

Other factors affecting outcomes

Table 3 shows the hazard ratios (HRs) and 95% confidence intervals (CI) for all-cause mortality and re-hospitalization before and after PSM.

As shown in Table 3, COPD and age ≥80 years were associated with higher mortality rates after PSM with respective HRs of 1.118 (95% CI 1.028–1.217) and 2.970 (95% CI 1.533–5.755). In addition, AAA and TAAA were associated with a higher risk of re-hospitalization than TAA after PSM, and AAA was also associated with a lower risk of mortality than TAAA.

Other comorbidities associated with a higher risk of mortality after PSM included diabetes, dyslipidemia, CHF, atrial fibrillation, VHD, stroke, malignancy, CKD, and peptic ulcer disease. Among the patients with multiple comorbidities, only CAD and CKD were associated with a significantly higher risk of re-hospitalization. Medications that showed an apparent protective effect on mortality after PSM were ARBs, BBs, and CCBs. Patients prescribed CCBs had a lower risk of re-hospitalization, and those prescribed α blockers presented a higher risk of re-hospitalization. After PSM, AA patients had a lower risk of mortality if they were receiving ARBs than if they were receiving ACEIs, with HRs of 0.846 (95% CI 0.766–0.934) and 1.170 (95% CI 1.058–1.293). However, there was no significant

difference in the re-hospitalization rates between patients receiving ACEIs and those receiving ARBs after PSM.

Mortality analysis in patients with AA and COPD

Table 4 shows the results of a subgroup analysis for mortality in AA patients defined by the presence or absence of COPD. AA patients with COPD had higher mortality rates than those without COPD. Patients ≥70 years of age (HR 1.117, 95% CI, 1.021–1.223) or with TAA (HR 1.262, 95% CI 1.075–1.482) also showed higher risks of mortality. The HR for mortality in the patients with AA, COPD, and hypertension was also significant (HR 1.111, 95% CI 1.019–1.211). Other comorbidities, including diabetes, dyslipidemia, atrial fibrillation, stroke, and CKD, were not associated with increased risks of mortality in AA patients with COPD. There was also no significant difference in the mortality rates between the operation procedures for patients with COPD and AA.

Figure 2 shows the cumulative risk of AA mortality in patients with and without COPD and is stratified by patients who underwent an operation and by the AA site. Analysis of the patients with TAAA who underwent an operation showed no significant difference in mortality between the COPD and non-COPD patients (p=0.6516). However, for all other subgroups of AA patients, there were significant differences in mortality based on the presence or absence of COPD.

Discussion

This nationwide population-based study showed that AA patients with COPD had a higher risk of all-cause death and re-hospitalization than those without COPD. Analysis of the AA patients who underwent an operation showed that those with

COPD had the greatest risk of re-operation for AAs. However, no differences in mortality in AA patients with COPD were found among the different procedures for AA.

Prognosis of AA patients with COPD

A previous study showed that the increased prevalence of COPD in AAA patients was independent of smoking.[1] Other studies have found that COPD is associated with a high prevalence of AAA with rates ranging from 7.7% to 9.9% and that the prevalence is increased in severe emphysema and in cases with a decreased forced expiratory volume/vital capacity ratio.[12,13] The aneurysm rupture rates have also been shown to correlate with COPD risk factors, initial aneurysm size, and diastolic hypertension,[14] but surgeons are hesitant to repair AAAs electively because of the associated high morbidity and mortality.[15] Through a database review of 1053 patients undergoing surgery for intact or ruptured AAAs in a hospital between 1997 and 1998, David et al.[5] showed that mortality was not higher in patients with COPD compared with patients without COPD. Notably, these researchers also showed that patients with COPD required longer hospital stays, longer intensive care unit stays, and more days of ventilation. However, their study was performed more than 15 years ago and only focused on AAA patients who underwent operations. David et al.[5] did not find an increased risk in patients undergoing surgery, which might be due to adequate patient selection in an era of open repair.

Our study included patients with a first-time AA diagnosis between 2005 and 2011 and who were followed to December 31, 2012. The final cohort of AA patients comprised 2,854 controls without COPD and 3,263 cases with COPD, and these were further divided into those who did and did not undergo operation. Our study indicated that AA patients with COPD had a higher rate of re-hospitalization and higher mortality compared with patients without COPD. In patients undergoing operation for

AAs, we found that the mortality and re-hospitalization rates were not significantly different between those with and without COPD, although the re-operation rate was higher in those with COPD. Among those not undergoing operation for AA, the all-cause mortality rate was also higher among COPD patients than those without COPD.

Surgical procedure and mortality in patients with COPD and AA

Christopher et al.[16] retrospectively reviewed 44 patients with oxygen-dependent COPD undergoing AAA repair; of these, 24 underwent endovascular aneurysm repair, and 20 underwent open procedures. These researchers showed that the type of repair, comorbidities, and lung function test results did not significantly affect survival. Many other studies have also shown that endovascular AAA repair offers long-term survival similar to open AAA repair in patients with COPD.[17-19] Moqueet et al.[20] performed a prospective study of high-risk patients undergoing endovascular repair of AAAs or TAAAs between 1998 and 2009 and showed that mortality was no different between patients with and without COPD when endovascular techniques were used. In our study comparing all types of AA in COPD and non-COPD patients, we found no significant difference in mortality rates for either procedure between the two groups.

Patient characteristics

In our study, patients with COPD had higher rates of AA than those without COPD. Most AA patients were males regardless of whether they had COPD. The most common comorbidities in AA patients with COPD were hypertension, CAD, stroke, dyslipidemia, and CHF. These results are similar to those reported by Flessenkaemper et al.,[21] who suggested that risk factors such as male gender and CAD could be used to increase the efficiency of screening for AAA. We suggest that other risk factors, such as hypertension, stroke, dyslipidemia, and CHF, might be useful in future

screening for AA in patients with COPD.

A survey of 231 patients with COPD by Katsutoshi et al.[22] reported that only 27 (11.7%) had AA and 20 (8.7%) had AAA. This finding contrasts with the results of our nationwide study, in which 2089 (64%) AAA patients also had comorbid COPD. To the best of our knowledge, with the exception of two studies with conflicting results,[23,24] there have been no major reports on the prevalence or incidence of AA in the Asian population. Poon et al.[25] reported that the prevalence of AAA in Chinese patients was low and that their results did not support routine screening for AAA; however, another study showed that AAA was not uncommon and had a comparable incidence to that in the West.[24] To clarify these issues, a study that includes more Asian countries and a larger population is needed.

