Chronic Obstructive Pulmonary Disease is Associated with an Increased Risk of Peripheral Arterial Disease

Te-Chun Shen[1,2], Wei Chen[3,4], Cheng-Li Lin[5,6], Kuo-Yang Huang[1], Chia-Hung Chen[1,4], Chih-Yen Tu[1], Te-Chun Hsia[1,4], Chuen-Ming Shih[1,4], Wu-Huei Hsu[1], and Yen-Jung Chang[7]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital and China Medical University, Taichung, Taiwan;
[2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chu Shang Show Chwan Hospital, Nantou, Taiwan;
[3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan;
[4]Department of Respiratory Therapy, [5]Institute of Public Health, College of Public Health, China Medical University, Taichung, Taiwan;
[6]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan;
[7]Department of Health Promotion and Health Education, National Taiwan Normal University, Taipei, Taiwan

Abstract

Chronic obstructive pulmonary disease (COPD), peripheral arterial disease (PAD) and ischemic heart disease are considered to be a smoking-related triad. However, only a few studies investigated the relationship between COPD and PAD using limited study sample. We aimed to examine the risk of PAD among patients with COPD using a nationwide cohort database in Taiwan. We conducted a retrospective cohort study using data from the National Health Insurance system of Taiwan. The COPD cohort included 361,023 patients who were newly diagnosed and recruited between 1998 and 2008. Each patient with COPD was randomly frequency-matched with two participants without COPD on age, sex, and the year of index date. The newly diagnosis of PAD was followed up until the end of 2010. The relative risks of PAD were estimated using Cox proportional hazard models after adjusting for age, sex, index year and comorbidities. The overall incidence rate of PAD was 2.34–fold greater in the COPD cohort than in the non-COPD cohort (3.71 vs. 1.58 per 1000 person-years). Further analyses indicated that the risk of PAD was higher in males, individuals younger than 50 years, and without comorbidity among the subgroups. This nationwide population-based study indicates that the incidence of PAD is significantly higher in patients with COPD than in those without COPD and the hazard ratio was especially high in younger patients. Therefore, regular examination for PAD in patients with COPD may be considered. (J Intern Med Taiwan 2014; 25: 272-280)

Key Words: Peripheral arterial disease (PAD); Chronic obstructive pulmonary disease (COPD); Epidemiology

Reprint requests and correspondence：Dr. Yen-Jung Chang
Address：Department of Health Promotion and Health Education, National Taiwan Normal University, Taipei, Taiwan, No. 162, Heping East Road Section 1, Taipei, Taiwan

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1] It is the 4th leading cause of death worldwide, with reported prevalence rates between 5% and 13%.[2-5] Among the possible factors that influence the disease, cigarette smoking has the greatest impact on the development of COPD.[6, 7] Several studies have proposed mechanisms for the pathogenesis of smoking-induced COPD, including deacetylases and NF-kappaB in redox regulation,[8] decreased airway expression of vascular endothelial growth factor,[9] and modulation of epithelial expression of toll-like receptor 4 (TLR4).[10] In addition, the harmful effects of smoking are not limited to the lungs; it damages the cardiovascular system. This is a major cormorbidity that must be managed in patients with COPD.[11-13] Recent studies have produced further evidence that COPD is an independent risk factor for cardiovascular diseases.[11, 14-16] Consequently, the relationship between COPD and peripheral arterial disease (PAD) needs to be further investigated.

PAD involves an atherosclerotic process caused by blockages of arteries that provide blood flow to the lower limbs.[17] The prevalence of PAD in general populations ranges widely, from 3% to 20%, depending on the characteristics of the various populations.[18-20] Previous studies also suggest that the prevalence of PAD in patients with COPD also ranges widely due to varying numbers of additional cardiovascular risk factors in patients with COPD.[21-23] In a previous report, conducted in a community hospital, Lin et al. found that the prevalence of asymptomatic PAD in patients with COPD is 8.4%.[24] Nevertheless, additional studies using nationally representative samples are required. Taiwan's National Health Insurance (NHI) database is a nationwide, large-scale cohort dataset, which provides reliable data and has been used for a variety of studies over the course of many years.[25-27]

In the present study, we aim to determine whether COPD is associated with an increased risk of PAD using this Taiwanese NHI dataset. To the best of our knowledge, this is the first nationwide population-based study evaluating the relationship between COPD and the incidence of PAD.

