

Chronic obstructive pulmonary disease predicts chronic rhinosinusitis without nasal polyps: A population-based study

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ABSTRACT

Background: Few studies have investigated the relationship between chronic obstructive pulmonary disease (COPD) and chronic rhinosinusitis without nasal polyps (CRSsNP) outcomes. The aim of this study was to investigate the association between COPD and the risk of CRSsNP in a large national sample.

Methods: Patients 15 years or older with a new primary diagnosis of COPD (International Classification of Diseases, Ninth edition [ICD-9], 491, 492, 494, and 496) between 2000 and 2007 were identified from the National Health Insurance Research Database of Taiwan. The patients were compared with sex-, age-, residence-, and insurance premium-matched controls, and both groups were followed up until the end of 2008 for instances of CRSsNP, defined as ICD-9 codes CRS (473, 473.0, 473.1, 473.2, 473.3, 473.8, and 473.9), excluding NP (471, 471.0, 471.1, 471.8, and 471.9). Competing risk-adjusted Cox regression analyses were applied after adjusting for sex, age, residence, insurance premium, steroid use (topical or systemic), hyperlipidemia, diabetes, hypertension, coronary artery disease, hospital admission days, and mortality.

Results: We included 34,029 cases and 34,029 matched controls in this study. Among the 68,058 subjects, 569 developed CRSsNP during a mean (standard deviation [SD]) follow-up period of 5.0 years (SD 2.2 years). COPD was an independent predictor of CRSsNP in the fully adjusted model (hazard ratio = 3.24; 95% CI = 2.65–3.96; $p < 0.01$).

Conclusion: COPD was associated with an increased risk of CRSsNP in this study population, independent of a number of potential confounding factors. (Am J Rhinol Allergy 29, e75–e80, 2015; doi: 10.2500/ajra.2015.29.4172)

Chronic obstructive pulmonary disease (COPD), which encompasses both chronic bronchitis and emphysema, is a common respiratory disease in adults living in the developed world. In the United States, COPD affects 4% of the population, which makes it the fourth leading cause of death worldwide and has a rising mortality rate.^{1,2} By 2020, COPD may be the third leading cause of death. If mortality from comorbid conditions associated with COPD is considered, then this disease affects health outcomes substantially. Rhinosinusitis is a common disease diagnosed in the United States. More than 30 million people have chronic rhinosinusitis (CRS) in the United States. The annual prevalence of CRS is 13% to 16%. The costs associated with CRS are estimated as US\$4.3 billion annually in the United States.³

CRS without nasal polyps (CRSsNP) has been shown to differ pathophysiologically from CRS with nasal polyps (CRSwNP); the two subconditions have been shown to be characterized by opposing immune responses.^{4,5} CRSwNP is characterized by skewed T-helper 2 (Th2) responses and tissue eosinophilia, and CRSsNP is more likely to exhibit T-helper 1 (Th1) responses and predominantly neutrophilic inflammation.^{3,5–7} The immunopathologic characteristics of CRSwNP are different between white and Asian patients.⁸ More than a half of

Chinese patients with CRSwNP (53.6%) presented noneosinophilic inflammation in the histologic study.⁹ In Chinese patients, CRSsNP is confirmed to be a predominant Th1 milieu, whereas Th2 skewed inflammation can be demonstrated only in eosinophilic CRSwNP but not in noneosinophilic CRSwNP.⁹ COPD is characterized by skewed Th1 responses, whereas asthma is more likely to exhibit Th2 responses.⁶ Disorders associated with a bias toward Th1 immunity have been proposed to skew comorbidities away from manifestations conventionally attributed to Th2-mediated pathways.^{5,10} Given the presence of a Th1 disorder such as COPD, this hypothesis would predict a higher prevalence of CRSsNP than observed in the general population.

A relationship between COPD and CRSsNP has been reported.¹¹ Few studies have shown that patients with COPD exhibited increased nasal symptoms^{12,13} and nasal inflammation.^{14–16} However, previous studies that involved large patient samples for evaluating the risk of CRSsNP after COPD diagnosis have yet to be conducted. This study tested the hypothesis, by using a nationwide population-based Taiwanese data base, that states that COPD is a risk factor for CRSsNP.

