



Increased risk of chronic liver disease in patients with bipolar disorder: A population-based study



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ABSTRACT

Objective: This study aimed to investigate the prevalence and incidence of chronic liver disease in patients with bipolar disorder.

Methods: We used a random sample of 766,427 subjects aged ≥18 years from the National Health Research Institute database in the year 2005. Subjects with at least one primary diagnosis of bipolar disorder in 2005 were identified. Patients with a primary or secondary diagnosis of chronic liver disease were also defined. We compared the prevalence and associated factors of chronic liver disease between patients with bipolar disorder and the general population in 2005. We also compared the incidence of chronic liver disease in patients with bipolar disorder and the general population from 2006 to 2010.

Results: The prevalence of chronic liver disease in patients with bipolar disorder (13.9%) was 2.68 times higher than that of the general population (5.8%) in 2005. The average annual incidence of chronic liver disease in patients with bipolar disorder from 2006 to 2010 was also higher than that of the general population (2.95% vs. 1.73%; risk ratio: 1.71; 95% confidence interval: 1.46–2.01).

Conclusions: Patients with bipolar disorder had a significantly higher prevalence and incidence of chronic liver disease than those in the general population, and younger patients with bipolar disorder have a much higher prevalence and incidence than those in the general population. Male sex, second-generation antipsychotic or antidepressant use, and hyperlipidemia were associated factors for chronic liver disease in patients with bipolar disorder.

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1. Introduction

Studies focusing on bipolar disorder and liver disease are relatively limited in Western societies. Bipolar disorder affects patients' cognition, mood and behavior profoundly and may cause long-term and personal or social/family dysfunction. It is a multifactorial mental disorder involving development, neurophysiological and environmental stressors [1]. Studies have reported that inflammatory dysregulation was related to clinical mood symptoms and somatic diseases, which may have influences on patients with bipolar disorder [2].

Co-occurrence with somatic diseases is common among patients with bipolar disorder, especially in a majority of those with multiple mood episodes. Women and men with bipolar disorder die earlier

than the general population, with a twofold increase in all-cause mortality [3]. Therefore, it is important for clinical workers to pay much attention not only to mood symptoms but also to treatment of underlying somatic illness because comorbid medical conditions affect more than 40% of patients with bipolar disorder [4,5]. However, a previous study has reported that underrecognized and suboptimally treated somatic illness was common in patients with bipolar disorder [6].

Among medical conditions in bipolar disorder, metabolic disturbance/syndrome and cardiovascular/circulatory system diseases have been commonly investigated in previous studies [6–9]. Other medical comorbidities, such as neurological, respiratory and infectious diseases, were also common in patients with bipolar disorder [5,6]. Notably, the more somatic disorders present in patients with bipolar disorder, the more likely they are to show poor treatment outcomes [10].

Chronic liver disease, including alcoholic and nonalcoholic liver disease and other causes of hepatitis, has become a worldwide public health issue because of its high prevalence and progressive effects on individual's health, ranging from simple hepatic steatosis and liver cirrhosis to hepatocellular carcinoma. Nonalcoholic fatty liver disease

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(NAFLD) is the most common liver disease, with a prevalence of 15% to 30% in the Western general population [11]. The overall prevalence of NAFLD was 29% and 24.6% of Japanese adults in studies from 2002 to 2003 and 2011 to 2012, respectively [12]. According to previous community studies, the prevalence of NAFLD and elevated liver enzymes occurred in 11.5% and 11.4% of Taiwanese adults, respectively [13,14]. Not only liver disease itself but also predisposing factors to developing illnesses have negative impacts on extrahepatic organ systems, such as neurological or cerebrovascular insults with impaired cognition or stroke, cardiovascular or metabolic disturbances with coronary artery disease, and cancer [15,16].

According to one study conducted with a MEDLINE search, the current and lifetime prevalence of hepatic comorbidities is 17% and 21% in patients with bipolar disorder [6]. One large-scale, retrospective chart review study reported that patients with bipolar disorder have a higher prevalence of liver disease than do matched controls [21.5% vs. 3.5%, respectively; odds ratio (OR): 7.58] [17]. Similarly, another retrospective study of administrative claims from 1996 to 2001 found that liver diseases are 3.97 times more prevalent in patients with bipolar disorder [4].

Taiwan implemented a National Health Insurance (NHI) program in March 1995, offering a comprehensive, unified and universal health insurance program to all citizens. We conducted this nationwide study to investigate the epidemiology of chronic liver diseases in patients with bipolar disorder. First, we compared the prevalence of chronic liver diseases between patients with bipolar disorder and the general population in 2005. Second, we investigated factors associated with the prevalence of chronic liver diseases in patients with bipolar disorder. Third, we compared the incidence of chronic liver diseases in patients with bipolar disorder and the general population from 2006 to 2010. Finally, we detected risk factors for chronic liver diseases in patients with bipolar disorder during this period.