Materials and methods

Data source

Taiwan has launched a single-payer National Health Insurance (NHI) program on March 1, 1995 and the coverage rate of the NHI is approximately 99% of total population of 23.74 million. The National Health Research Insurance (NHRI), in cooperation with the National Health Insurance Bureau (NHIB), has established a National Health Insurance Research Database (NHIRD). The NHIB has established a uniform system to control the quality of medical services and coding. The NHRI, which maintains the annual claims data of the NHIRD, scrambled the identification data to protect the privacy of its beneficiaries before releasing the data for research use (http://nhird.nhri.org.tw/en/index.htm). This study was exempted from full review by the institutional Research Ethic Committee (CMU-REC-101-012).

Study population

Patients with COPD (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes 491, 492, and 496) were identified from the dataset. Patients aged 20 years and more with an initial COPD diagnosis between 1998 and 2008 were recruited. The index date was defined as the date for COPD diagnosis. Subjects who had been diagnosed with PAD (ICD-9-CM code 443.9, 444.21, 444.22 and 444.89) before index date were excluded. A non-COPD comparison cohort

was randomly selected from all NHI beneficiaries aged 20 years and more and was matched with the COPD cohort at a 2:1 ratio based on age (every 5 years span), sex, and the year of COPD diagnosis. The same exclusion criteria were also applied to non-COPD subjects.

Primary outcome and comorbidities

The follow-up duration starts from the index date to the occurrence of PAD diagnosis, or to the time the subjects was lost of follow-up, due to death or withdrawal from NHI, or until the end of 2010. Baseline comorbidities including hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (CAD) (ICD-9-CM codes 410–414), cerebrovascular disease (CVA) (ICD-9-CM codes 430–438), and chronic kidney disease (CKD) (ICD-9-CM codes 585) were identified according to the diagnosis records prior to the index date. In order to evaluate COPD severity to the risk of PAD, we defined patients in the COPD cohort who were hospitalized registered with any COPD codes as an inpatient admission.

Statistical analysis

Demographic and clinical characteristics of COPD patients and non-COPD comparison controls were compared using Chi-square test. The differences in continuous variables were evaluated using unpaired Student's t test. The incidence densities were calculated for both cohorts, and the Poisson regression analysis was used to estimate incidence rate ratio (IRR) of the COPD cohort to the non-COPD cohort with a 95% confidence interval (CI). Multivariate Cox proportional hazard regression was used to assess the risk of PAD associated with COPD, the hazard ratios (HRs) are presented with 95% confidence intervals, with the adjustment for demographic covariates. PAD-free proportions were compared using the Kaplan-Meier method, and the difference between two cohorts was compared using the log-rank test. All statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC). A two-tailed probability was considered statistically significant at p-value < 0.05.

Results

Table 1 compares the demographics and comorbidities between COPD cohort and non-COPD cohort. Of the study subjects, 72.1% were male, with a predominance (74.7%) of elderly patients. The mean age of the COPD cohort was 69.9 years (SD=11.7). Comorbidities were more prevalent in the COPD cohort. The incidence and adjusted HRs of PAD are shown in Table 2. The overall incidence of PAD was 2.34–fold greater in the COPD cohort than in the non-COPD cohort (3.71 vs. 1.58 per 1000 person-years), with an adjusted HRs of 1.48 (95%

Table 1. Demographic characteristics and baseline comorbidities in patients with and without COPD

