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# Increased Subsequent Risk of Peptic Ulcer Diseases in Patients With Bipolar Disorders

*Yi-Chao Hsu, PhD, Chih-Chao Hsu, MD, Kuang-Hsi Chang, PhD, Chang-Yin Lee, MD, PhD, Lee-Won Chong, MD, PhD, Yu-Chiao Wang, MSc, and Chia-Hung Kao, MD*

**Abstract:** Previous studies have reported that patients with bipolar disorders (BDs) exhibit increased physical comorbidity and psychological distress. Studies have shown that schizophrenia and anxiety increase the risk of peptic ulcer diseases (PUDs). Therefore, we conducted this study to determine the association between these 2 diseases and examine the possible risk factors.

We used patients diagnosed with BDs from the Taiwan National Health Insurance Research Database. A comparison cohort comprising patients without BDs was frequency matched by age, sex, and comorbidities, and the occurrence of PUDs was evaluated in both the cohorts.

The BD and non-BD cohort consisted of 21,060 patients with BDs and 84,240 frequency-matched patients without BDs, respectively. The incidence of PUDs (hazard ratio, 1.51; 95% confidence interval, 1.43–1.59; $P < 0.001$) was higher among the patients with BDs than the control patients. Cox models showed that irrespective of comorbidities, BDs were an independent risk factor for PUDs.

Patients with BDs exhibit a substantially higher risk for developing PUDs. According to our data, we suggest that, following a diagnosis of BD, practitioners could notice the occurrence of PUD and associated prevention. Further prospective clinical studies investigating the relationship between BDs and PUDs are warranted.

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**Abbreviations**: BDs = bipolar disorders, CI = confidence interval, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, IRR = incidence rate ratio, NHIRD = National Health Insurance Research Database, PUDs = peptic ulcer diseases.

## INTRODUCTION

Bipolar disorders (BDs) have been reported to lead to impaired physical function and multiple physical comorbidities, which might entail an increased medical burden for patients with BDs.[1] Peptic ulcer diseases (PUDs) are associated with high morbidity and mortality.[2] Although physical illness and psychological distress are associated with PUDs,[3,4] recent studies have indicated a relationship between mental disorders and PUDs. People affected by PUDs are more likely to exhibit anxiety disorder.[5,6] Cross-sectional studies on community-dwelling people have shown that people with mental illnesses such as schizophrenia,[7] anxiety,[5,6] and panic disorders[8] exhibit high risks for subsequent PUDs.

However, little evidence regarding the relationship between BDs and PUDs has been presented. We hypothesized that a history of BDs increases the risk of PUDs. To prove our hypothesis, we designed a nationwide population-based study and investigated the incidence of PUDs among patients with BDs.

## PATIENTS AND METHODS

### Data Source

We used the claims data of Taiwan residents obtained from the Taiwan National Health Insurance program, which is a single-payer compulsory insurance program that was established in 1995. Until 2007, it covered nearly 99% of the population of Taiwan (23.74 million people). We designed this study as a population-based retrospective cohort study based on the Longitudinal Health Insurance Database 2000 (LHID2000) and the Registry for Catastrophic Illness Patients (RCIP) released by the National Health Research Institutes. The LHID2000 is subset of the National Health Insurance Research Database (NHIRD) and contains outpatient and inpatient department treatment and payment data, which are available for research. The LHID2000 contains original claims data of 1 million enrollees randomly sampled from the patients in the

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From the Department of Psychiatry (C-CH), Kaohsiung Veterans General Hospital, Kaohsiung; Institute of Biomedical Sciences (Y-CH), Mackay Medical College, Taipei; Department of Medical Research (K-HC), Taichung Veterans General Hospital, Taichung; School of Chinese Medicine for Post-Baccalaureate (C-YL), I-Shou University, Kaohsiung; Division of Hepatology and Gastroenterology (L-WC), Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei; Management Office for Health Data (Y-CW), China Medical University Hospital, Taichung; College of Medicine (Y-CW), China Medical University, Taichung; Department of Nuclear Medicine and PET Center (C-HK), China Medical University Hospital, Taichung; Graduate Institute of Clinical Medical Science and School of Medicine (C-HK), College of Medicine, China Medical University, Taichung, Taiwan.