Prescription patterns

Medical management is important in the control of AAs, with the main goal of therapy being to decrease shear stress by reducing blood pressure and contractility.[26] In a small retrospective study, BBs were shown to effectively decrease AAA growth.[27] In another study, prophylactic BBs were found to be associated with a slowing in the rate of aortic dilatation.[28] Indeed, BBs can not only reduce left ventricular contractility but also reduce shear stress in the aorta. However, a prospective randomized double-blind study showed that AAA patients do not tolerate BBs and that these medications have no significant effect on the growth rates of small AAAs.[29]

In our study, before PSM, the most common medications for AA were CCBs, followed by diuretics and BBs. Although the prescribing rates of BBs were associated with significant differences between the COPD and non-COPD patients, this difference did not persist after PSM. BBs are often prescribed for AA, but physicians may be concerned about contraindications and may fear inducing adverse reactions or bronchospasm, particularly in patients with obstructive airway disease. In our analysis,

BBs were well tolerated in patients with AA and COPD and had a clear protective effect on reducing mortality. This is consistent with their use being recommended. Notably, the safety of BBs has long been proven in COPD patients, and there is a growing body of evidence from clinical trials showing that BBs should not be withheld in this patient group.[30]

ACEI and ARB in AA

In our analysis, ARBs, BBs, CCBs, and diuretics, but not ACEIs, were associated with reduced mortality in patients with AA and COPD. In an animal model, AAs were associated with increased transforming growth factor-β signaling, and the ARB losartan has been shown to block transforming growth factor-β.[31] Losartan can therefore prevent elastic fiber fragmentation and blunt transforming growth factor-β signaling in the aorta, thereby reducing the growth rates of AAs.[32] However, ACEIs were shown to prevent aortic dissection and the apoptosis of vascular smooth muscle cells in another animal model;[33] Hackam et al. reported that ACEIs were protective against aortic expansion and rupture, whereas ARBs did not protect against AAA rupture.[34] Other experimental evidence shows that ACEIs increase collagen synthesis, improve plaque stabilization, and diminish aortic stiffness.[35] To further complicate matters, in a prospective cohort study of 1701 patients in the UK, Sweeting et al.[36] showed that aneurysm growth was faster in patients receiving ACEIs. This finding conflicts with previous research and observational data from Canada showing that ACEIs have protective benefits.[35]

Considering all the data, the inconsistent results regarding the efficacies of ARBs and ACEIs in reducing AA growth limit any meaningful conclusion. Undoubtedly, these problems result from differences in the models used, selection bias, unaccounted confounding factors, and the multiple possible pathways of AA development.

A recently systematic review of the current data on pharmaceutical therapies for AAA

showed that pharmaceutical therapies cannot halt AAA growth.[37] Small AAA growth rates were lower than anticipated, and ACEI had no significant impact in reducing the small AAA growth rate.[38]

Limitations

This study has some important limitations. Our study relies on diagnosed COPD; however, according to a previous study[1], a large proportion of the cases might be missed. We did not have access to data on vital signs (i.e., blood pressure and heart rate) or to imaging results (i.e., we could not estimate the size or progression of AAs). We also did not include data on pulmonary function tests or the severity of COPD, and we were unable to find a clear relationship between the size of AA and the severity of COPD. However, we focused on all-cause mortality, re-hospitalization rates, and re-operation rates and performed a subgroup analysis (operation vs non-operation) to reduce bias. This was also a large nationwide study of all registered AA patients in Taiwan, which should allow generalization to other COPD populations. Finally, we also performed PSM, which reduced the bias in estimating the treatment effects and reduced the likelihood of confounding data. We excluded patients who died within 30 days and individuals with a COPD diagnosis after the index date. Additionally, chronic conditions such as COPD and aneurysms might have been present at the time of inclusion.

Conclusions

Improvements in the pre- and postoperative management of COPD patients undergoing major operation have resulted in reduced mortality and morbidity rates. However, although we showed improvement in the safety and outcomes of COPD patients undergoing AAA repair, we also showed that the overall mortality remains higher than that in patients without COPD. In addition, we also observed high mortality rates among COPD patients who did not undergo operation. Further

research is clearly needed to identify the most appropriate therapy for reducing mortality in patients with AA and COPD.

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Table 1. Characteristics of patients with aortic aneurysms in Taiwan

