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Increased Risk of Dementia in Patients With Chronic Obstructive Pulmonary Disease

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Abstract: Neurodegenerative disease in patients with chronic obstructive pulmonary disease (COPD) was observed. We aim to clarify the risk of dementia in patients with COPD.

The study used claims data from Taiwan's National Health Insurance Research Database. Subjects were those who received a discharge diagnosis of COPD between January 1, 2002 and December 31, 2011. Only the first hospitalization was enrolled, and the index date was the first day of admission. Patients younger than 40 years or those with a history of Alzheimer disease (AD) or Parkinson disease (PD) before the index date were excluded. The patients with COPD were then followed until receiving a diagnosis of AD or PD, death, or the end of the study. Control subjects were selected from hospitalized patients without a history of COPD, AD, or PD and were matched according to age (± 3 years), gender, and the year of admission at a 2:1 ratio. The comorbidities were measured from 1 year before the index date based on the ICD-9-CM codes. The study included 8640 patients with COPD and a mean age of 68.76 (± 10.74) years. The adjusted hazard ratio of developing dementia (AD or PD) was 1.74 (95% confidence interval = 1.55–1.96) in patients with COPD compared with patients without COPD after adjusting for age, gender, and comorbidities.

This nationwide cohort study demonstrates that the risk of dementia, including AD and PD, is significantly increased in patients with COPD compared with individuals in the general population.

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Abbreviations: AD = Alzheimer disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, IRR = incidence rate ratio, NHI = National Health Insurance, OR = odds ratio, PD = Parkinson disease.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease characterized by airflow restriction.¹ Many studies have showed that cognitive function is impaired in patients with COPD with or without hypoxemia.^{2,3} Cerebral disturbance is noted in patients with COPD and may be related to hypoxia in the brain.³

Dementia is a broad category of brain diseases. The most common type of dementia, Alzheimer disease (AD) and Parkinson disease (PD), is the second most common neurodegenerative disorder,⁴ after AD. Other types include vascular dementia, dementia with Lewy bodies, frontotemporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, Huntington Disease, and mixed dementia.

Cytokines and inflammatory may play an important role in promoting the degenerative processes involved in a wide variety of cognitive disorders, including AD and PD. In many diseases, inflammation is a marker of tissue damage, and may either occur after tissue damage in neurodegenerative diseases or serve as a marker of an immunological response.⁵ COPD is a systemic inflammatory disease, and inflammation and cytokines may contribute to neuron damage and result in neurodegenerative disorders. Patients with COPD may have a higher risk of becoming AD or PD compared with that found in the general population. There has been only 1 nationwide retrospective cohort study,⁶ which indicated that PD risk is increased in patients with COPD compared with those without COPD.

However, there has been no description in the literature of a relationship between COPD and dementia. We thereby aim to clarify the risk of developing AD or PD in patients with COPD using the nationwide database in Taiwan. Patients older than 40 years of age with COPD without previous history of AD or PD will be included in the study. Our study highlighted the important role of dementia in association with the patients with COPD in a wide range of conditions and irrespective of sex. Patients with PD or AD represent dementia in this study.

METHODS

Source of Database

Taiwan launched a single-payer National Health Insurance (NHI) program in March 1995. More than 99% of citizens are enrolled in the program. The NHI Research Database is a medical claims database that was established and is used for research purposes. There are patients' demographic characteristics, disease diagnoses, prescription records, and medical expenditures in the claim data. Approximately 99% of the total population in Taiwan is enrolled in the NHI Program.⁷ In this study, we retrieved our study sample from 1 million beneficiaries randomly sampled from all beneficiaries registered in 2000. All medical claims from January 1, 1997 to December 31, 2011 for those 1 million beneficiaries are available. Before the NHI Research Database released database to the researchers, the confidential data for individuals were scrambled and

encrypted, and informed consent forms were therefore waived by the Institutional Review Board.

Study Design

This is a retrospective cohort design in which the eligible study subjects were patients who received a discharge diagnosis of COPD (ICD-9-CM codes: 490–492, 496) during a hospitalization between January 1, 2002 and December 31, 2011. Only the first hospitalization was enrolled. Control subjects were selected from hospitalized patients without COPD, AD, or PD and were matched according to age (based on year of birth), gender, and the year of admission at a 2:1 ratio. All patients with COPD were then considered if the first admission for COPD occurred between January 1, 2002 and December 31, 2011. The first date of admission is the index date. Patients younger than 40 years and those with a history of PD (ICD-9-CM = 332) or AD (ICD-9-CM = 331) before the index date were excluded. Patients in the study cohort were then followed to the end of 2011 to investigate the incidence of AD or PD. Comorbidities were evaluated from 1 year before the index day according to ICD-9-CM codes in outpatient and inpatient departments.

