General Hospital Psychiatry 41 (2016) 6–12

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

Risk of bipolar disorder in patients with COPD: a population-based cohort study☆

Pei-Jung Tsai, M.D. [a,b], Yin-To Liao, M.D. [c,d,1], Charles Tzu-Chi Lee, Ph.D. [e,f,1], Chung-Yao Hsu, M.D., Ph.D. [g], Ming-Hong Hsieh, M.D., Ph.D. [c,d], Chia-Jui Tsai, M.D. [h], Ming-Han Hsieh, M.D. [i], Vincent Chin-Hung Chen, M.D., Ph.D. [j,k,*]

[a] Department of Psychiatry, Lu-Tung Christian Hospital, Lukang, Taiwan
[b] Department of Psychiatry, Changhua Christian Hospital, Changhua, Taiwan
[c] Department of Psychiatry, Chung Shan Medical University Hospital, Taichung, Taiwan
[d] Department of Psychiatry, School of Medicine, Chung Shan Medical University, Taichung, Taiwan
[e] Department of Public Health, Kaohsiung Medical University, Kaohsiung, Taiwan
[f] Department of Health Promotion and Health Education, National Taiwan Normal University, Taipei, Taiwan
[g] Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[h] Department of Psychiatry, Taichung Veterans General Hospital, Taichung, Taiwan
[i] Department of Psychiatry, Tung's Taichung Metro Harbor Hospital, Taichung, Taiwan
[j] Chang Gung Medical Foundation, Chiayi Chang Gung Memorial Hospital Chiayi, Puzi City, Taiwan
[k] Chang Gung University, Taoyuan, Taiwan

ARTICLE INFO

Article history:
Received 12 July 2015
Revised 15 April 2016
Accepted 26 April 2016

Keywords:
Bipolar disorder
COPD
Prednisone

ABSTRACT

Bakcground: Few studies have investigated the relationship between chronic obstructive pulmonary disease (COPD) and bipolar outcomes in the world. We sought to investigate the association between COPD and risk of bipolar disorder in a large national sample.
Methods: The insured aged 15 years or more with a new primary diagnosis of COPD (ICD-9: 491, 492, 494 and 496) between 2000 and 2007 were identified from Taiwan's National Health Insurance Research Database. We included individuals with an inpatient diagnosis of COPD and/or at least 1 year of two diagnoses of COPD in outpatient services. These 35,558 cases were compared to 35,558 sex-, age-, residence- and insurance premium-matched controls. We followed both groups until the end of 2008 for incidence of bipolar disorder, defined as ICD-9 codes 296.0–296.16, 296.4–296.81 and 296.89. Competing risk-adjusted Cox regression analyses were applied with adjusting for sex, age, residence, insurance premium, prednisone use, Charlson comorbidity index, diabetes, hypertension, hyperlipidemia, cardiovascular diseases, hospital admission days, outpatients' visits and mortality.
Results: Of the total 71,116 subjects, 202 were newly diagnosed with bipolar disorder during the study period. The mean follow-up time was 6.0 (SD=2.2) years. COPD, younger age, lower economic status, lower dose of prednisone use, higher hospital admission days and higher outpatient visits were independent predictors of bipolar disorder.
Conclusions: COPD was associated with increased risk of bipolar disorder independent of a number of potential confounding factors in this study.

1. Background

Chronic obstructive pulmonary disease (COPD) remains a major public health problem such that the World Health Organization (WHO) reported COPD as the fourth leading cause of death worldwide in 2004 in the Global Burden of Disease Project. Estimates suggest that COPD will rise from the sixth to the third most common cause of death worldwide by 2020 [1]. COPD is primarily a pulmonary disease, characterized by progressive and irreversible airflow obstruction. COPD commonly results from smoking-related inflammation and destruction of lung. Cigarette smoke induces macrophages to release neutrophil chemotactic factors and elastases. Also, increased proinflammatory cytokines such as interleukin IL-8 and tumor necrosis factor TNF-alpha lead to neutrophil recruitment. Subsequently, inflammatory processes result in changes in large airways, small airways and lung parenchyma. Airflow limitation, the major physiologic change in COPD, ensues from airway inflammation. As in COPD, past studies also implicated inflammation as a critical mediator in the pathophysiology

☆ Conflicts of interest: the authors declare that they have no conflicts of interest.

* Corresponding author. Chang Gung Medical Foundation, Chiayi Chang Gung Memorial Hospital, No. 6, W. Sec., Jiapu Rd., Puzi City, Chiayi County, Taiwan. Tel.: +886-5-3621000.
E-mail address: hjcch@yahoo.com.tw (V.C.-H. Chen).

[1] Yin-To Liao and Charles Tzu-Chi Lee contributed equally as first author.

http://dx.doi.org/10.1016/j.genhosppsych.2016.04.004
0163-8343/

of mood disorders. Elevated levels of proinflammatory cytokines have been repeatedly demonstrated in patients with major depressive disorder and bipolar disorder [2]. IL-2 was indicated as putative agents associating COPD and depression [3]. Mood symptoms of patients with bipolar disorder showed a positive correlation with IL-2 and IL-6 [4].