Variable	No-COPD (n=2854) No	%	COPD (n=3263) No	%	p	PS-matching No-COPD (n=2127) No	%	PS-matching COPD (n=2127)	p
Age group (yr)					<0.001				0.436
<50	273	(9.6)	61	(1.9)		64	(3.0)	61 (2.9)	
50-60	356	(12.5)	113	(3.5)		134	(6.4)	112 (5.3)	
60-70	508	(17.8)	388	(11.9)		327	(15.4)	354 (16.6)	
70-80	932	(32.6)	1183	(36.2)		837	(39.4)	853 (40.1)	
>80	785	(27.5)	1515	(46.5)		763	(35.9)	747 (35.1)	
Gender					<0.001				0.971
Female	745	(26.1)	631	(19.3)		509	(23.9)	508 (23.9)	
Male	2109	(73.9)	2632	(80.7)		1618	(76.1)	1648 (76.1)	
Urbanicity					<0.001				0.733
Urban	724	(25.4)	1011	(31.0)		592	(27.8)	602 (28.3)	
Rural	2130	(74.6)	2252	(69.0)		1535	(72.2)	1525 (71.7)	
Income (NT)					<0.001				0.831
Low (<24,000)	2564	(89.8)	3136	(96.1)		2002	(94.1)	2011 (94.6)	
Middle (24,000-42,000)	149	(5.2)	74	(2.3)		71	(3.3)	65 (3.1)	
High (>42,000)	141	(5.0)	53	(1.6)		54	(2.5)	51 (2.4)	
Aortic aneurysm site					<0.001				0.918
TAA	965	(33.8)	1018	(31.2)		664	(31.2)	662 (31.1)	
AAA	1689	(59.2)	2089	(64.0)		1355	(63.7)	1351 (63.5)	
TAAA	200	(7.0)	156	(4.8)		108	(5.1)	114 (5.4)	
Operation	1181	(41.4)	1018	(31.2)	<0.001	823	(38.7)	753 (35.4)	0.026
Open repair	689	(58.3)	455	(44.7)		425	(51.6)	340 (45.2)	
Endovascular repair	492	(41.7)	563	(55.3)		399	(48.4)	413 (54.7)	
Smoking rate	26.3 (±13.4)		28.6 (±12.3)		<0.001	27.0 (±13.1)		27.0 (±13.1)	0.921
Co-morbidities									
Diabetes	414	(14.5)	450	(13.8)	0.423	310	(14.6)	307 (14.4)	0.896
Hypertension	2766	(96.9)	3138	(96.2)	0.112	2055	(96.6)	2051 (96.4)	0.738
Dyslipidemia	944	(33.1)	1032	(31.6)	0.227	727	(34.2)	725 (34.1)	0.948
CHF	561	(19.7)	1019	(31.2)	<0.001	488	(22.9)	482 (22.7)	0.826
Atrial fibrillation	230	(8.1)	384	(11.8)	<0.001	196	(9.2)	189 (8.9)	0.708
VHD	594	(20.8)	556	(17.0)	<0.001	377	(17.7)	368 (17.3)	0.717
PAD	152	(5.3)	222	(6.8)	0.016	128	(6.0)	139 (6.5)	0.487
CAD	1135	(39.8)	1685	(51.6)	<0.001	965	(45.4)	974 (45.8)	0.782
Stroke	736	(25.8)	1127	(34.5)	<0.001	642	(30.2)	646 (30.4)	0.894
Malignance	479	(16.8)	645	(19.8)	0.003	402	(18.9)	407 (19.6)	0.560
CKD	453	(15.9)	597	(18.7)	0.012	374	(17.6)	378 (17.8)	0.872
Thyroid disease	87	(3.1)	97	(3.0)	0.863	59	(2.8)	64 (3.0)	0.647
Liver disease	343	(12.0)	441	(13.5)	0.081	267	(12.6)	254 (11.9)	0.543
Sleep apnea	317	(11.1)	533	(16.3)	<0.001	271	(12.7)	268 (12.6)	0.890
Peptic ulcer disease	257	(9.0)	361	(11.1)	0.007	215	(10.1)	218 (10.3)	0.879
Gout	520	(18.2)	628	(19.5)	0.305	414	(19.5)	411 (19.3)	0.974
Prescribed drugs									
ACEI	691	(24.2)	857	(26.3)	0.066	521	(24.5)	507 (23.8)	0.616
ARB	948	(33.2)	1058	(32.4)	0.510	695	(32.7)	679 (31.9)	0.600
BB	1737	(60.9)	1583	(48.5)	<0.001	1174	(55.2)	1178 (55.4)	0.902
CCB	2187	(76.6)	2419	(74.13)	0.024	1607	(75.4)	1616 (76.7)	0.747
Diuretics	1874	(65.7)	2158	(66.1)	0.697	1371	(64.5)	1388 (65.3)	0.585
Alpha-blocker	457	(16.0)	541	(16.6)	0.549	344	(16.2)	346 (16.2)	0.934
Statin	480	(16.8)	535	(16.4)	0.658	373	(17.5)	378 (17.8)	0.841
Fibrate drugs	68	(2.4)	61	(1.9)	0.163	41	(1.9)	42 (1.9)	0.912
Antiplatelet drugs	1349	(47.3)	1742	(53.4)	<0.001	1083	(50.9)	1084 (50.9)	0.976
OAD	236	(8.3)	293	(8.9)	0.324	192	(9.0)	186 (8.7)	0.747

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CCB, calcium channel blockers; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OAD, oral anti-diabetic agent; VHD, valvular heart disease; PAD, peripheral artery disease; CAD, coronary artery disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

Table 2. Outcome of aortic aneurysms stratified by the presence or absence of chronic obstructive pulmonary disease

Outcome	No. of person-yr	Events after discharge: COPD (n=3263)	Events after discharge: Non-COPD (n=2854)	Cox regression unadjusted HR	p	Cox regression Adjusted HR [a]	p	PS-matching Cox regression Adjusted HR [a]	p
Total population									
All-cause mortality	15403	1795/3263 (55.0)	1198/2854 (41.9)	1.503 (1.397-1.617)	<0.001	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009
AA re-hospitalization	11958	1159/3263 (35.5)	941/2854 (33.0)	1.241 (1.138-1.353)	<0.001	1.100 (1.004-1.206)	0.042	1.114 (1.007-1.232)	0.036
Operation (operation and re-operation)	8262	384/3263 (11.8)	367/2854 (12.9)	0.897 (0.777-1.036)	0.897	0.909 (0.779-1.061)	0.227	0.972 (0.822-1.149)	0.738
Operation									
All-cause mortality	6104	324/1018 (31.8)	308/1181 (26.1)	1.373 (1.174-1.605)	<0.001	1.092 (0.925-1.288)	0.299	0.985 (0.819-1.185)	0.873
AA re-hospitalization	5286	252/1018 (24.8)	238/1181 (20.2)	1.376 (1.152-1.643)	<0.001	1.242 (1.031-1.496)	0.022	1.172 (0.950-1.446)	0.138
Re-operation	188	38/1018 (3.7)	68/1181(5.8)	1.182 (0.789-1.772)	0.417	1.214 (0.665-2.218)	0.527	3.134 (1.394-7.043)	0.006
Non-operation									
All-cause mortality	9299	1471/2245 (65.5)	890/1673 (53.2)	1.401 (1.289-1.523)	<0.001	1.233 (1.130-1.344)	<0.001	1.105 (1.004-1.216)	0.042
AA re-hospitalization	6672	907/2245 (40.4)	703/1673 (42.0)	1.085 (0.983-1.198)	0.106	1.070 (0.966-1.186)	0.963	1.022 (0.910-1.148)	0.713
Operation	8074	346/2245 (15.4)	299/1673 (17.8)	0.971 (0.831-1.134)	0.971	0.980 (0.829-1.158)	0.808	1.045 (0.872-1.252)	0.633

