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The incidence and all-cause mortality of pneumonia in patients with schizophrenia: A nine-year follow-up study

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ABSTRACT

Objective: This study sought to estimate the incidence, all-cause mortality and relative risks for patients with schizophrenia after a pneumonia diagnosis.
Methods: The population was identified from the Taiwanese National Health Insurance Research Database (NHIRD) in 1999 and included 59,021 patients with schizophrenia and 236,084 age- and sex-matched control participants without schizophrenia. These participants were randomly selected from the 23,981,020-participant NHIRD, which contain 96% of the entire population. Using the 2000–2008 NIHRD, the incidence and nine-year pneumonia-free survival rate of pneumonia (ICD-9-CM codes 486 and 507.0–507.8) were calculated.
Results: Over nine years, 6055 (10.26%) patients with schizophrenia and 7844 (3.32%) controls had pneumonia. The pneumonia incidence density was 11.4/1000 person-years among the patients with schizophrenia, who experienced a 3.09-fold increased risk of developing pneumonia. After adjusting for other covariates, the patients with schizophrenia still experienced a 1.77-fold increased risk of developing pneumonia. Although, without adjustment, fewer schizophrenia patients than controls died after having pneumonia (2121 [35.12%] vs. 3497 [44.62%]), after adjusting for other variables, the mortality hazard ratio for patients with schizophrenia was 1.39.
Conclusions: During a nine-year follow-up, the likelihood of developing pneumonia and all-cause mortality among patients with schizophrenia was higher than that of the non-schizophrenia group as was the mortality rate. Interestingly, the psychiatric proportion of days covered (PDC) was positively associated with pneumonia (OR: 2.51) but negatively associated with death (HR: 0.72). These findings imply the importance of iatrogenic factors and psychotropic drugs (including their benefits and side effects) and highlight the directions for future studies.

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1. Introduction

Pneumonia is an inflammatory condition of the lungs that affects approximately 3 million each year in United States. The incidence of pneumonia is approximately between 5 and 11/1000 person-years in adults (Marrie and Huang, 2005; Jokinen et al., 1993), and the incidence of hospitalization for pneumonia is 1.1–2.7/1000 person-years (Monge et al., 2001; Marrie and Huang, 2005). In a population-based study conducted in Finland, the incidence of pneumonia was 11.6/1000 persons/year. In the Finnish working population (ages 15–64 years), the mean annual hospitalization rate was 2.67/1000 persons for men and 1.10/1000 persons for women (Saynajakangas et al., 1997).

Pneumonia is one of the most common causes of death (Copeland et al., 2007) and poor prognosis (Chen et al., 2011) in schizophrenia. Patients with schizophrenia and pneumonia have poorer prognoses (Chafetz et al., 2005). Additionally, in the last year of life, schizophrenia is a risk factor for pulmonary disease after controlling for history of smoking and other covariates (Copeland et al., 2007). Excluding the information that should be collected from clinical practice, such as pleuritic chest pain, hypothermia, systolic hypotension, tachypnea, bacteremia, leukopenia, and multilobar radiographic pulmonary infiltrate (Fine et al., 1996), many risk factors for pneumonia remain, including smoking,

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diabetes mellitus, neoplastic disease, neurologic disease, male gender, and aging (Fine et al., 1996; Almirall et al., 1999; Mandell et al., 2007). The use of psychotropic drugs may induce extrapyramidal syndrome (EPS) and lead to dysphagia, hypersalivation (Hinkes et al., 1996), or esophageal dilation and hypomotility.

The use of psychotropic drugs has been reported to be associated with pneumonia (Knol et al., 2008; Kuo et al., 2012) and to result an increased risk of hospitalization (Lin et al., 2011). Some antipsychotics, such as clozapine, can modulate the cytokine network (Raaska et al., 2002.), influence the plasma levels of several cytokines (Haack et al., 1999), and might enhance susceptibility to infections during treatment (Haack et al., 2003). The use of second-generation antipsychotic medication has been reported to be associated with increased risk of pneumonia (Kuo et al.). The use of clozapine (adjusted risk ratio = 3.18, 95% CI: 2.62–3.86, $P < .001$) is associated with a dose-dependent increase in risk. Antipsychotics have immunoregulatory effects, anti-inflammatory (but also pro-inflammatory) effects, and clozapine may have inflammatory effects. Clozapine has a direct influence on different cytokines that resembles an inflammatory reaction. Infection or inflammation could induce bioactivation of clozapine into its nitrenium ion, which can result in a toxic reaction that induces apoptosis, gives rise to elevated cytokine levels (Haack et al., 2003), and may increase the risk of pneumonia, particularly when combined with other antipsychotics (Kuo et al.).