Statistical Analysis

During the statistical analysis, we first described the demographic characteristics and comorbidities of the study patients. Student *t*-test was used to estimate the mean difference of the continuous variables, and Pearson Chi-square was applied to the categorical variables. The incidence rate of dementia (AD or PD) was evaluated as the number of the patients with COPD and dementia divided by the total person-years, yielding rates per 10,000 person-years of observation. The incidence rate ratios (IRRs) of dementia were estimated under Poisson regression. Cox proportional hazard regression model with

adjustment for potential confounders was used to assess the risk of dementia. The potential confounders included age, gender, urbanization, coronary artery disease, stroke, hyperlipidemia, hypertension, diabetes, and head injury. Subjects who did not present AD or PD before the end of study period (ie, December 31, 2011) were considered censored. We also performed Kaplan-Meier analysis to compare the cumulative incidence of dementia (AD or PD) in the patients with COPD and those without COPD. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Analysis Software (SAS) System, version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

The cohort comprised 8640 patients with COPD with first hospitalization records from 2002 to 2010. The mean age and corresponding standard deviation (SD) of the study population was 68.76 (± 10.74) years, and males were predominant (62.04%). More than 68% of patients were older than 65 years. Table 1 shows the distributions of demographic characteristics and comorbidities among the 8640 patients with COPD.

In this cohort, patients with COPD had a higher prevalence of coronary artery disease, stroke, hypertension, diabetes, and head injury. The incidence rate of dementia (AD or PD) (per 10,000 person-years) and adjusted hazard ratio (HR) between the patients with COPD and patients without COPD are present in Table 2. Patients with COPD had higher overall incidence rate of dementia than in the non-COPD group (152.89 vs 83.65 per 10,000 person-years), with an IRR of 1.83 (95% confidence interval [CI] = 1.63–2.05). The adjusted HR of dementia in patients with COPD is 1.74 (95% CI = 1.55–1.96) compared with patients without COPD after adjusting for age, gender,

TABLE 1. Demographic Characteristics and Comorbidities in Patients With and Without Chronic Obstructive Pulmonary Disease

	Non-COPD (N = 17,280)	COPD (N = 8640)	P-Value
Age, years (mean \pm SD)	68.76 \pm 10.74	68.76 \pm 10.74	0.9976
Age stratification (%)			
≤ 64	5463 (31.61)	2732 (31.62)	0.9983
65–74	6524 (37.75)	3259 (37.72)	
≥ 75	5293 (30.63)	2649 (30.66)	
Gender (%)			
Male	10,720 (62.04)	5360 (62.04)	1.0000
Female	6560 (37.96)	3280 (37.96)	
Urbanization*			
1 (highest)	4969 (28.76)	2168 (25.09)	<0.0001
2	5938 (34.36)	3647 (42.21)	
3	2178 (12.60)	860 (9.95)	
4 (lowest)	4195 (24.28)	1965 (22.74)	
Comorbidities			
Coronary artery disease	1703 (9.86)	1627 (18.83)	<0.0001
Stroke	1261 (7.30)	1414 (16.37)	<0.0001
Hyperlipidemia	2071 (11.98)	950 (11.00)	0.0193
Hypertension	6423 (37.17)	4095 (47.70)	<0.0001
Diabetes	2962 (17.14)	2043 (23.65)	<0.0001
Head injury	122 (0.71)	178 (2.06)	<0.0001

COPD = chronic obstructive pulmonary disease.

*The level of urbanization was categorized into four levels based on the population density of the subject's area of residence, where "1" was most urbanized and "4" was least urbanized.