[a] Adjusted for age, gender, geographical region, comorbidity and prescribed drugs

Table 3. Hazard ratios for all-cause mortality and re-hospitalization in patients with aortic aneurysms

	All-cause mortality				AA re-hospitalization			
	No matching		PS-matching		No matching		PS-matching	
Variable	HR	p	HR	p	HR	p	HR	p
COPD	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009	1.100 (1.004-1.206)	0.042	1.114 (1.007-1.232)	0.036
Age group (yr)								
<50	1		1		1			
50-60	0.981 (0.582-1.652)	0.943	0.825 (0.340-2.002)	0.671	1.160 (0.772-1.743)	0.475	1.033 (0.907-1.177)	0.623
60-70	0.873 (0.564-1.350)	0.542	0.798 (0.389-1.637)	0.538	0.866 (0.605-1.239)	0.430	0.920 (0.465-1.820)	0.811
70-80	1.435 (0.963-2.139)	0.076	1.256 (0.642-2.460)	0.506	1.057 (0.752-1.485)	0.751	0.586 (0.326-1.052)	0.074
>80	3.392 (2.306-4.989)	<0.001	2.970 (1.533-5.755)	0.001	1.374 (0.988-1.912)	0.059	0.760 (0.438-1.319)	0.330
Gender								
Female	1		1		1			
Male	0.798 (0.579-1.099)	0.167	0.73 (0.502-1.062)	0.099	0.806 (0.553-1.175)	0.263	0.992 (0.638-1.542)	0.970
Urbanicity								
Urban	1		1		1			
Rural	0.969 (0.896-1.049)	0.441	1.006 (0.914-1.107)	0.902	0.984 (0.894-1.083)	0.741	0.995 (0.887-1.116)	0.931
Income (NT)								
Low (<24,000)	1		1		1			
Middle (24,000-42,000)	0.671 (0.488-0.923)	0.014	0.603 (0.389-0.936)	0.024	0.893 (0.686-1.163)	0.402	0.711 (0.496-0.019)	0.063
High (>42,000)	0.558 (0.389-0.801)	0.002	0.525 (0.336-0.821)	0.005	0.792 (0.591-1.063)	0.121	0.787 (0.55-1.127)	0.191
Aortic aneurysm site								
TAA	1		1		1		1	
AAA	0.876 (0.805-0.954)	0.002	0.870 (0.785-0.964)	0.008	1.235 (1.110-1.373)	<0.001	1.418 (1.248-1.611)	<0.001
TAAA	1.312 (1.122-1.535)	<0.001	1.385 (1.157-1.657)	<0.001	1.294 (1.064-1.573)	0.010	1.66 (1.325-2.081)	<0.001
Smoking rate	1.005 (0.995-1.016)	0.322	1.008 (0.995-1.020)	0.222	1.009 (0.997-1.021)	0.141	0.999 (0.985-1.014)	0.910
Co-morbidities								
Diabetes	1.142 (0.992-1.314)	0.064	1.169 (0.993-1.377)	0.061	0.960 (0.801-1.151)	0.662	0.976 (0.794-1.201)	0.821
Hypertension	0.937 (0.764-1.148)	0.529	0.894 (0.702-1.138)	0.362	0.866 (0.678-1.107)	0.250	0.863 (0.644-1.157)	0.325
Dyslipidemia	0.686 (0.612-0.768)	<0.001	0.675 (0.591-0.770)	<0.001	0.938 (0.827-1.064)	0.320	0.913 (0.79-1.055)	0.218
CHF	1.434 (1.316-1.563)	<0.001	1.406 (1.268-1.558)	<0.001	0.976 (0.874-1.090)	0.666	0.955 (0.555-1.644)	0.868
Atrial fibrillation	1.304 (1.166-1.457)	<0.001	1.320 (1.149-1.517)	<0.001	1.053 (0.906-1.225)	0.500	1.017 (0.843-1.226)	0.863
VHD	0.801 (0.720-0.891)	<0.001	0.801 (0.707-0.908)	<0.001	0.967 (0.854-1.095)	0.601	0.935 (0.808-1.081)	0.363
PAD	1.092 (0.944-1.264)	0.237	1.030 (0.863-1.229)	0.745	1.061 (0.893-1.261)	0.501	1.065 (0.869-1.306)	0.543
CAD	0.920 (0.851-0.994)	0.035	0.954 (0.870-1.045)	0.310	1.124 (1.022-1.235)	0.016	1.201 (1.077-1.34)	0.001
Stroke	1.344 (1.245-1.451)	<0.001	1.347 (1.229-1.475)	<0.001	1.016 (0.922-1.119)	0.746	1.004 (0.895-1.126)	0.948
Malignance	1.538 (1.411-1.675)	<0.001	1.557 (1.408-1.721)	<0.001	0.978 (0.869-1.100)	0.709	0.961 (0.836-1.103)	0.570
CKD	1.732 (1.585-1.894)	<0.001	1.788 (1.610-1.986)	<0.001	1.309 (1.168-1.468)	<0.001	1.327 (1.161-1.516)	<0.001
Thyroid disease	0.861 (0.696-1.064)	0.166	0.807 (0.625-1.042)	0.100	1.060 (0.828-1.357)	0.642	1.134 (0.85-1.513)	0.392
Liver disease	1.037 (0.932-1.154)	0.503	1.054 (0.928-1.196)	0.422	1.010 (0.888-1.148)	0.884	1.016 (0.874-1.181)	0.839
Sleep apnea	0.927 (0.836-1.027	0.145	0.921 (0.810-1.047)	0.210	1.079 (0.956-1.217)	0.217	1.073 (0.927-1.242)	0.348
Peptic ulcer	1.233 (1.106-1.375)	<0.001	1.149 (1.009-1.310)	0.037	1.132 (0.985-1.302)	0.081	1.118 (0.95-1.317)	0.180
Gout	1.011 (0.921-1.111	0.816	1.002 (0.898-1.119)	0.965	0.992 (0.887-1.109)	0.883	0.973 (0.854-1.109)	0.685
Prescribed drugs								
ACEI	1.171 (1.077-1.273)	<0.001	1.170 (1.058-1.293)	0.002	1.109 (1.002-1.227)	0.045	1.082 (0.958-1.222)	0.204
ARB	0.893 (0.822-0.971)	0.007	0.846 (0.766-0.934)	<0.001	1.055 (0.958-1.162)	0.275	1.016 (0.906-1.139)	0.786
BB	0.875 (0.808-0.948)	0.011	0.852 (0.776-0.937)	<0.001	1.103 (1.003-1.214)	0.044	1.100 (0.982-1.231)	0.099
CCB	0.812 (0.742-0.889)	<0.001	0.832 (0.748-0.926)	<0.001	0.999 (0.892-1.118)	0.980	0.975 (0.854-1.112)	0.704
Diuretics	1.372 (1.259-1.495)	<0.001	1.358 (1.229-1.501)	<0.001	0.916 (0.830-1.011)	0.082	0.856 (0.764-0.96)	0.008
Alpha-blocker	0.924 (0.836-1.022)	0.125	0.928 (0.824-1.045)	0.220	1.112 (0.990-1.249)	0.074	1.173 (1.023-1.345)	0.022
Statin	1.098 (0.952-1.267)	0.200	1.112 (0.941-1.315)	0.212	1.099 (0.942-1.282)	0.230	1.039 (0.868-1.242)	0.679
Fibrate drugs	1.095 (0.822-1.459)	0.536	1.018 (0.714-1.451)	0.923	0.919 (0.669-1.261)	0.599	0.840 (0.568-1.242)	0.382
Antiplatelet drugs	1.224 (1.085-1.381)	0.001	1.058 (0.961-1.165)	0.249	1.114 (1.010-1.228)	0.031	1.092 (0.973-1.225)	0.135
OAD	1.106 (1.020-1.200)	0.015	1.135 (0.986-1.307)	0.077	1.001 (0.862-1.162)	0.993	0.996 (0.839-1.183)	0.966