Correspondence: Chia-Hung Kao, Professor, Graduate Institute of Clinical Medical Science and School of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan (e-mail: d10040@mail.cmuh.org.tw).

Y-CH and Ch-CH contributed equally to this work.

Author contributions—Conception/Design: Y-CH, C-CH, C-HK; Provision of study materials: C-HK; Collection and/or assembly of data: Y-CH, C-CH, Y-CW, C-HK; Data analysis and interpretation: all authors; Manuscript writing: all authors; Final approval of manuscript: all authors.

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NHIRD between 1996 and 2011. The RCIP is a separate subset that includes patients with severe diseases, including mental disease, autoimmune disease, and cancer. Catastrophic illnesses are defined by the Taiwan government, and patients with a catastrophic illness card receive free health care for their illness and related conditions. Usage of the catastrophic illness card is reviewed using medical records and a process of equal reviews. Therefore, using the diagnoses in the RCIP database in combination with the clinical diagnoses increases the reliability. We used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to determine patient diagnoses. All data were deidentified, and therefore, this study was approved to exempt from full ethical review by the institutional review board of China Medical University (CMU-REC-101-012).

## Study Patients

We selected as the study population patients who had a catastrophic illness card because of BD (ICD-9-CM: 296) according to the RCIP database. We identified patients with BDs who had been newly diagnosed between 2001 and 2008 (N = 21,060). The date of BD diagnosis was used as the index date. For the non-BD cohort, we randomly selected 84,240 patients without BDs from the LHID2000 database and frequency matched them with the patients with BDs by sex, age (every 5 years), and index year in a 4:1 ratio. Our major outcome in this study was PUDs (ICD-9-CM: 531–535). The exclusion criteria were the date of diagnosis of PUDs being before the index date and incomplete age or sex information. The follow-up person-years were calculated from the index date until the diagnosis of PUDs, withdrawal from the insurance system, or the end of 2011.

The following confounding factors were included for adjustment: diabetes mellitus (DM; ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272), hypertension (HTN; ICD-9-CM: 401–405), cirrhosis (ICD-9-CM: 571), rheumatoid arthritis (RA; ICD-9-CM: 714), chronic renal disease (CRD; ICD-9-CM: 585), heart disease (HD; ICD-9-CM: 420-429), alcohol-related illness (ICD-9-CM: 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3), chronic obstructive pulmonary disease (COPD; ICD-9-CM: 585), anxiety (ICD-9-CM: 300), and schizophrenia (ICD-9-CM: 295). We selected anxiety as the comorbidities in this study because of the fact that BDs and anxiety share high levels of comorbidity in the clinic.[9,10] We have also tried to analyze the panic disorders and schizophrenia; however, only schizophrenia (ICD-9-CM 295) could have enough patient numbers to be analyzed in the multivariable Cox proportional hazard regression model for adjustment. We also considered the antidepressants treatment in BD and non-BD cohorts, when subjects used the antidepressants drug before the end date was estimated. We chose these comorbidities because patients with BDs are usually treated by atypical antipsychotics, which may result in metabolic syndromes, cardiovascular diseases and HDs.[11,12] It has been suggested that BDs are associated with chronic inflammatory diseases and neuroinflammation; therefore, we listed common chronic inflammatory diseases as the comorbidities, such as RA,[13] ischemic stroke, pneumonia, bronchitis, COPD, type-2 DM, and HTN.[14]