Pneumonia is the 8th leading cause of death in the USA and the 7th leading cause of death in Canada. In Taiwan, where pneumonia is the 3rd or 4th leading cause of death, approximately 160,000 people are hospitalized annually for pneumonia treatment. The overall mortality for patients with pneumonia is 13.7% and ranges from 5.1% for hospitalized and ambulatory patients to 36.5% for intensive care unit patients (Fine et al., 1996). The factors associated with mortality are male gender, pleuritic chest pain, hypothermia, systolic hypotension, tachypnea, diabetes mellitus, neoplastic disease, neurologic disease, bacteremia, and leucopenia (Fine et al., 1996). Advanced age has also been reported to be associated with mortality (Seymour and Vaz, 1989).

One study mentioned that the prognoses of patients with pneumonia are not associated with pneumonia within 28 days but rather with aging or physical illness (El et al., 2006). However, a one-year follow-up survival study showed the mortality rate of pneumonia patients to be 40.9%, which is higher than that for non-pneumonia patients (29.1%) after adjusting for age and physical illness (Kaplan et al., 2003). Another 90-month follow-up study produced similar results (Bordon et al., 2010). Therefore, pneumonia might be a risk factor for long-term mortality in discharged patients.

There is no systematic prospective long-term follow-up study that has explored the incidence and all-cause mortality of pneumonia in patients with schizophrenia. Previous studies have reported a high mortality rate among patients with schizophrenia after being diagnosed with cancer (Chou et al., 2011) or stroke (Tsai et al., 2012). However, the long-term survival course of schizophrenia patients with pneumonia is not clear. Therefore, we conducted a nested case-control study to explore the incidence of pneumonia, risks associated with pneumonia, and the all-cause mortality of schizophrenia patients after having pneumonia over a nine-year follow-up.

2. Methods

2.1. Database subjects

Taiwan initiated a single-payer National Health Insurance (NHI) program in 1995. More than 98% of Taiwan's population was enrolled in this program in 2007. The National Health Insurance Bureau of Taiwan randomly reviews the charts of one per 100 ambulatory and one per 20 inpatient claimed cases and interviews patients to verify the accuracy of the diagnosis according to its website (2000). This study used the National Health Insurance Research Database (NHIRD), which was published by the National Health Research Institute in Taiwan and covered the years from 1999 to 2008. Using the NHIRD, we were able to determine the probability that patients with schizophrenia would develop pneumonia versus the probability for the general population not affected by schizophrenia. Because the NHIRD consists of de-identified, secondary, publicly available data released for research purposes, the study was exempted from full review by the Internal Review Board (IRB) at the Kai-Syuan Psychiatric Hospital. Nevertheless, the study protocol conformed to the ethical standards established by the 2004 Declaration of Helsinki.

The diagnostic coding of the NHI in Taiwan was performed according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9–CM) diagnostic criteria. In Taiwan, patients with any type of severe disease, including schizophrenia (ICD-9–CM 295), can apply for catastrophic illness registration (CIR) cards, which are given by the Bureau of National Health Insurance (BNIH). To receive these cards, patients with these illnesses must have a conclusive diagnosis made by a specialist. Persons with a CIR card do not need to pay co-payments when they seek health care or treatment for a registered severe disease (Chou et al., 2011).

In this study, all patients with schizophrenia possessed a CIR card, meaning they had been diagnosed with schizophrenia by a psychiatrist, had applied for their CIR cards prior to the end of 1999 and had been issued a CIR card by the Taiwan National Health Insurance Bureau (Tsai et al., 2012). Using the catastrophic illness registration file for the dates prior to the end of 1999, the participants in this study were randomly selected from the 23,981,020-participant NHIRD, which contains 96% of the entire Taiwanese population. The authors identified 59,021 patients with schizophrenia (ICD-9-CM code 295 except 295.8). From the remaining subjects in the 1999 administrative data, subjects who developed schizophrenia between 2000 and 2008 were excluded, and 236,084 (1:4) subjects without schizophrenia chosen randomly using a SAS program were extracted as a control group that was matched for age and gender.

2.2. Measurements

The key dependent variables in this study were pneumonia incidence and the survival time of the pneumonia patients. The independent variables were age, gender, enrollee category (EC), income-related insurance payment (as a proxy for monthly income), level of urbanization, co-morbidities and antipsychotic proportion of days covered (PDC). The experimental groups were those diagnosed with schizophrenia and the control group that had not been diagnosed with schizophrenia. The participants of the National Health Insurance in Taiwan were classified into four subgroups: EC 1 (civil servants, full-time, or regular paid personnel with a government affiliation), EC 2 (employees of privately owned institutions), EC 3 (self-employed individuals, other employees, and members of the farmers' or fishermen's associations), and EC 4 (veterans, members of low-income families, and substitute service draftees) (Chen et al., 2007).

From the 2000–2008 NHRID, the subjects who were admitted to a hospital with a diagnosis of pneumonia (ICD-9 CM = 486) or aspiration pneumonia (ICD-9 CM = 507.0–507.8) were classified as having pneumonia during the follow-up period. If a subject had more than one pneumonia episode, only the first was considered.

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