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CCB, calcium channel blockers; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OAD, oral anti-diabetic agent; VHD, valvular heart disease; PAD, peripheral artery disease; CAD, coronary artery disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

Table 4. Subgroup analysis for all-cause mortality in patients with aortic aneurysms and chronic obstructive pulmonary disease

	COPD			
	No matching		PS-matching	
Variable	HR	p	HR	p
COPD	1.104 (1.022-1.192)	0.012	1.118 (1.028-1.217)	0.009
Age group (yr)				
<70	1.161 (0.933-1.444)	0.181	1.184 (0.926-1.514)	0.179
≥70	1.103 (1.016-1.198)	0.020	1.117 (1.021-1.223)	0.016
Aortic aneurysm site				
TAA	1.205 (1.042-1.392)	0.012	1.262 (1.075-1.482)	0.004
AAA	1.048 (0.952-1.154)	0.340	1.055 (0.949-1.173)	0.318
TAAA	1.074 (0.775-1.488)	0.670	0.986 (0.687-1.414)	0.939
Comorbidities				
Diabetes (Yes)	0.911 (0.711-1.166)	0.458	0.826 (0.624-1.093)	0.181
Diabetes (No)	1.137 (1.048-1.234)	0.002	1.164 (1.064-1.272)	<0.001
Hypertension (Yes)	1.103 (1.020-1.193)	0.014	1.111 (1.019-1.211)	0.017
Hypertension (No)	1.467 (0.923-2.331)	0.105	1.173 (0.710-1.939)	0.532
Dyslipidemia (Yes)	1.100 (0.949-1.275)	0.206	1.141 (0.969-1.344)	0.113
Dyslipidemia (No)	1.105 (1.009-1.210)	0.031	1.116 (1.011-1.233)	0.030
Atrial fibrillation (Yes)	1.141 (0.900-1.446)	0.276	1.182 (0.902-1.548)	0.226
Atrial fibrillation (No)	1.099 (1.012- 1.193)	0.024	1.111 (1.016-1.216)	0.022
Stroke (Yes)	1.085 (0.954-1.234)	0.212	1.089 (0.942-1.259)	0.248
Stroke (No)	1.118 (1.014- 1.231)	0.025	1.140 (1.026-1.267)	0.015
CKD (Yes)	1.021 (0.869-1.199)	0.805	0.998 (0.834-1.194)	0.982
CKD (No)	1.131 (1.036-1.235)	0.006	1.153 (1.046-1.270)	0.004
Prescribed drugs				
ACEI (Yes)	1.199 (1.032-1.393)	0.018	1.198 (1.017-1.412)	0.030
ACEI (No)	1.068 (0.976-1.169)	0.151	1.087 (0.984-1.200)	0.099
BB (Yes)	1.130 (1.015-1.259)	0.025	1.167 (1.030-1.323)	0.015
BB (No)	1.080 (0.965-1.207)	0.179	1.080 (0.961-1.214)	0.194
CCB (Yes)	1.133 (1.034-1.241)	0.007	1.141 (1.032-1.261)	0.009
CCB (No)	1.005 (0.868-1.165)	0.945	1.034 (0.879-1.217)	0.684
Statin (Yes)	1.114 (0.904-1.373)	0.313	1.140 (0.904-1.438)	0.2681
Statin (No)	1.103 (1.015-1.199)	0.021	1.117 (1.019-1.223)	0.018
Antiplatelet drugs (Yes)	1.080 (0.971-1.202)	0.156	1.082 (0.960-1.219)	0.196
Antiplatelet drugs (No)	1.132 (1.012-1.267)	0.029	1.163 (1.030-1.312)	0.015
Operation type				
Open repair (Yes)	1.069 (0.855-1.338)	0.558	1.009 (0.830-1.226)	0.930

Endovascular repair (Yes)	0.911 (0.705-1.179)	0.479	1.029 (0.793-1.334)	0.832

ACEI, angiotensin-converting enzyme inhibitors; BB, beta-blockers; CCB, calcium channel blockers; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

Figure Legends

Figure 1. Study flow diagram

Figure 2. Cumulative risk of all-cause mortality between the COPD and non-COPD patients

(A) Operation and TAA, (B) operation and AAA, (C) operation and TAAA, (D) non-operation and TAA, (E) non-operation and AAA, and (F) non-operation and TAAA. *Abbreviations:* AAA, abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm.