## Statistical Analysis

We performed all statistical analyses by using SAS 9.4 software for Windows (SAS Institute, Cary, NC). A 2-sided *P* value <0.05 was considered statistically significant. Summary statistics are presented as numbers and percentages for categorical data and means ± standard deviations for continuous variables. Chi-squared and Student *t* tests were used to compare categorical and continuous variables between the BD and non-BD cohorts. The incidence of PUDs was estimated according to age, sex, and various types of comorbidity for both the cohorts. Poisson regression analysis was performed to estimate the incidence rate ratio (IRR) in the BD and non-BD cohorts. The adjusted hazard ratios (HRs) and 95% confidence interval (95% CI) obtained through a multivariable Cox proportional hazards model analysis reflect the risk of developing PUDs in the 2 cohorts after adjustment for age, sex, and history of comorbidity.

We further analyze risk of gastric ulcer (ICD-9-CM: 531), duodenal ulcer (ICD-9-CM: 532), peptic ulcer site unspecified (ICD-9-CM: 533), gastrojejunal ulcer (ICD-9-CM: 534), and gastritis and duodenitis (ICD-9-CM: 535) between BD and non-BD cohorts. Those outcomes are separated by ICD-9-CM, when subjects had the peptic ulcer event.

R software (R Foundation for Statistical Computing, Vienna, Austria) was used to create Kaplan–Meier curves and calculate the cumulative incidence of the PUDs in the control and study groups. In addition, the log-rank test was used to measure the differences of the 2 cumulative incidence curves.

# RESULTS

Our initial sample comprised 105,300 patients. After we excluded ineligible patients, 84,240 patients without BDs and 21,060 patients with BDs remained. Table 1 shows the demographic characteristics and comorbidities among the BD and non-BD cohorts at the baseline. After the sample was frequency matched, the distribution of age and sex between the 2 cohorts was similar. Table 1 shows that most patients were women (54.4%) and 35 to 64 years of age (53.0%). The mean age of the patients was 40 years. Patients in the BD cohort exhibited a significantly higher prevalence of DM, HTN, hyperlipidemia, cirrhosis, anxiety, HD, COPD, alcohol-related illness, CRD, RA, and schizophrenic at the baseline ($P < 0.05$). The BD cohort had more common used the antidepressants treatment than the non-BD cohort (90% vs 14%, $P < 0.0001$).

Table 2 shows the overall IRR of PUDs that was increased 1.59-fold in the BD cohort compared with the non-BD cohort (35.9 vs 22.6 per 1000 person-years). The overall adjusted HR of PUDs in patients with BDs was 1.51 (95% CI: 1.43–1.59) after we controlled for sex, age, and comorbidities. Notably, PUDs is the outcome of several complications, such as bleeding, perforation, and obstruction that result from local ulcer and gastritis is local inflammation. We further presented that BD patient had higher risk of gastrojejunal ulcer and gastric ulcer than non-BD patient (adjusted HR: 2.49, 95% CI: 1.69–3.66; adjusted HR: 1.90, 95% CI: 1.65–2.18). The incidence of gastritis and duodenitis was higher in BD cohort (18.6 per 1000 person-years vs 13.3 per 1000 person-years) and the adjusted HR was 1.40 (95% CI: 1.31–1.51) compared with non-BD cohort. BD patient had 1.64-fold (95% CI: 1.30–2.07) and 1.49-fold (95% CI: 1.33–1.65) risk to develop duodenal ulcer and peptic ulcer site unspecified than non-BD patient, respectively. Sex-specific analysis revealed BD incidence rates of 39.0 and 32.2 per 1000 person-years among women and men, respectively; these values are higher than those in the non-BD cohort (24.4 and 20.4 per 1000 person-years, respectively). Regardless of sex, the adjusted HR of PUDs was higher in the BD cohort than in the non-BD cohort (adjusted HR: 1.48,