TABLE 2. Incidence of Dementia in Patients With/Without Chronic Obstructive Pulmonary Disease

Characteristics	Non-COPD (N = 17,280)			COPD (N = 8640)			IRR (95% CI)	Adjusted HR (95% CI)
	Event	PY	Incidence Rate	Event	PY	Incidence Rate		
Alzheimer disease or Parkinson disease	706	84,398.17	83.65	522	34,141.80	152.89	1.83 (1.63–2.05)	1.74 (1.55–1.96)
Age stratification								
≤64	74	28,762.72	25.73	92	12,538.43	73.37	2.85 (2.10–3.87)	2.45 (1.78–3.37)
65–74	320	33,251.87	96.24	208	13,230.45	157.21	1.63 (1.37–1.95)	1.47 (1.23–1.76)
≥75	312	22,383.58	139.39	222	8372.92	265.14	1.90 (1.60–2.26)	1.82 (1.52–2.17)
Gender								
Male	358	51,729.31	69.21	280	20,890.35	134.03	1.94 (1.66–2.26)	1.88 (1.60–2.21)
Female	348	32,668.86	106.52	242	13,251.45	182.62	1.71 (1.46–2.02)	1.60 (1.35–1.90)
Comorbidities coronary artery disease								
Yes	95	7723.53	123.00	121	5996.62	142.48	1.64 (1.25–2.15)	1.58 (1.20–2.08)
No	611	76,674.63	79.69	401	28,145.18	201.78	1.79 (1.58–2.03)	1.76 (1.55–2.00)
Stroke								
Yes	99	5429.58	182.33	118	4528.71	260.56	1.43 (1.09–1.87)	1.47 (1.11–1.94)
No	607	78,968.58	76.87	404	29,613.08	136.43	1.77 (1.57–2.01)	1.79 (1.57–2.03)
Hyperlipidemia								
Yes	85	8465.34	100.41	69	3133.48	220.20	2.19 (1.60–3.01)	2.29 (1.64–3.19)
No	621	75,932.83	81.78	453	31,008.32	146.09	1.79 (1.58–2.02)	1.68 (1.48–1.90)
Hypertension								
Yes	342	28,707.93	119.13	277	14,683.87	188.64	1.58 (1.35–1.86)	1.57 (1.34–1.85)
No	364	55,690.24	65.36	245	19,457.93	125.91	1.93 (1.64–2.27)	1.92 (1.63–2.27)
Diabetes								
Yes	164	12,902.82	127.10	137	6906.88	198.35	1.56 (1.24–1.96)	1.57 (1.24–1.98)
No	542	71,495.35	75.81	385	27,234.92	141.36	1.86 (1.64–2.12)	1.79 (1.56–2.05)
Head injury								
Yes	5	515.32	97.03	19	607.65	312.68	3.22 (1.20–8.63)	4.28 (1.42–12.93)
No	701	83,882.85	83.57	503	33,534.15	150.00	1.79 (1.60–2.01)	1.72 (1.53–1.94)

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PY = per 10,000 person-years, IRR = incidence rate ratio.

coronary artery disease, stroke, hyperlipidemia, hypertension, diabetes, and head injury.

The incidence of dementia was higher in patients with COPD than in those without COPD, and the incidence rate of dementia increased with age in patients with and without COPD. Patients with COPD had a higher risk of dementia than patients without COPD among patients younger than 65 years, with an IRR of 2.85 (95% CI = 2.10–3.87) and an adjusted HR of 2.45 (95% CI = 1.78–3.37). Among subjects older than 75 years of age, patients with COPD had a higher risk of dementia than the patients without COPD, with an IRR of 1.90 (95% CI = 1.60–2.26) and an adjusted HR of 1.82 (95% CI = 1.52–2.17).

The incidence rate of dementia was higher in female patients with COPD than male patients with COPD (182.62 vs 134.03 per 10,000 person-years). The adjusted HR of dementia observed in male patients with COPD in comparison with male patients without COPD was 1.88 (95% CI = 1.60–2.21). The adjusted HR of dementia observed in female patients with COPD in comparison with female patients without COPD was 1.60 (95% CI = 1.35–1.90).

Table 3 shows the incidence of dementia stratified by age, gender, and medical conditions. The risk of dementia was significantly greater in male patients with COPD who were younger than 65 years of age, with IRR = 3.82 (95% CI = 2.55–5.71) and adjusted HR = 3.46 (95% CI = 2.27–5.25) compared

with patients without COPD who were younger than 65 years of age.

Among patients age 75 and older, the adjusted HR of dementia was 2.05 (95% CI = 1.53–2.75) in male patients with COPD and 1.76 (95% CI = 1.41–2.20) in female patients with COPD compared with patients without COPD. Among patients with comorbidities who were younger than 65 years of age, the adjusted HR of dementia was 2.19 (95% CI = 1.42–3.39) in patients with COPD compared with patients without COPD.