Variable	COPD		p-value
	No	Yes	
	N =722046	N =361023	
Sex	n (%)	n (%)	
Female	201244 (27.9)	100622 (27.9)	0.99
Male	520802 (72.1)	260401 (72.1)	
Age stratified			
< 50	53640 (7.43)	26820 (7.43)	0.99
50–64	128802 (17.8)	64401 (17.8)	
≥ 65	539604 (74.7)	269802 (74.7)	
Age, mean(SD)#	68.9 (11.7)	69.9 (11.7)	<0.0001
Comorbidity			
Hypertension	253738 (35.1)	217324 (60.2)	<0.0001
Diabetes	129770 (18.0)	119254 (33.0)	<0.0001
Hyperlipidemia	49483 (6.85)	46028 (12.8)	<0.0001
CAD	116114 (16.1)	139396 (38.6)	<0.0001
CVA	125279 (17.4)	128991 (35.7)	<0.0001
CKD	25567 (3.5)	30460 (8.4)	<0.0001

Chi-Square Test #: unpaired Student's t test.

Table 2. Incidence and hazard ratio of PAD, stratified by sex and age, comparing COPD with non-COPD cohorts

Variables (smoking rate[Π])	COPD						IRR [&] (95% CI)	Adjusted HRs[†] (95% CI)
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]		
All	7512	4743706	1.58	6032	1627351	3.71	2.34 (2.31,2.37)***	1.48 (1.43, 1.54)***
Sex								
Female (4.1%)	2008	1384428	1.45	1580	504999	3.13	2.16 (2.11, 2.21)***	1.33 (1.24, 1.43)***
Male (35.0%)	5504	3359279	1.64	4452	1122352	3.97	2.42 (2.39, 2.46)***	1.54 (1.48, 1.61)***
Stratify age								
< 50 (25.0%)	42	413881	0.10	141	180937	0.78	7.67 (7.24, 8.14)***	2.48 (1.69, 3.65)***
50–64 (14.9%)	559	967527	0.58	917	368739	2.49	4.30 (5.18, 4.43)***	1.80 (1.61, 2.02)***
≥ 65 (11.0%)	6911	3362298	2.06	4974	1077675	4.62	2.25 (2.21, 2.28)***	1.43 (1.38, 1.49)***
Comorbidity[‡]								
No	681	2563815	0.27	310	342143	0.91	3.41 (3.33, 3.49)***	3.95 (3.45, 4.52)***
Yes	6831	2179891	3.13	5722	1285208	4.45	1.42 (1.40, 1.44)***	1.59 (1.53, 1.65)***

PY, person-years;
Rate[#], incidence rate, per 1,000 person-years;
IRR [&] , incidence rate ratio;
Adjusted HRs[†]: multivariable analysis including age, sex, and comorbidities;
Comorbidity[‡]: only to have one of comorbidities classified as the comorbidity group;
Smoking rate[Π]: current smoking rate of an official report in Taiwan in 2010
***p<0.001

CI = 1.43–1.54). Figure 1 displays that COPD cohort had significantly lower PAD-free rate than the non-COPD cohort (log-rank p <0.001). Sex-specific analysis showed that male had a greater incidence of PAD than female in both cohorts. Male patients with COPD had a 1.54–fold greater risk of developing PAD compared to male participants without COPD (95% CI = 1.48–1.61). Age-specific analysis showed that the incidence of PAD increased with age in both cohorts. Among the subgroup aged 50 or less, patients with COPD had a 2.48–fold greater risk of PAD than non-COPD cohort (95% CI = 1.69–3.65).

In patients without any comorbidity, the risk of PAD was 3.95–fold greater in the COPD cohort than in the non-COPD cohort (95% CI = 3.45–4.52). Comorbidity-specific analysis showed that the incidence of PAD was greater for those with comorbidities in both cohorts (Table 3). The data in Table 4 show that the risk of developing PAD increased from 1.12 (95% CI = 1.08–1.17) in patients presenting