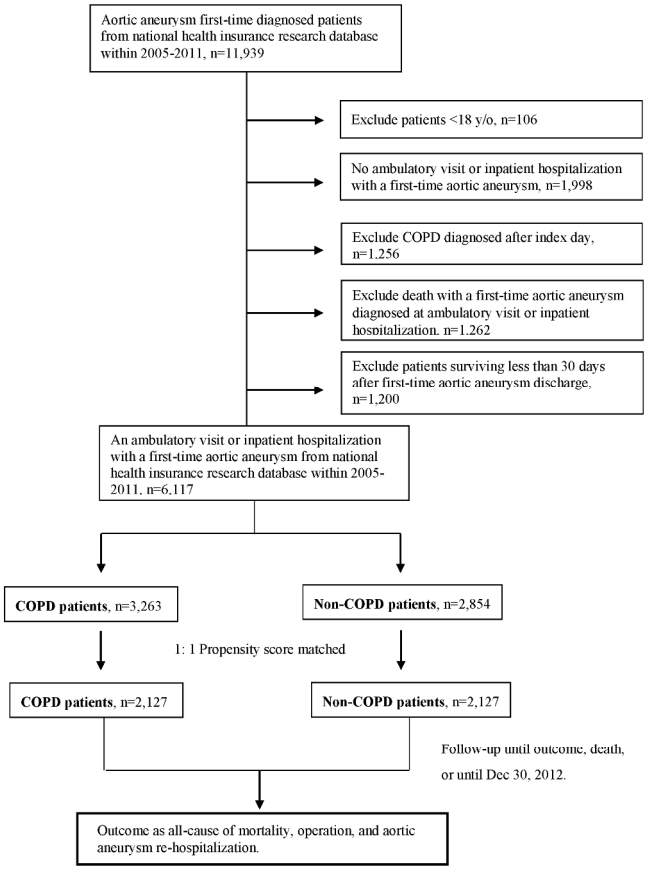
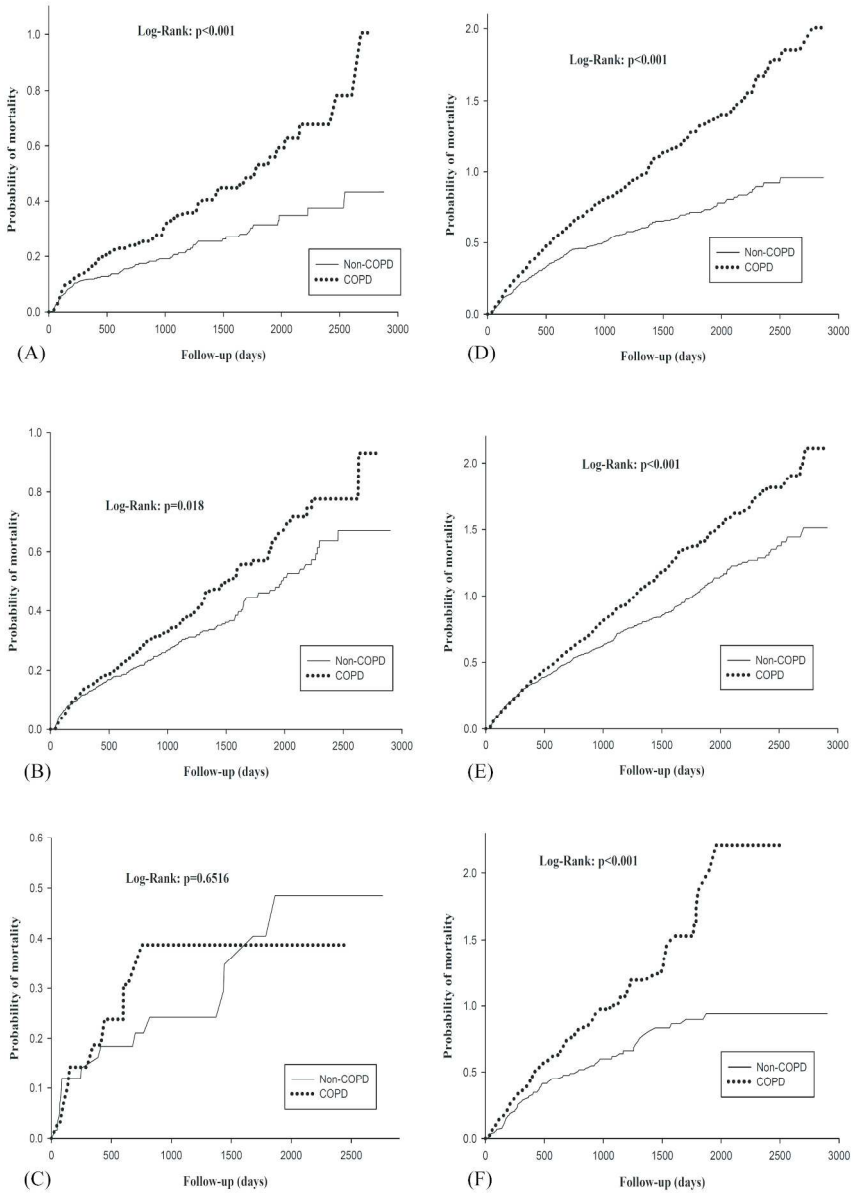


Fig 1

210x297mm (300 x 300 DPI)



Cumulative risk of mortality between the COPD and non-COPD groups
(A) Operation and TAA, (B) operation and AAA, (C) operation and TAAA, (D) non-operation and TAA, (E) non-operation and AAA, and (F) non-operation and TAAA. Abbreviations: AAA, abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm.

206x288mm (300 x 300 DPI)

Performing a 1:1 COPD-Not COPD Match on Propensity Score

Propensity Scores

We use the SAS software to perform multivariate logistic regression with the LOGISTIC procedure. PROC LOGISTIC will calculate and save the predicted probability of the dependent variable (included age, demographic characteristics, comorbidities, and co-medications), the propensity score, for each observation in the database. This single score (between 0 and 1) then represents the relationship between multiple characteristics and the dependent variable as a single characteristic. The distribution of predicted probability are showed in figure 1.