MATERIALS AND METHODS

Sample

A retrospective cohort study was assembled by using data from the Taiwan National Health Insurance Research Database (NHIRD), which is provided by the National Health Research Institute and includes data on outpatient, ambulatory, and inpatient care as well as dental services. The National Health Insurance (NHI) program was implemented in March 1995 and provides compulsory universal health insurance, which covers all delivery of health care to 98% of the national population. In cooperation with the Bureau of the NHI, the National Health Research Institute extracted a randomly sampled representative data base of 1 million people from the 2005 registry of all NHI enrollees by using a systematic sampling method used for research purposes, which forms the Longitudinal Health Insurance Database. No statistically significant differences in age, sex, or health care costs between this sample and all of the enrollees were observed.¹⁷

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Table 1. Characteristics of COPD cases and their matched^a controls in Taiwan, 2000–2007

Characteristic	COPD		Non-COPD*		χ^2 test, <i>p</i> value
	<i>n</i>	%	<i>n</i>	%	
Sex					
Female	14,561	42.79	14,561	42.79	1.000
Male	19,468	57.21	19,468	57.21	
Age group					
15–24 years	1012	2.97	1012	2.97	1.000
25–44 years	5737	16.86	5737	16.86	
45–64 years	12,513	36.77	12,514	36.77	
65+ years	14,767	43.4	14,766	43.39	
Residence					
Urban	23,778	69.88	23,778	69.88	1.000
Rural	10,251	30.12	10,251	30.12	
Insurance premium					
Fixed premium and dependent	10712	31.48	10,712	31.48	1.000
Less than NTD20,000#	8836	25.97	8836	25.97	
NTD20,000 or more	14,481	42.55	14,481	42.55	
Steroid use					
0–30	30,850	90.66	33,385	98.11	< 0.001
31–60	1547	4.55	355	1.04	
60+	1632	4.8	289	0.85	
CRSsNP§					
No	33,595	98.72	33,894	99.6	< 0.001
Yes	434	1.28	135	0.4	
CRSwNP¶					
No	33,995	99.90	34,011	99.95	0.026
Yes	34	0.10	18	0.05	
Hyperlipidemia					
No	27,912	82.02	29,784	87.53	< 0.001
Yes	6117	17.98	4245	12.47	
Diabetes**					
No	25,286	74.31	27,573	81.03	< 0.001
Yes	8743	25.69	6456	18.97	
Hypertension##					
No	14,725	43.27	19,379	56.95	< 0.001
Yes	19,304	56.73	14,650	43.05	
Coronary artery disease§§					
No	26,396	77.57	30,116	88.5	< 0.001
Yes	7633	22.43	3913	11.5	
Hospital days (days, mean [SD])	14.60 (SD 90.55)		6.65 (SD 56.79)		< 0.001

*Matched by sex and age (± 1 year old).

#1 US \$ = 32.1 NTD in 2008.

§ICD-9: CRS (473, 473.0, 473.1, 473.2, 473.3, 473.8, 473.9) excluded NP (471, 471.0, 471.1, 471.8, 471.9).

¶ICD-9: CRS (473, 473.0, 473.1, 473.2, 473.3, 473.8, 473.9) included NP (471, 471.0, 471.1, 471.8, 471.9).

||ICD-9: Hyperlipidemia (272.2, 272.4).

**ICD-9: Diabetes (250.x).

##ICD-9: Hypertension (401.x, 402.x, 403.x, 404.x).

§§ICD-9: Coronary artery disease (410.x, 411.x, 412.x, 413.x, 414.x, 415.x).