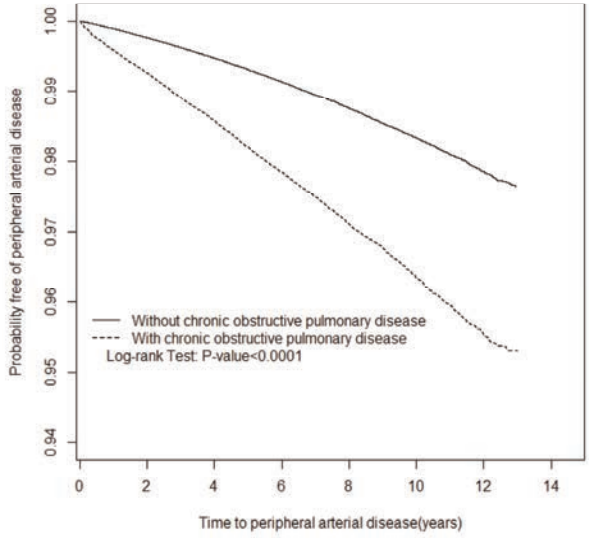

Figure 1. Probability free of PAD for patients with (dashed line) and without (solid line) COPD.

with 2 or fewer annual admissions to 6.68 (95% CI = 6.32–7.06) in the case of those exhibiting 3 and more annual admissions compared with those in the non-COPD cohort (trend test, p < 0.0001). Within 3

Table 3. Incidence and hazard ratio of PAD, stratified by the presence of baseline comorbidities, comparing COPD with non-COPD cohorts

	COPD							
	No			Yes				
Variables	Event	PY	Rate[#]	Event	PY	Rate[#]	IRR [&] (95% CI)	Adjusted HRs[†] (95% CI)
Hypertension								
No	2136	3091321	0.69	1221	626482	1.95	2.82 (2.77, 2.87)***	1.83 (1.70, 1.98)***
Yes	5376	1652385	3.25	4811	1000869	4.81	1.48 (1.45, 1.50)***	1.36 (1.30, 1.41)***
Diabetes								
No	3585	3943284	0.91	2902	1105583	2.62	2.89 (2.85, 2.93)***	1.84 (1.74, 1.93)***
Yes	3927	800243	4.91	3130	521769	6.00	1.22 (1.20, 1.25)***	1.18 (1.12, 1.24)***
Hyperlipidemia								
No	6117	4414476	1.39	4639	1381356	3.36	2.42 (2.39, 2.45)***	1.51 (1.45, 1.58)***
Yes	1395	329230	4.24	1393	245995	5.66	1.34 (1.29, 1.39)***	1.32 (1.22, 1.42)***
CAD								
No	4129	4006721	1.03	2400	968879	2.48	2.40 (2.37, 2.44)***	1.78 (1.69, 1.87)***
Yes	3383	736986	4.59	3632	658472	5.52	1.20 (1.17, 1.23)***	1.23 (1.17, 1.29)***
CVA								
No	4702	3971606	1.18	3112	1090285	2.85	2.41 (2.38, 2.45)***	1.54 (1.47, 1.62)***
Yes	2810	772100	3.64	2920	537066	5.44	1.49 (1.46, 1.53)***	1.38 (1.31, 1.46)***
CKD								
No	6589	4607641	1.43	5071	1513668	3.35	2.34 (2.31, 2.37)***	1.54 (1.48, 1.60)***
Yes	923	136065	6.78	961	113683	8.45	1.25 (1.19, 1.31)***	1.14 (1.04, 1.26)**

PY, person-years;
Rate[#], incidence rate, per 1,000 person-years;
IRR [&], incidence rate ratio;
Adjusted HRs[†]: multivariable analysis including age, sex, and comorbidities;
**p<0.01, ***p<0.001

Table 4. Risk of PAD by mean annual admissions for COPD patients compared with non- COPD subjects in Cox proportional hazards regression analysis

Mean annual admissions	Event n	PY	Rate[#]	IRR [&] (95% CI)	Adjusted HR[†] (95 % CI)
COPD					
Non- COPD	7512	4743706	1.58	1(Reference)	1(Reference)
≤2	4136	1532090	2.70	1.75(1.68, 1.82)***	1.12(1.08, 1.17)***
≥3	1896	95261	19.9	15.2(14.4, 5.99)***	6.68(6.32, 7.06)***
p for trend					<0.0001

PY, person-years;
Rate[#], incidence rate, per 1,000 person-years;
IRR [&], incidence rate ratio;
Adjusted HRs[†]: multivariable analysis including age, sex, and comorbidities;
***p<0.001