SAS code for multivariate logistic regression

```
/* ********************************** */
/* Perform the Logistic Regression */
/* Calculate and save propensity score */
/* Propensity score name = PROB */
/* Output file = psm.psmscore */

/* ********************************** */
PROC LOGISTIC DATA = db.case_ctrl_nomix descend;
MODEL  case=
age_gp sex urban_2 income smokerate diseasetype  cad gi htn diabete lipid stroke crf af
sleep cancer thyroid vhd gout liver  pad chf acei arb ccb beta diu alpha stat firb  odm
anti;
OUTPUT OUT=db.psmscore_nomix prob=prob ;
RUN;
```

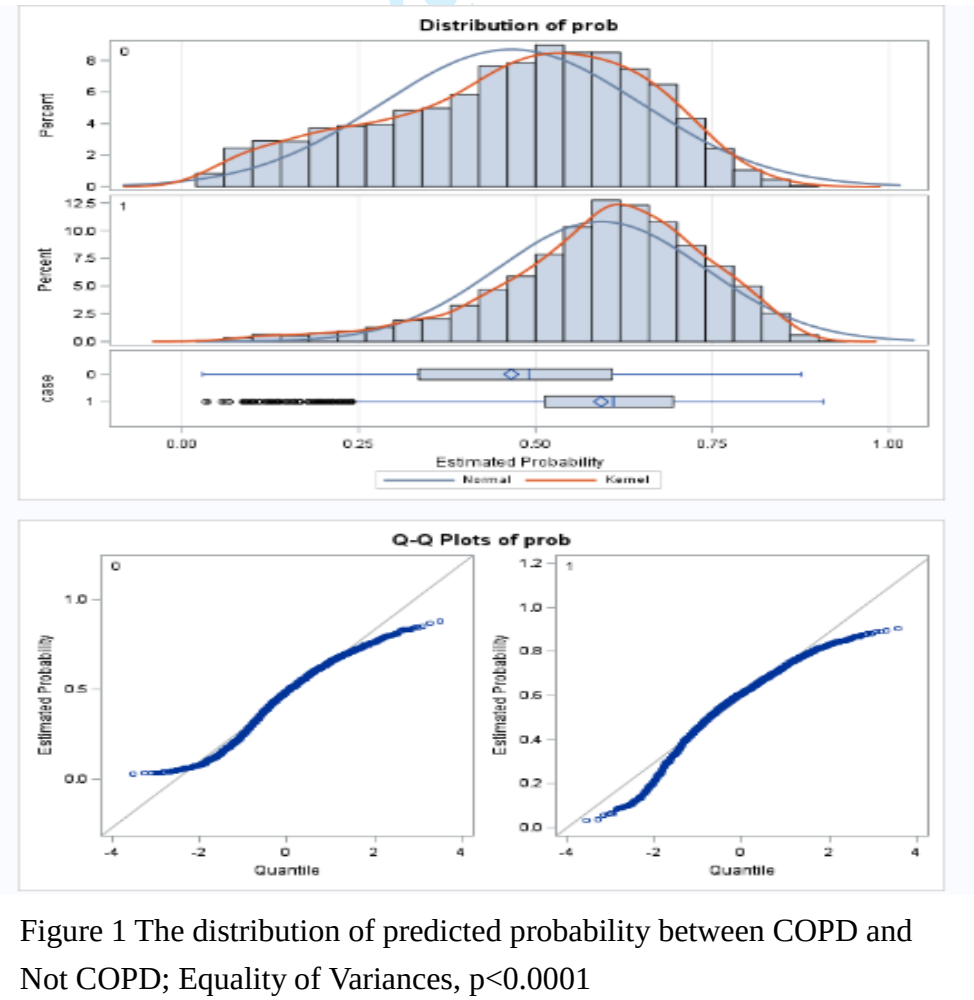


Figure 1 The distribution of predicted probability between COPD and Not COPD; Equality of Variances, p<0.0001

The 1:1 Case-Control Matching Macro

The matching macro presented in our study is using a macro previously presented by Parsons LS (2004) in appendix 1. [1] The procedure of 1:1 Case-Control Matching in SAS:

Step A: The macro creates separate files for the cases and controls.

Step B: Next, it performs the initial 8 ® 1 Digit Match.

Step C: It then outputs a file of the matched pairs. This file contains the field to link the matched pairs (MATCH_1).

Step D: Finally, it outputs a file of un-matched controls. This will be the pool from which the matches are made in the next iteration.

The distribution of predicted probability between COPD and Not COPD after 1:1 PS matching are showed in figure 2. The results of performing a 1:1 COPD and Not COPD match on the our data are showed in table 1.

References

[1]. Parsons LS (2004) Performing a 1:N Case-Control Match on Propensity Score. Proceedings of the 29th SAS Users Group International Conference. Montréal, Canada.

SAS code for 1:1 Case-Control Matching Macro

```
%include "E:\HV\2015_hormone replacement and af\programe\ PSM_macro_12182012.sas";
%OneToManyMTCH (
db, /* Library Name */
psmscore_nomix, /* Data set of all patients */
case, /* Dependent variable that indicates Case or Control */
      /* Code 1 for Cases, 0 for Controls */
id, /* Patient ID */
matches_nomix, /* Output data set of matched pairs */
1); /* Number of controls to match to each case */
;
```

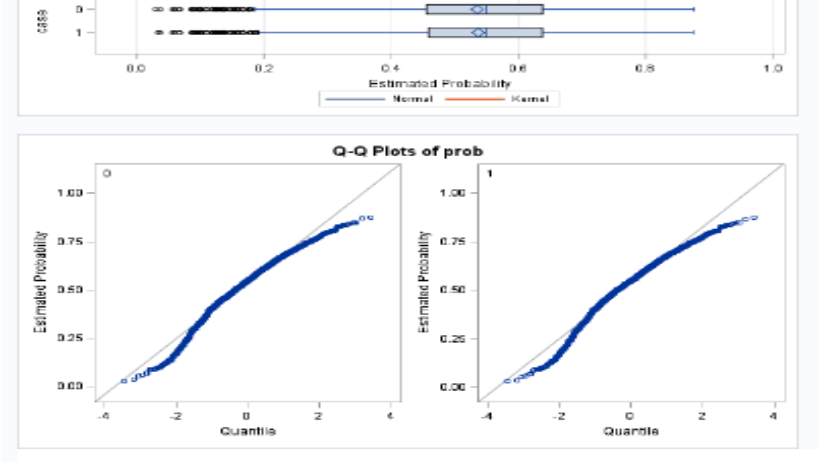


Figure 2 The distribution of predicted probability between COPD and Not COPD after PS matching; Equality of Variances, p=0.8410