The association between bipolar disorder and COPD has been scarcely reported. Most of these studies viewed COPD as a complication of chronic cigarette smoking habits in persons with bipolar disorder [5,6]. Other studies focused on comorbidities and mortalities in bipolar disorder or prevalence of bipolar disorder in the COPD population [7,8]. Some research has indicated a higher prevalence of psychiatric disorders in COPD patients. In particular, the prevalence of anxiety and depressive disorders was higher in patients with COPD [9,10]. One population-based cohort study also demonstrated a strong correlation between COPD and subsequent depression [11]. Some studies investigated prevalence of COPD in patients with bipolar disorder. Kilbourne et al. reported that patients with bipolar disorder had higher prevalent rate of comorbid COPD comparing to national cohort (10.6% vs. 9.4%) in the veteran patient population. Beyer et al. utilized the electronic medical record database of a single university medical center and found that 6.1% of outpatients with bipolar disorder had COPD or asthma [5,6]. No study has been reported on the risk of bipolar disorder in patients with COPD. Since combination of the two conditions will lead to significant worldwide health problems, a population-based study is required to establish the aggravated incidence and risk of bipolar disorder in patients with COPD. This population-based cohort study investigated the association between COPD and risk of bipolar disorder using data from the National Health Insurance (NHI) of Taiwan.

2. Methods

2.1. Sample

This retrospective cohort study used data from the Taiwan National Health Insurance Research Database (NHIRD). NHIRD provided by the National Health Research Institute (NHRI) of Taiwan included outpatient, ambulatory and hospital inpatient care. The NHI program providing compulsory universal health insurance began in March 1995. It covered all delivery of health care in 98–99% of the national population. In cooperation with the Bureau of NHI, the NHRI extracted a randomly sampled representative database of 1,000,000 people from the year 2005 registry of all NHI enrollees. This 1,000,000 people sample from the Longitudinal Health Insurance research database had no statistically significant differences in age, sex or health care costs from all NHI enrollees [12].

COPD cases were identified by the recorded International Classification of Disease, Ninth revision (ICD-9) codes of 491, 492, 494 and 496. All medical claims made under these diagnostic codes during 1997 and 2008 were collected from NHIRD for further analysis. **Diagnoses of COPD and bipolar disorder were defined by either two outpatient diagnoses or one inpatient diagnosis in a year as in previous studies** [13,14]. To define new cases, people who had received any COPD diagnosis in the medical claim data from 1997 to 1999 were excluded from the analysis. Patients with bipolar disorder before COPD were also excluded from the analysis; 35,558 new COPD cases aged more than 15 years were defined. For assessing the association between COPD and risk of bipolar disorder, one control per case was randomly sampled from the remaining sample, matching for sex, age within 1 year, residence and insurance premium. Both subjects and controls were followed for bipolar disorder as the primary outcome. Bipolar disorder was defined in this study as codes 296.0–296.16, 296.4–296.81 and 296.89 in ICD-9.

2.2. Variables

Covariates considered in this analysis included age, sex, area of residence (urban/rural), insurance premium, prednisone use, Charlson comorbidity index and hospital admission days. The insurance premium served as an indicator of economic status and was classified into one of three categories: fixed premium and dependent, less than New Taiwan Dollars (NTD) 20,000, NTD 20,000 (income per month) or more (1 USD = 32.1 NTD in 2008). The fixed premium group depended on social welfare support, comprised by mostly low-income citizens and veterans. The dependent insurance group referred to family members that did not have fixed salary income. The prednisone uses were classified into **three** groups by annual average cumulative Defined Daily Dose (DDD): **0, 1–29, 30** and more. The DDD is a unit for assessing the standard dose of a certain drug designed by the WHO. It stands for the assumed average maintenance dose per day for a drug used for its main indication in adults. Cumulative DDD indicates the exposed duration of drug use over a period. The estimation of cumulative DDD is the sum of the dispensed DDDs of a drug within a time period. We used the annual average cumulative DDD presented as the equivalent dose of prednisone to assess the dose usage of prednisone in the follow-up time period. General physical health was quantified using the Charlson comorbidity index [15] at the index date. Diabetes (ICD-9: 250), hypertension (ICD-9: 401–406), hyperlipidemia (ICD-9: 272.2, 272.4) and cardiovascular diseases (ICD-9: 430–436) at the index date were also included in the analysis for controlling purpose. The hospital admission days served as an indicator of COPD severity at 1 year past the index date. The index date was the first diagnosis date of COPD and we also assigned this date to their matched controls. The number of outpatient visits within 1 year past the index date was also included in the analysis.

2.3. Statistical analysis

A death prior to bipolar disorder was considered as a competing risk event. The death-adjusted cumulative incidences of bipolar disorder were calculated using the Fine and Gray method [16]. Each person's first presentation within the study period was used in the calculation of outcome risk over given time intervals. The risks of bipolar disorder during the follow-up period were calculated using survival analysis, with the time function 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 models [16] were fitted to estimate the associations of COPD, adjusting for covariates. Competing risk-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. All data management was performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). Calculations of cumulative incidences and Cox models in the competing risk analysis were carried out using the R package "cmprsk" [17].

2.4. Sensitivity analysis

Time-dependent Cox regression model was used for multivariate assessment of prednisone use on bipolar disorder by controlling the potential confounding covariates. Instead of modeling prednisone as a cumulative effect by calculating the cumulative annual average DDD during the follow-up period, time-dependent model can take dynamic changing of prednisone use into account by assessing the yearly DDD of prednisone use effect during the following period in this study. HRs and 95% CI for bipolar were reported and comparing to the main analysis.

3. Results

3.1. Characteristic of subjects

The two cohorts comprised 35,558 people with new diagnoses of COPD and 35,558 sex-, age-, residence- and insurance premium-