Table 5. The PAD risk by stratified follow-up years

	Non- COPD Cohort			COPD Cohort				
Follow time	Event	PY	Rate[#]	Event	PY	Rate[#]	IRR [&] (95% CI)	Adjusted HRs[†] (95% CI)
PAD								
≤ 3 years	2538	2023575	1.25	2984	801332	3.72	2.97 (2.93, 3.01)***	1.92 (1.81, 2.03)***
4–6 years	2405	1474034	1.63	1079	478093	2.26	2.19 (2.16, 2.23)***	1.34 (1.25, 1.43)***
7–9 years	1716	867638	1.98	914	248046	3.68	1.86 (1.83, 1.90)***	1.13 (1.04, 1.23)**
> 9 years	853	378460	2.25	425	99880	4.26	1.89 (1.83, 1.94)***	1.12 (0.99, 1.27)

PY, person-years;
Rate[#], incidence rate, per 1,000 person-years;
IRR [&], incidence rate ratio;
Adjusted HRs[†], multiple analysis including age, sex and comorbidities;
**p<0.01, ***p<0.001

years of follow-up, patients with COPD had a 1.92–fold higher risk of developing PAD than their counterparts (95% CI = 1.84–2.06) (Table 5).

Discussion

In evaluating the relationship between COPD and PAD, we found that the incidence of PAD in patients with COPD was higher than that in patients without COPD. In addition, our study showed that the risk of developing PAD increased as the number of COPD exacerbations that required hospitalizations increased. This result suggests that poor control of disease status is a key factor that affects PAD development in patients with COPD. Age-specific analyses indicated that adjusted HRs associated with PAD was highest in subjects younger than 50 years, although the PAD incidence increased with age. There are some possible explanations for the age distribution of PAD. First, young patients with COPD may truly have a shorter time course for the development of PAD. Second, older patients are more likely to have comorbid diseases in either COPD or non-COPD cohorts, and these may be risk factors for atherosclerotic events. Therefore, higher PAD incidence in aged patients although adjusted HRs progressively decreased with age.

There are several well-known comorbidities associated with PAD, including hypertension, diabetes, hyperlipidemia, CAD, CVA, and CKD. We found that they were all more prevalent in the COPD cohort with the following prevalence rates: hypertension (60.2%), CAD (38.6%), CVA (35.7%), diabetes (33.0%), hyperlipidemia (12.8%), and CKD (8.4%). In addition, we performed a comorbidity-specific analysis, which showed that the incidence of PAD was indeed greater than those with any comorbidity in both cohorts (adjusted HRs: 1.59, 95% CI = 1.53–1.65).

In this study, the most important potential confounding factor was tobacco smoking exposure. Although the NHI database does not contain personal smoking habits, we expect that there are more than 50% ex-smokers or current smokers in the COPD cohort based on previous studies.[28, 29] In a recent public health report from the Ministry of Health and Welfare of Taiwan, the current smoking rate in the general population is 19.8% (male is 35.0%, female is 4.1%, Table 2) (http://www.hpa.gov.tw/BHPNet/Web/HealthTopic/Topic.aspx?id=200712250024). This represents a reliable current smoking rate for the non-COPD cohort in our study. Because it is difficult to choose a good non-COPD cohort with a very high smoking rate, we combine COPD and smoking effects in our evaluation of increased

incidence of PAD.

PAD is a medical condition caused by blockage of the arteries that provide blood flow to the limbs. In PAD, the arteries become blocked by cholesterol plaque caused by athrosclerosis, which is a common medical problem worldwide. PAD and certain cardiovascular diseases, such as heart attack and stroke, may share the same risk factors including smoking, high blood pressure, diabetes, hyperlipidemia, and advanced age. Because PAD-related blockages in the arteries limit blood flow to the legs, patients with PAD have low blood pressures in the ankles. The ratio of the leg pressure to the arm pressure (ankle blood pressure divided by arm blood pressure) is called ankle brachial index (ABI). The ABI test can be used as a screening tool to diagnose PAD in patients without symptoms who have risk factors for atherosclerosis.[30] Lower ABI categories (<0.9) were associated with increased risk of cardiovascular events and death. The risk of mortality was similar in symptomatic and asymptomatic patients with PAD, and was significantly higher than in those without PAD.[31]