**TABLE 1.** Demographics Factors and Comorbidity Between Bipolar and Nonbipolar Cohorts

| | Bipolar | | | | |
|---|---|---|---|---|---|
| | No (N = 84,240) | | Yes (N = 21,060) | | |
| | n | % | n | % | *P* Value |
| Age, y* | | | | | 0.99 |
| <35 | 33,780 | 40.1 | 8445 | 40.1 | |
| 35–64 | 44,648 | 53.0 | 11,162 | 53.0 | |
| ≥65 | 5812 | 6.90 | 1453 | 6.90 | |
| Mean (SD)# | 40.2 (15.2) | | 40.2 (15.1) | | 0.80 |
| Sex* | | | | | 0.99 |
| Women | 45,804 | 54.4 | 11,451 | 54.4 | |
| Men | 38,436 | 45.6 | 9609 | 45.6 | |
| Comorbidity* | | | | | |
| Diabetes | 4246 | 5.04 | 1832 | 8.70 | <0.0001 |
| Hypertension | 10,078 | 12.0 | 3782 | 18.0 | <0.0001 |
| Hyperlipidemia | 6213 | 7.38 | 2252 | 10.7 | <0.0001 |
| Cirrhosis | 6570 | 7.80 | 2749 | 13.1 | <0.0001 |
| Anxiety | 3967 | 4.71 | 11,149 | 52.9 | <0.0001 |
| HD | 5200 | 6.17 | 2017 | 9.58 | <0.0001 |
| COPD | 2497 | 2.96 | 1163 | 5.52 | <0.0001 |
| Alcohol-related illness | 418 | 0.50 | 1231 | 5.85 | <0.0001 |
| CRD | 318 | 0.38 | 139 | 0.66 | <0.0001 |
| RA | 74 | 0.09 | 29 | 0.14 | 0.0384 |
| Schizophrenia | 289 | 0.34 | 1116 | 5.30 | <0.0001 |
| Antidepressants treatment* | | | | | <0.0001 |
| No | 72,466 | 86.0 | 1954 | 9.3 | |
| Yes | 11,774 | 14.0 | 19,106 | 90.7 | |

COPD = chronic obstructive pulmonary disease, CRD = chronic renal disease, HD = heart disease, RA = rheumatoid arthritis, SD = standard deviation.
*Chi-squared test.
#Student *t* test.

95% CI: 1.38–1.59 for women; adjusted HR: 1.55, 95% CI: 1.43–1.69 for men). The incidence of PUDs increased with age in both the cohorts. Age-specific analysis showed that patients in the BD cohort exhibited a significantly higher risk of PUD development than that of the patients in the non-BD cohort at ages <35 and between 35 and 64 years. For patients with comorbidities, the incidence was increased. Patients with BDs and comorbidities exhibited a 1.40-fold increased risk (95% CI: 1.31–1.49) of PUDs compared with non-BD patients with comorbidities. Subject with antidepressants treatment had higher incidence of PUDs in both the cohorts (IRR: 1.56, 95% CI: 1.47–1.65). After adjusted for age, sex, and comorbidities history, BD patient with antidepressants treatment had 1.53-fold (95% CI: 1.44–1.63) risk of PUDs than non-BD patient with antidepressants treatment.

Table 3 shows a comparison between the BD and non-BD cohorts stratified by various types of comorbidity and presents the risk of PUDs in patients with BDs and comorbidities, namely, DM (adjusted HR: 1.38, 95% CI: 1.19–1.61), HTN (adjusted HR: 1.34, 95% CI: 1.21–1.49), hyperlipidemia (adjusted HR: 1.50, 95% CI: 1.31–1.72), cirrhosis (adjusted HR: 1.40, 95% CI: 1.22–1.60), anxiety (adjusted HR: 1.25, 95% CI: 1.13–1.38), HD (adjusted HR: 1.44, 95% CI: 1.25–1.66), COPD (adjusted HR: 1.35, 95% CI: 1.11–1.64), alcohol-related illness (adjusted HR: 1.66, 95% CI: 1.15–2.41), and CRD (adjusted HR: 2.17, 95% CI: 1.19–3.96). Regardless of comorbidities, the patients with BDs exhibited a higher risk of PUDs than that of the non-BD patients. We measured the association between the average number of hospital care services used because of BD exacerbation and the development of PUDs (Table 4). The adjusted HR increased with an increasing number of used hospital care services. Compared with the non-BD cohort, the adjusted HR of PUDs increased from 1.16 (95% CI: 1.08–1.24) for patients with ≤5 visits to 3.61 (95% CI: 3.34–3.91) for patients with >17 visits (*P* value for trend <0.0001). By the end of the follow-up period, the cumulative incidence of PUDs was 6.81% higher in the BD cohort than the non-BD cohort (25.5% vs 18.4%; Figure 1).