Figure 1 shows the cumulative incidence of dementia in patients with COPD and those without COPD. The incidence of dementia (log-rank test, *P* < 0.0001) was significantly different in patients with COPD than in those without COPD.

DISCUSSION

Study Strength

This is the first study to employ a nationwide, population-based, follow-up study design to explore the relationship between COPD and dementia. The overall incidence rate of dementia was 152.89 per 10,000 person-years and 74% higher in the patients with COPD than in the patients without COPD and an adjusted HR of 1.74 after adjusting for age, gender, and medical comorbidities. COPD cohort had a higher risk of developing dementia than non-COPD cohort.

TABLE 3. Incidence of Dementia Stratified by Sex, Age, and Comorbidity, With the Hazards Ratio for Patients With Chronic Obstructive Pulmonary Disease Compared With Those Without Chronic Obstructive Pulmonary Disease

Characteristics	Non-COPD (N = 17,280)			COPD (N = 8640)			IRR (95% CI)	Adjusted HR (95% CI)
	Event	PY	Incidence Rate	Event	PY	Incidence Rate		
Male								
≤64	38	19,480.84	19.51	62	8329.31	74.44	3.82 (2.55–5.71)	3.46 (2.27–5.25)
65–74	210	23,970.29	87.61	137	9430.56	145.27	1.66 (1.34–2.06)	1.52 (1.22–1.90)
≥75	110	8278.18	132.88	81	3130.48	258.75	1.95 (1.46–2.59)	2.05 (1.53–2.75)
Female								
≤64	36	9281.88	38.79	30	4209.12	71.27	1.84 (1.13–2.98)	1.50 (0.90–2.49)
65–74	110	9281.57	118.51	71	3799.89	186.85	1.58 (1.17–2.12)	1.36 (0.99–1.86)
≥75	202	14,105.40	143.21	141	5242.43	268.96	1.88 (1.51–2.33)	1.76 (1.41–2.20)
Comorbidities								
≤64	36	8892.28	40.49	57	5788.12	98.48	2.43 (1.60–3.69)	2.19 (1.42–3.39)
65–74	217	16,466.22	131.79	148	8063.12	183.55	1.39 (1.13–1.72)	1.28 (1.03–1.58)
≥75	194	12,126.27	159.98	159	5843.75	272.09	1.70 (1.38–2.10)	1.66 (1.34–2.07)

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PY = per 10,000 person-years, IRR = incidence rate ratio.

Association Between COPD and Dementia

A population-based study used self-administered questionnaire in Eastern Finland⁸ showed that COPD (HR 1.85, 95% CI 1.05–3.28), asthma (HR 1.88, 95% CI 0.77–4.63), and both pulmonary diseases combined (HR 1.94, 95% CI 1.16–3.27) increased the risk of cognitive impairment. We have found similar results in our study, and our diagnosis of COPD is made by a physician. The physician-diagnosed COPD was more accurate than the information was inquired in the self-administered questionnaire. Another population-based cohort study found that COPD significantly increased the risk for mild cognitive impairment by 83% (HR 1.83, 95% CI 1.04–3.23).⁹ They defined COPD as physician diagnosed and did not base the definition of spirometry. The definition was similar in our study, and pulmonary function test was also not available in our database. However, previous studies have shown that mild COPD is underdiagnosed in the population, and physician-diagnosed COPD may overdiagnose COPD without the pulmonary function data.^{10–12} A retrospective study revealed that the odds ratio (OR) for cognitive impairment was almost 2 times higher in patients with COPD than in those without COPD. The study also used physician-diagnosed COPD cases identified by using the data source and followed by the electronic medical record review and not by spirometry.

Risk Factors of Dementia

Patients with COPD age older than 75 years had a higher incidence rate of dementia than patients with COPD who were younger than 65 years of age. Age is a risk factor for dementia not only in the general population but also in the COPD patient population.