COPD cases were identified based on recorded International Classification of Diseases, Ninth Revision (ICD-9) codes 491, 492, 494, and 496. All medical claims made by using these diagnostic codes during 1997 and 2008 were collected from the NHIRD for further analysis. The definition of COPD for this analysis was an inpatient diagnosis or diagnosed COPD of at least 1 year from outpatient services, which is consistent with that of other research that involved using this data base.¹⁸ To define new cases, people who received any COPD diagnosis in the medical claims data from 1997 to 1999 were excluded from the analysis. Thus, 29,951 new patients with COPD, ages older than 15 years, were defined. For assessing the association between COPD and CRSsNP risk, one control per case was randomly sampled from the remaining sample and matched for sex, age within 1 year, residence,

and insurance premium. Both the cases and controls were followed up for CRSsNP as an outcome. CRSsNPs were defined in this study as ICD-9 codes CRS¹⁹ (473, 473.0, 473.1, 473.2, 473.3, 473.8, and 473.9), excluding NP (471, 471.0, 471.1, 471.8, and 471.9). CRSwNP were defined in this study as ICD-9 codes CRS¹⁹ (473, 473.0, 473.1, 473.2, 473.3, 473.8, and 473.9), including NP (471, 471.0, 471.1, 471.8, and 471.9).

We used the standardized definitions and management guidelines for CRS in Taiwan, for example, the Rhinosinusitis Task Force²⁰ and Clinical Practice Guidelines: Adult Sinusitis.²¹ The COPD diagnosis in Taiwan followed the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Guideline.²²

The covariates considered in this analysis included age, sex, area of residence (urban or rural), insurance premium, steroid use (topical or

systemic), hyperlipidemia, diabetes, hypertension, coronary artery disease, hospital admission days, and mortality. The insurance premium served as an indicator of economic status and was classified into one of four categories: fixed, dependent, less than NTD20,000, and NTD20,000 (income per month) or more (US\$1 = NTD32.1 in 2008). The fixed premium group was the group that required social welfare support and included low-income citizens and veterans. The dependent insurance group referred to family members who did not have a fixed income. The annual average cumulative defined daily dose (DDD) of steroid was calculated, divided into 3 groups. Steroid use of less than 30 annual average cumulative DDDs per year was classified as no-use compared with the 31–60 DDDs and 60 DDDs or more use groups. The DDD recommended by the World Health Organization is a unit for assessing the standard dose of drug. Cumulative DDD, which indicates the exposed duration of drug use for a period, was estimated as the sum of dispensed DDD of drug within a time period. The annual average cumulative DDD was used to access the dose usage of steroid in the follow-up time period. General physical health was quantified by using the Charlson comorbidity index²³ on the index date. Hospital admission days served as an indicator of COPD severity on the index date. The index date was the first date of COPD diagnosis. We also assigned this date to the matched controls.

This study was exempt from full review by the Institutional Review Board of Kaohsiung Medical University Hospital because the NHIRD consists of deidentified secondary data released to the public for research purposes (KMUH-IRB-EXEMPT-20140032).

Statistical Analysis

Death before CRSsNP was considered as a competing risk event. The death-adjusted cumulative incidences of CRSsNP were calculated by using the Fine and Gray method.²⁴ The first presentation of each person within the study period was used in the calculation of outcome risk over given time intervals. The risks of CRSsNP during the follow-up period were calculated by using survival analysis. The time function was calculated as the number of years from the index date of COPD diagnosis to December 31, 2008 (end of follow-up) or until the date of death or migration if earlier. Competing risk-adjusted Cox regression models²⁴ were fitted to estimate the associations of COPD after adjusting for covariates. Competing risk-adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated. The model was tested first with all the sample cases included. The subgroups were then divided according to sex and age group tested next. All of the data management was performed by using SAS 9.3 software (SAS Institute Inc., Cary, NC). Calculations of cumulative incidences and Cox models in the competing risk analysis were performed by using the R package *cmprsk*.²⁵

Sensitivity Analysis

In Taiwanese data base, when epidemiologic study about the relationship between COPD and CRS is planned, COPD and both CRSwNP and CRSsNP should be analyzed. Therefore, we also performed similar analysis to reveal the association between COPD and the risk of CRSwNP in our study sample for comparison purpose. Because the incidence of CRSwNP was relative small in our data, and only eosinophilic CRSwNP (fewer than half of Chinese patients with CRSwNP) exhibit Th2 response, this study was focused on the CRSsNP.