## DISCUSSION

This population-based study specifically examined BDs as a risk factor for PUDs by using a matched cohort and an 8-year follow-up period. The major finding of our study is the discovery of a higher incidence of subsequent PUDs among patients with BDs. Furthermore, regardless of whether the patients had DM, HTN, hyperlipidemia, cirrhosis, anxiety, HD, CRD, COPD, alcohol-related illness, CRD, or RA, BDs appear to be an independent risk factor for PUDs. Anxiety has been suggested as the risk factor of PUD.[15] Although the data we showed in Table 3 were not very significant before adjustment (IRR: 1.00, 95% CI: 0.92–1.09), it showed significant difference after adjustment (HR: 1.25, 95% CI: 1.13–1.38, $P < 0.001$).

**TABLE 2.** Incidence and Adjusted HR of Peptic Ulcer in Bipolar and Nonbipolar Cohorts Stratified by Sex, Age, Comorbidity, and Antidepressants Treatment

| | Bipolar | | | | | | Compared to Nonbipolar | |
|---|---|---|---|---|---|---|---|---|
| | No | | | Yes | | | | |
| Variables | Event | PY | Rate | Event | PY | Rate | IRR (95% CI) | Adjusted HR[†] (95% CI) |
| Overall | 11,987 | 531,521 | 22.6 | 4359 | 121,597 | 35.9 | 1.59 (1.54–1.64)*** | 1.51 (1.43–1.59)*** |
| Gastric ulcer (ICD-9-CM: 531) | 1391 | 531,521 | 2.62 | 697 | 121,597 | 5.73 | 2.19 (2.10–2.28)*** | 1.90 (1.65–2.18)*** |
| Duodenal ulcer (ICD-9-CM: 532) | 645 | 531,521 | 1.21 | 217 | 121,597 | 1.78 | 1.47 (1.40–1.54)*** | 1.64 (1.30–2.07)*** |
| Peptic ulcer site unspecified (ICD-9-CM: 533) | 2725 | 531,521 | 5.13 | 1079 | 121,597 | 8.87 | 1.73 (1.66–1.80)*** | 1.49 (1.33–1.65)*** |
| Gastrojejunal ulcer (ICD-9-CM: 534) | 171 | 531,521 | 0.32 | 105 | 121,597 | 0.86 | 2.68 (2.56–2.81)*** | 2.49 (1.69–3.66)*** |
| Gastritis and duodenitis (ICD-9-CM: 535) | 7055 | 531,521 | 13.3 | 2261 | 121,597 | 18.6 | 1.40 (1.35–1.46)*** | 1.40 (1.31–1.51)*** |
| Sex | | | | | | | | |
| Women | 6987 | 286,099 | 24.4 | 2545 | 65,234 | 39.0 | 1.60 (1.53–1.67)*** | 1.48 (1.38–1.59)*** |
| Men | 5000 | 245,422 | 20.4 | 1814 | 56,362 | 32.2 | 1.58 (1.50–1.66)*** | 1.55 (1.43–1.69)*** |
| Age, y | | | | | | | | |
| <35 | 3555 | 223,379 | 15.9 | 1465 | 52,494 | 27.9 | 1.75 (1.66–1.85)*** | 1.77 (1.59–1.96)*** |
| 35–64 | 7043 | 276,582 | 25.5 | 2516 | 62,366 | 40.3 | 1.58 (1.51–1.66)*** | 1.35 (1.26–1.44)*** |
| ≥65 | 1389 | 31,559 | 44.0 | 378 | 6737 | 56.1 | 1.27 (1.12–1.45)*** | 1.46 (1.25–1.69)*** |
| Comorbidity | | | | | | | | |
| No | 7536 | 407,579 | 18.5 | 1049 | 40,045 | 26.2 | 1.42 (1.34–1.50)*** | 1.68 (1.55–1.82)*** |
| Yes | 4451 | 123,942 | 35.9 | 3310 | 81,551 | 40.6 | 1.13 (1.08–1.19)*** | 1.40 (1.31–1.49)*** |
| Antidepressants treatment | | | | | | | | |
| No | 10,216 | 455,976 | 22.4 | 353 | 11,741 | 30.1 | 1.34 (1.21–1.49)*** | 1.35 (1.21–1.51)*** |
| Yes | 1771 | 75,545 | 23.4 | 4006 | 109,856 | 36.5 | 1.56 (1.47–1.65)*** | 1.53 (1.44–1.63)*** |