The comorbidity-specific incidence rate of dementia was higher in both the patients with and without COPD. Head trauma is one of the risk of PD and has been related to the pathogenesis of PD. The results of meta-analysis and system review show that a history of head trauma is implicated in developing PD.¹³ Otherwise, there has been an identification of the relationship between head injury and AD. Research has linked head injury to a greater risk of developing of AD,¹⁴ an

animal study revealed that traumatic brain injury can hasten the occurrence of extracellular A β aggregation in mice,¹⁵ and epidemiological studies show that 30% of patients with brain injury have A β plaques and this is the mechanism of AD.¹⁶ Thus, head injury plays an important role in the etiology of dementia. In our study, patients with COPD had a higher risk of dementia (adjusted HR 4.28, 95% CI 1.42–12.93) compared with the non-COPD cohort among individuals with a head injury.

Patients with COPD but without diabetes had a 79% high-risk of dementia in comparison with patients without COPD or diabetes. Patients with COPD and diabetes only had a 57% high-risk of dementia in comparison with patients without COPD but with diabetes. The relationship between patients with PD and diabetes remains controversial.¹⁷ One study demonstrated that diabetes may have a greater risk of developing AD.¹⁸ Another study found that diabetes did not add to the risk of AD in a population study; however, diabetes may play an important role in developing AD in the absence of other known major AD-risk factors.¹⁹ In the study, patients with COPD and diabetes did not add to the risk of developing dementia compared with patients with COPD without diabetes, and this result was similar to that of a previous database study.⁶ It can be seen

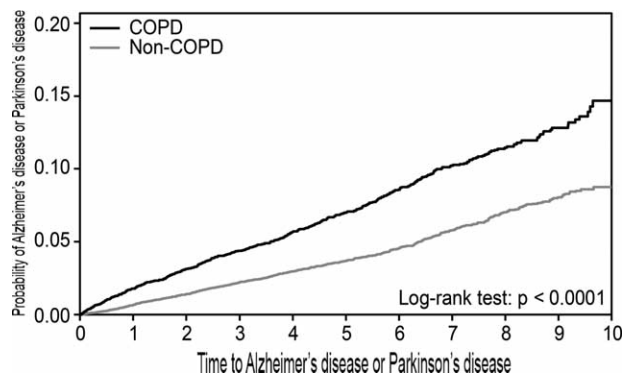


FIGURE 1. Cumulative incidence of dementia in patients with chronic obstructive pulmonary disease and patients without chronic obstructive pulmonary disease.

that the incidence of dementia increases with age in patients with or without COPD. Among patients with COPD who were younger than 65 years of age, the adjusted HR of dementia is 2.45 compared with patients without COPD. Among patients with COPD who reach age 75 and over, the adjusted HR of dementia is 1.82 compared with patients without COPD. COPD increases the risk of developing dementia in younger populations (under 65-years old); this effect was observed in the male population but was not found in the female population after age stratification.

Mechanisms Contributing to Dementia

COPD is a chronic and systemic inflammatory disease, and the inflammatory markers have been associated with cognitive impairment and dementia.^{20,21} COPD is also associated with an increased risk for cardiovascular disease and this one of the mechanisms contributing to dementia.²² The association between COPD and dementia still observed after adjustment for vascular diseases, suggesting that COPD is an independent predictor of dementia.²³

Patients with COPD have a higher chance of developing neuronal damage, and the high risk is due to either hypoxia or associated comorbidities. Aging and the low cerebral perfusion are the key pathologic events associated with the development of dementia.⁹

Impact of Dementia on the Patients with COPD

In our study, patients with COPD and dementia, the incidence rate of severe sepsis and hospital mortality, were higher than the patients with COPD without dementia. Dementia will increase the risk of severe sepsis with an adjusted OR of 1.38 (95% CI 1.10–1.72) and hospital mortality with an adjusted OR 1.69 (95% CI 1.18–2.43). Dementia also increased acute respiratory failure after adjusting for the confounding factors. Dementia is associated with an increased risk of adverse reactions and causes an increase in mortality. Smoking, diabetes, high blood pressure, high cholesterol and COPD were the risks of dementia. Patients need to avoid smoking, control diabetes, dyslipidemia... to prevent dementia or delay dementia onset.

Limitations

The limitations of our study are a lack of data on smoking status, the performance on a pulmonary function test, and COPD severity in the database. The relationship between dementia and COPD severity needs to be further investigated. The present study is a nationwide cohort study, and we believe that the large number of participants and the comprehensive enrollment of patients with COPD in Taiwan ensure that the data are normally distributed and the results are significant.

Patients with COPD have a high-risk of developing dementia compared with patients without COPD according to a nationwide cohort study, and COPD plays an important role in the development of dementia in male patients younger than 65 years of age.

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