The underlying mechanism of PAD could be endothelial dysfunction due to longstanding vascular inflammation. Endothelial function has been found to be impaired in patients with COPD, and the impairment is proportional to the severity of bronchial obstruction.[32] Some studies indicated that patients with COPD and PAD tended to be thin and had less visceral obesity. The greatest mortality rates are observed in this group of patients who are underweight. This phenomenon has been referred to as the "obesity paradox".[32-35] The prognosis for people with both diseases is poor and patients experience a reduced quality of life.

The strength of this study is in providing a nationwide population-based longitudinal cohort study of Asian people with COPD that evaluates their risks of developing PAD. There are several limitations to be considered when interpreting the present findings. First, the diagnosis selected from the ICD-9 code depends on the performance of clinical physicians; we are unable to check the validity. Second, NHRID does not provide detailed information on diet preference, physical activity, and family history, although these are potential confounding factors for this study. Third, information on medication was not available; thus, we were unable to observe whether pharmaceutical uses of bronchodilators and glucocorticoids were associated with the risk of PAD for patients with COPD. Moreover, evidence derived from a retrospective cohort study is insufficient to establish a causal relationship between COPD and PAD. In spite of our meticulous study design and the adjustment for certain confounding factors, the possible omission of other unknown confounders should be taken into account. In addition, relevant clinical variables, such as serum laboratory data, body mass index, ankle brachial index, pulmonary function tests, and imaging results were unavailable for patients in our study.

Conclusion

This nationwide population-based study indicates that the incidence of PAD is significantly higher in patients with COPD than in those without COPD and the HRs was especially high in younger patients. Therefore, regular examination for PAD in patients with COPD may be considered.

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慢性阻塞性肺病伴隨著增加周邊動脈疾病的風險

沈德群[1,2] 陳煒[3,4] 林橙莉[5,6] 黃國揚[1] 陳家弘[1,4]
涂智彥[1] 夏德椿[1,4] 施純明[1,4] 徐武輝[1] 張晏蓉[7]

[1]中國醫藥大學暨中國醫藥大學附設醫院 內科部胸腔暨重症系
[2]竹山秀傳醫院 胸腔內科
[3]嘉義基督教醫院 胸腔內科
中國醫藥大學 [4]呼吸治療學系 [5]公共衛生研究所
[6]中國醫藥大學附設醫院健康資料管理辦公室
[7]臺灣師範大學健康促進與衛生教育學系

摘 要

慢性阻塞性肺病、周邊動脈疾病與缺血性心臟病被並稱為抽菸的三合症，然而只有少數小型的研究探討過慢性阻塞性肺病與周邊動脈疾病之間的關係，我們嘗試使用台灣健保資料庫來檢驗慢性阻塞性肺病的病人之後罹患周邊動脈疾病的風險。我們利用台灣的健保資料庫來設計一個回溯性的世代研究，慢性阻塞性肺病群組包含了361,023位自1998至2008被新診斷為慢性阻塞性肺病的病人，每一位病人根據年齡、性別與疾病診斷時間隨機分配兩位對照個案作為對照群組，我們持續追蹤兩組是否有新診斷的周邊動脈疾病至2010年底，並評估發生周邊動脈疾病的相對風險。慢性阻塞性肺病群組比對照組發生周邊動脈疾病的比例整體高出2.34倍(每千人年為3.71比1.58)，深入分析發現發生周邊動脈疾病的風險在男性較女性、年紀低於50歲較年紀大於50歲與沒有併發症較有併發症者相對要來得高。此一研究顯示患有慢性阻塞性肺病的病人比對照組有較高的風險罹患周邊動脈疾病，而且年紀愈輕的患者相對風險更高，因此，在患有慢性阻塞性肺病的病人當中篩檢是否罹患周邊動脈疾病，也許是個可以推行的方案。