CI = confidence interval, HR = hazard ratio, IRR = incidence rate ratio, PY = person-year. Rate is defined as the incidence rate (per 1000 PY).
[†]Adjusted HR: multiple analysis including age, sex, comorbidities history, and antidepressants treatment by Cox proportional hazard regression model.
*** $P < 0.001$.

**TABLE 3.** Incidence and Adjusted HR of Peptic Ulcer Stratified by Different Types of Comorbidities, Compared With Nonbipolar Cohort

| | Bipolar | | | | | | Compared to Nonbipolar | |
|---|---|---|---|---|---|---|---|---|
| | No | | | Yes | | | | |
| Variables | Event | PY | Rate | Event | PY | Rate | IRR (95% CI) | Adjusted HR† (95% CI) |
| Diabetes | | | | | | | | |
| No | 11,047 | 507,839 | 21.8 | 3873 | 112,696 | 34.4 | 1.58 (1.52–1.64)*** | 1.53 (1.44–1.62)*** |
| Yes | 940 | 23,682 | 39.7 | 486 | 8901 | 54.6 | 1.38 (1.22–1.56)*** | 1.38 (1.19–1.61)*** |
| Hypertension | | | | | | | | |
| No | 9740 | 474,646 | 20.5 | 3393 | 102,513 | 33.1 | 1.61 (1.55–1.67)*** | 1.55 (1.46–1.65)*** |
| Yes | 2247 | 56,875 | 39.5 | 966 | 19,084 | 50.6 | 1.28 (1.18–1.39)*** | 1.34 (1.21–1.49)*** |
| Hyperlipidemia | | | | | | | | |
| No | 10,600 | 495,913 | 21.4 | 3747 | 110,249 | 34.0 | 1.59 (1.53–1.65)*** | 1.50 (1.42–1.59)*** |
| Yes | 1387 | 35,608 | 39.0 | 612 | 11,348 | 53.9 | 1.38 (1.24–1.54)*** | 1.50 (1.31–1.72)*** |
| Cirrhosis | | | | | | | | |
| No | 10,600 | 493,332 | 21.5 | 3633 | 107,318 | 33.9 | 1.58 (1.52–1.63)*** | 1.53 (1.45–1.62)*** |
| Yes | 1387 | 38,189 | 36.3 | 726 | 14,279 | 50.8 | 1.40 (1.26–1.55)*** | 1.40 (1.22–1.60)*** |
| Anxiety | | | | | | | | |
| No | 11,086 | 509,705 | 21.8 | 1822 | 60,379 | 30.2 | 1.39 (1.32–1.45)*** | 1.63 (1.53–1.73)*** |
| Yes | 901 | 21,816 | 41.3 | 2537 | 61,217 | 41.4 | 1.00 (0.92–1.09) | 1.25 (1.13–1.38)*** |
| HD | | | | | | | | |
| No | 10,809 | 502,927 | 21.5 | 3833 | 111,488 | 34.4 | 1.60 (1.54–1.66)*** | 1.51 (1.42–1.60)*** |
| Yes | 1178 | 28,594 | 41.2 | 526 | 10,109 | 52.0 | 1.26 (1.12–1.42)*** | 1.44 (1.25–1.66)*** |
| COPD | | | | | | | | |
| No | 11,384 | 518,222 | 22.0 | 4045 | 116,092 | 34.8 | 1.59 (1.53–1.64)*** | 1.53 (1.44–1.61)*** |
| Yes | 603 | 13,299 | 45.3 | 314 | 5505 | 57.0 | 1.26 (1.07–1.47)** | 1.35 (1.11–1.64)** |
| Alcohol-related illness | | | | | | | | |