RESULTS

Characteristics of the Subjects

The two cohorts comprised 34,029 people with newly diagnosed COPD and 34,029 sex-, age-, residence-, and insurance premium-matched controls ascertained from the data base that covered 2000–

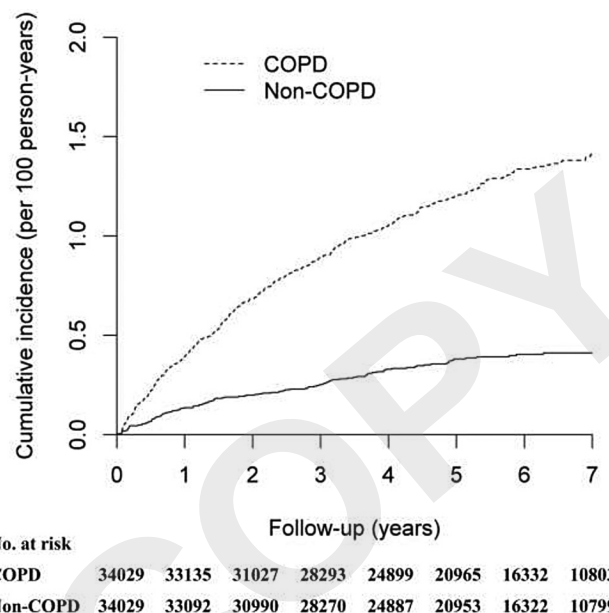


Figure 1. Cumulative incidence on chronic rhinosinusitis without nasal polyp (CRSsNP) by study groups (COPD vs non-COPD). Modify log-rank test p value < 0.001.

2007. A description and comparison of the cohort characteristics are presented in Table 1. Among the COPD cases, 57% were men, and most of the subjects were in the 45–64 and 65+ year age range. Approximately 70% were urban residents, and one-third received social welfare support or were dependent on their families. The COPD cohort used steroids during the follow-up period more frequently than the non-COPD cohort. The patients with COPD were predominately diagnosed with hyperlipidemia, diabetes, hypertension, and coronary artery disease ($p < 0.01$). Hospital admission days were higher for the COPD cohort than for the non-COPD cohort (t test, $p < 0.01$).

Incidence of CRSsNP

Among the 68,058 subjects, 569 developed CRSsNP during the follow-up period: 434 (1.28%) in the COPD cohort and 135 (0.40%) in the non-COPD cohort. During the follow-up period, only 52 patients developed CRSwNP: 34 (0.10%) in the COPD cohort and 18 (0.05%) in the non-COPD cohort (Table 1). The mean (SD) follow-up interval for all of the subjects was 5.0 years (SD 2.2 years). The CRSsNP incidence was 25.4 per 10⁵ person-years (95% CI = 23.1–28.0) and 7.9 per 10⁵ person-years (95% CI = 6.6–9.4) for the COPD group and the non-COPD group, respectively. Kaplan-Meier analysis of the cumulative incidence from CRSsNP revealed that patients with COPD exhibited a significantly higher rate of incident CRSsNP than did the non-COPD group ($p < 0.01$, based on a modified log-rank test) (Fig. 1).

Association Between COPD and Risk of CRSsNP

The analyses of associations of interest are summarized in Table 2. In the fully adjusted Cox regression model for competing risk analysis for which sex, age, residence, insurance premium, steroid use, hyperlipidemia, diabetes, hypertension, coronary artery disease, hospital admission days, and mortality were adjusted, COPD was positively associated with CRSsNP (HR = 3.24; 95% CI = 2.65–3.96; $p < 0.01$). In the stratified analysis, associations of interest were significant for both sex and different ages in the fully adjusted Cox regression models (Table 3).