2. Methods

2.1. Sample

The National Health Research Institute (NHRI) medical claims database includes data on outpatient care, hospital inpatient care and prescription drugs. The NHRI provided a randomly sampled database of 1,000,000 for study. From this database, we examined the 766,427 individuals aged ≥ 18 years in 2005. This study was approved by the institutional review board of Jianan Mental Hospital. No statistically significant differences in age, sex or average insured payroll-related amount were present between the sample group and all enrollees.

2.2. Definition of bipolar disorder

The diagnosis of bipolar disorder was coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic criteria of the NHI program in Taiwan [18]. Study subjects with one primary diagnosis of bipolar disorder (ICD-9-CM: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7 or 296.8) for either outpatient or inpatient care (by primary care physicians, psychiatrists or other physicians) were identified [19]. Only individual who have had a clinical encounter are included in the NHI, which likely means that a minority on individuals with bipolar disorder are not represented due to not seeking care in 2005.

2.3. Definition of chronic liver disease

Study subjects with one primary or secondary diagnosis of chronic liver disease (ICD-9-CM: 571) for either outpatient or inpatient care were identified in this study period. Chronic liver disease included alcoholic fatty liver (571.0), acute alcoholic hepatitis (571.1), alcoholic cirrhosis of the liver (571.2), alcoholic liver damage, unspecified (571.3),

chronic hepatitis (571.4), cirrhosis of the liver without mention of alcohol (571.5), biliary cirrhosis (571.6), other chronic nonalcoholic liver disease (571.8) and unspecified chronic liver disease without mention of alcohol (571.9). Actually, we did not discuss viral hepatitis in this study. Therefore, viral hepatitis (ICD-9-CM: 070) was excluded in this study.

With regard to the prevalence of chronic liver disease in the general population and patients with bipolar disorder, the numerator was the number of prevalent cases of chronic liver disease, and the denominator was the total number of study subjects identified in 2005. With regard to the incidence of chronic liver disease, we identified new cases of chronic liver disease from 2006 to 2010. Subjects with newly diagnosed chronic liver disease and no chronic liver disease diagnosis before 2006 comprised the group with incident chronic liver disease, and we calculated the incidence from 2006 to 2010. The numerator was the number of incident cases of chronic liver disease, and the denominator was the number of person-years contributed by the study subjects.

2.4. Definition of diabetes

Study subjects who had at least one prescription (oral hypoglycemic agents or insulin) for the treatment of diabetes in 2005 for either outpatient or inpatient care were considered to have a diagnosis of diabetes.

2.5. Definition of hypertension

Study subjects who had a primary or secondary diagnosis of hypertension (ICD-9-CM: 401–405) in combination with antihypertensive drug treatment in 2005 were considered to have hypertension.

2.6. Definition of hyperlipidemia

Study subjects who had one primary diagnosis of hyperlipidemia (ICD-9-CM: 272) for either outpatient or inpatient care in 2005 were considered to have hyperlipidemia.

2.7. Measures

Demographic characteristics, including age, sex, antipsychotic use, antidepressant use, mood stabilizer use, insurance amount, region and urbanicity, were obtained directly from the files of BNHI insured individuals. Age was classified into one of six categories: 18–29, 30–39, 40–49, 50–59, 60–69 and ≥ 70 years. Antipsychotic use was divided into no antipsychotic use, first-generation antipsychotic use and second-generation antipsychotic (SGA) use [20]. Antidepressant use was divided into no antidepressant use, first-generation antidepressant (tricyclics and monoamine oxidase inhibitors) use and second-generation antidepressant (selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors and other antidepressants) use. Mood stabilizer use was defined as present or absent. The insurance amount was classified into one of five categories: fixed premium, dependent, less than US\$640 (NTD 20,000), US\$640–1280 (NTD 20,000–39,999) and US\$1281 (NTD 40,000) or more. With regard to geographical distribution, the study subjects were classified into one of four regions: northern, central, southern and eastern. Urbanicity was divided into urban, suburban and rural categories.

2.8. Statistical analysis

The differences in prevalence of chronic liver disease between patients with bipolar disorder and the general population, according to different age groups, sex, insurance amount, region and urbanicity, were tested by logistic regression, adjusted for the other covariates. Multiple logistic regression was used to analyze the risk factors for cases of chronic liver disease among patients with bipolar disorder in 2005 adjusted for the other covariates, including age, sex, insurance

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