Table 1. Characteristics of patients with aortic aneurysms in Taiwan

Variable	No-COPD (n=2854) No	%	COPD (n=3263) No	%	p	PS-matching No-COPD (n=2127) No	%	PS-matching COPD (n=2127)	p
Age group (yr)					<0.001				0.436
<50	273	(9.6)	61	(1.9)		64	(3.0)	61 (2.9)	
50-60	356	(12.5)	113	(3.5)		134	(6.4)	112 (5.3)	
60-70	508	(17.8)	388	(11.9)		327	(15.4)	354 (16.6)	
70-80	932	(32.6)	1183	(36.2)		837	(39.4)	853(40.1)	
>80	785	(27.5)	1515	(46.5)		763	(35.9)	747 (35.1)	
Gender					<0.001				0.971
Female	745	(26.1)	631	(19.3)		509	(23.9)	508 (23.9)	
Male	2109	(73.9)	2632	(80.7)		1618	(76.1)	1648 (76.1)	
Rubanicity					<0.001				0.733
Urban	724	(25.4)	1011	(31.0)		592	(27.8)	602 (28.3)	
Rural	2130	(74.6)	2252	(69.0)		1535	(72.2)	1525 (71.7)	
Income (NT)					<0.001				0.831
Low (<24,000)	2564	(89.8)	3136	(96.1)		2002	(94.1)	2011 (94.6)	
Middle (24,000-42,000)	149	(5.2)	74	(2.3)		71	(3.3)	65 (3.1)	
High (>42,000)	141	(5.0)	53	(1.6)		54	(2.5)	51 (2.4)	
Aortic aneurysm site					<0.001				0.918
TAA	965	(33.8)	1018	(31.2)		664	(31.2)	662 (31.1)	
AAA	1689	(59.2)	2089	(64.0)		1355	(63.7)	1351 (63.5)	
TAAA	200	(7.0)	156	(4.8)		108	(5.1)	114 (5.4)	
Operation	1181	(41.4)	1018	(31.2)	<0.001	823	(38.7)	753 (35.4)	0.026
Open repair	689	(58.3)	455	(44.7)		425	(51.6)	340 (45.2)	
Endovascular repair	492	(41.7)	563	(55.3)		399	(48.4)	413 (54.7)	
Smoking rate	26.3 (±13.4)		28.6 (±12.3)		<0.001	27.0 (±13.1)		27.0 (±13.1)	0.921
Co-morbidities									
Diabetes	414	(14.5)	450	(13.8)	0.423	310	(14.6)	307 (14.4)	0.896
Hypertension	2766	(96.9)	3138	(96.2)	0.112	2055	(96.6)	2051 (96.4)	0.738
Dyslipidemia	944	(33.1)	1032	(31.6)	0.227	727	(34.2)	725 (34.1)	0.948
CHF	561	(19.7)	1019	(31.2)	<0.001	488	(22.9)	482 (22.7)	0.826
Atrial fibrillation	230	(8.1)	384	(11.8)	<0.001	196	(9.2)	189 (8.9)	0.708
VHD	594	(20.8)	556	(17.0)	<0.001	377	(17.7)	368 (17.3)	0.717
PAD	152	(5.3)	222	(6.8)	0.016	128	(6.0)	139 (6.5)	0.487
CAD	1135	(39.8)	1685	(51.6)	<0.001	965	(45.4)	974 (45.8)	0.782
Stroke	736	(25.8)	1127	(34.5)	<0.001	642	(30.2)	646 (30.4)	0.894
Malignance	479	(16.8)	645	(19.8)	0.003	402	(18.9)	407 (19.6)	0.560
CKD	453	(15.9)	597	(18.7)	0.012	374	(17.6)	378 (17.8)	0.872
Thyroid disease	87	(3.1)	97	(3.0)	0.863	59	(2.8)	64 (3.0)	0.647
Liver disease	343	(12.0)	441	(13.5)	0.081	267	(12.6)	254 (11.9)	0.543
Sleep apenea	317	(11.1)	533	(16.3)	<0.001	271	(12.7)	268 (12.6)	0.890
Peptic ulcer disease	257	(9.0)	361	(11.1)	0.007	215	(10.1)	218 (10.3)	0.879
Gout	520	(18.2)	628	(19.5)	0.305	414	(19.5)	411 (19.3)	0.974
Prescribed Drugs									
ACEI	691	(24.2)	857	(26.3)	0.066	521	(24.5)	507 (23.8)	0.616
ARB	948	(33.2)	1058	(32.4)	0.510	695	(32.7)	679 (31.9)	0.600
BB	1737	(60.9)	1583	(48.5)	<0.001	1174	(55.2)	1178 (55.4)	0.902
CCB	2187	(76.6)	2419	(74.13)	0.024	1607	(75.4)	1616 (76.7)	0.747
Diuretics	1874	(65.7)	2158	(66.1)	0.697	1371	(64.5)	1388 (65.3)	0.585
Alpha-blocker	457	(16.0)	541	(16.6)	0.549	344	(16.2)	346 (16.2)	0.934
Statin	480	(16.8)	535	(16.4)	0.658	373	(17.5)	378 (17.8)	0.841
Fibrate drugs	68	(2.4)	61	(1.9)	0.163	41	(1.9)	42 (1.9)	0.912
Antiplatelet drugs	1349	(47.3)	1742	(53.4)	<0.001	1083	(50.9)	1084 (50.9)	0.976
OAD	236	(8.3)	293	(8.9)	0.324	192	(9.0)	186 (8.7)	0.747

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CCB, calcium channel blockers; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OAD, oral Anti-diabetic agent; VHD, valvular heart disease; PAD, peripheral artery disease; CAD, coronary artery disease; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; TAAA, thoracoabdominal aneurysm

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10-12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NP

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.