Table 2. Competing risk adjusted Cox regression analysis on CRSsNP in Taiwan, 2000–2007

Variable	Unadjusted hazard ratio		Adjusted hazard ratio	
	Estimate (95% CI)	<i>p</i> value	Estimate (95% CI)	<i>p</i> value
COPD				
No	1.00		1.00	
Yes	3.15 (2.6–3.83)	< 0.001	3.24 (2.65–3.96)	< 0.001
Sex				
Male	1.00		1.00	
Female	0.93 (0.79–1.1)	0.39	0.91 (0.77–1.08)	0.269
Age group				
15–24 years	1.00		1.00	
25–44 years	1.29 (1.06–1.58)	0.013	1.01 (0.64–1.60)	0.952
45–64 years	1.49 (1.26–1.75)	< 0.001	1.17 (0.75–1.82)	0.496
65+ years	0.53 (0.44–0.64)	< 0.001	0.63 (0.39–1.00)	0.050
Residence				
Rural	1.00		1.00	
Urban	1.17 (0.97–1.41)	0.096	1.09 (0.9–1.32)	0.370
Insurance premium				
Fixed premium and dependent	1.00		1.00	
Less than NTD20,000*	0.95 (0.79–1.15)	0.615	0.98 (0.78–1.24)	0.892
NTD20,000 or more	1.09 (0.92–1.29)	0.303	0.94 (0.76–1.16)	0.574
Steroid use (DDD)				
0–30	1.00		1.00	
31–60	1.52 (1.01–2.29)	0.045	1.35 (0.89–2.06)	0.161
60+	1.86 (1.28–2.71)	0.001	1.55 (1.06–2.27)	0.025
Hyperlipidemia				
No	1.00		1.00	
Yes	0.74 (0.58–0.96)	0.021	0.76 (0.58–0.99)	0.044
Diabetes				
No	1.00		1.00	
Yes	0.65 (0.52–0.81)	< 0.001	0.70 (0.55–0.89)	0.004
Hypertension				
No	1.00		1.00	
Yes	0.73 (0.62–0.86)	< 0.001	0.79 (0.65–0.96)	0.019
Coronary artery disease				
No	1.00		1.00	
Yes	1.00 (0.8–1.24)	0.97	1.15 (0.91–1.46)	0.245
Hospital admission days (100 days)	1.02 (0.94–1.1)	0.664	1.01 (0.91–1.11)	0.893

*1 US \$ = 32.1 NTD in 2008.

Association Between COPD and Risk of CRSwNP

Compared with the main interest finding, COPD was associated with CRSsNP, COPD was also associated, but less strongly, with CRSwNP (HR = 2.11; 95% CI = 1.16–3.84; $p = 0.014$) in the same fully adjusted Cox regression models.

DISCUSSION

This study determined that the patients with COPD were at a significantly high risk of developing CRSsNP (HR = 3.24; 95% CI = 2.65–3.96; $p < 0.01$), after adjusting for possible confounding factors, such as sex, age, residence, insurance premium, steroid use, comorbidities (hyperlipidemia, diabetes, hypertension, and coronary artery disease), hospital admission days, and mortality. This study adds credence to the theory that CRSsNP proceeds through a Th1 response.

CRSsNP is generally associated with Th1 and neutrophilic inflammation,⁹ whereas eosinophilic CRSwNP exhibits a Th2 skewing^{5,9} in Chinese patients. The presence of one Th1 pathology was determined to be strongly associated with the presence or occurrence of other comorbid Th1 pathologies^{4,26}; thus, COPD would likely be associated with other Th1 pathologies, including CRSsNP. In this study, we

found that, in Taiwan, COPD was predominately associated with CRSsNP than with CRSwNP.

Epidemiologic and physiologic studies have shown that lower and upper airway diseases often coexist. The association between allergic rhinitis and asthma is explained by the united airway disease hypothesis.²⁷ Recently, previous studies reported high prevalence rates of sinonasal symptoms in COPD, which ranged from 33% to 88%.^{12,13,28} Quality of life is greatly impaired when more daily nasal symptoms are experienced. Kelemence *et al.*²⁹ reported that 53% of patients with COPD had CRS according to criteria of major and minor symptoms, and 64% had CRS according to the Lund-Mackay scoring system of paranasal sinus computed tomography findings.

COPD is usually associated with increased neutrophil activity.³⁰ The patients with COPD exhibited higher nasal levels of eotaxin, granulocyte colony-stimulating factor, and interferon γ , compared with the controls.³¹ Granulocyte colony-stimulating factor is typically known as a growth factor promoting granulocyte production, maturation, and activation. Granulocyte colony-stimulating factor can be produced by airway epithelial cells and is associated with neutrophilic airway inflammation. The upper airway inflammation in COPD is characterized by neutrophil infiltration^{14,15} and increased neutrophil chemoattractant protein interleukin 8.¹⁶ Neu-

Table 3. **Effect*** of COPD on CRSsNP in Taiwan by sex and age group, 2000–2007.

Subgroup	Adjusted hazard ratio on CRSsNP	
	Estimate (95% CI)	p value
Total	3.24 (2.65–3.96)	< 0.001
Sex		
Male	2.98 (2.30–3.87)	< 0.001
Female	3.66 (2.67–5.03)	< 0.001
Age group		
15–24 years	2.82 (1.10–7.21)	0.031
25–44 years	4.75 (2.98–7.56)	< 0.001
45–64 years	2.97 (2.22–3.97)	< 0.001
65+ years	3.03 (2.09–4.41)	< 0.001

*Competing risk adjusted Cox regression analysis controlled by sex, age, residence, insurance premium, steroid use, hyperlipidemia, diabetes, hypertension, coronary artery disease, hospital admission days, and mortality.

trophil infiltration and increased level of transforming growth factor $\beta 2^7$ and interferon γ^8 were revealed in Chinese patients with CRSsNP. COPD and CRSsNP may have similar inflammatory responses (neutrophil infiltration) throughout the airway. Van Manen *et al.*³² investigated the prevalence of self-reported comorbidities in patients with COPD and revealed that the adjusted odds ratio of sinusitis in patients with COPD older than 40 years old was 6.08 in the Netherlands.

Among other host factors, a history of sinusitis was independently associated with treatment failure, which exacerbates COPD.³³ Therapy for nasal and sinus disease may be associated with improved pulmonary function in patients with COPD.³⁰ Nasal anti-inflammatory treatment of patients with COPD significantly reduced sinonasal symptoms, in parallel with reduced interleukin 8 in nasal secretion levels and cough.³⁴

Chronic rhinosinusitis can be incited by the interaction of multiple etiologies, including microbial factors; environmental factors (smoking, pollution, and allergy); and host factors, such as abnormalities in structure, genetics, physiology, and innate immunity.³ Smoking and exposure to secondhand smoke have been identified as morbid cofactors in CRS. Other environmental pollutants can also have adverse effects on the upper respiratory tract predisposing to CRS.³ Risk factors of COPD included cigarette smoking, air pollutions, and genes. These risk factors may influence both the upper and lower airway over a lifetime.

Possible mechanisms for the interaction between COPD and CRSsNP include loss of nasal conditioning function, direct passage of inflammatory mediators between the upper and lower airway, nasobronchial neuronal reflexes, and stimulation at one point of the respiratory mucosal surface, which results in a pan-airway inflammatory response.^{35,36}

Strengths and Limitations

The key strengths of this study were the nationally representative sample; physician-based diagnosis to identify COPD case; longitudinal analysis; and range of covariates that were considered, including sociodemographic and general health status. Nonetheless, substantial limitations of this study must be mentioned, particularly those caused by using routine data, such as little information on other potential confounders, for example, stressful life events, smoking, air pollution, and family history.

CONCLUSION

The findings from using a national health insurance data set are consistent with a link between COPD and CRSsNP. Because of the

high (and potentially increasing) prevalence of COPD, clinicians must consider the risk of CRSsNP in particular. Routine surveillance of CRSsNP signals should be incorporated into care programs for patients with COPD. Further research is required to explore the underlying mechanism that links these two adverse health outcomes.

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