| No | 11,901 | 529,497 | 22.5 | 4057 | 115,918 | 35.0 | 1.56 (1.50–1.61)*** | 1.50 (1.43–1.59)*** |
| Yes | 86 | 2024 | 42.5 | 302 | 5679 | 53.2 | 1.25 (0.95–1.64) | 1.66 (1.15–2.41)** |
| CRD | | | | | | | | |
| No | 11,918 | 530,002 | 22.5 | 4325 | 121,036 | 35.7 | 1.59 (1.54–1.64)*** | 1.51 (1.43–1.59)*** |
| Yes | 69 | 1519 | 45.4 | 34 | 561 | 60.6 | 1.33 (0.85–2.09) | 2.17 (1.19–3.96)** |
| RA | | | | | | | | |
| No | 11,969 | 531,146 | 22.5 | 4350 | 121,446 | 35.8 | 1.59 (1.54–1.64)*** | 1.51 (1.43–1.60)*** |
| Yes | 18 | 375 | 48.0 | 9 | 151 | 59.7 | 1.24 (0.49–3.18) | 1.26 (0.43–3.68) |
| Schizophrenic | | | | | | | | |
| No | 11,947 | 529,763 | 22.6 | 4157 | 113,958 | 36.5 | 1.62 (1.56–1.67)*** | 1.51 (1.43–1.60)*** |
| Yes | 40 | 1758 | 22.8 | 202 | 7638 | 26.5 | 1.16 (0.82–1.65) | 1.44 (1.01–2.06) |

CI = confidence interval, COPD = chronic obstructive pulmonary disease, CRD = chronic renal disease, HD = heart disease, HR = hazard ratio, IRR = incidence rate ratio, PY = person-year, RA = rheumatoid arthritis. Rate is defined as incidence rate (per 1000 PY). * $P < 0.05$.

† Adjusted HR: multiple analysis including age, sex, comorbidities history, and antidepressants treatment by Cox proportional hazard regression model.

** $P < 0.01$.

*** $P < 0.001$.

According to our analysis of the risk factors associated with subsequent PUDs in patients with BDs, we suggest that the mechanism is associated with the interaction between BDs and PUDs. Our findings reveal that patients with BDs were at a significantly increased risk for subsequent PUDs. Possible mechanisms may involve the hypothalamus–pituitary–adrenal (HPA) axis[16] and glucocorticoid resistance.[17–20] A study showed that manic states in patients with BDs are associated with enhanced dopaminergic transmission and experimental stress enhances dopamine neurotransmission and impairs cognition.[16] Furthermore, stress activates the HPA axis, and the disturbed axis impairs neurocognitive function, as demonstrated in patients with BDs.[16] A disturbed HPA axis caused by hippocampal damage and disinhibition was reported in patients with BDs.[21] In addition, BDs have been associated with chronic neuroinflammation,[22–24] which may induce glucocorticoid resistance under a chronic condition.[25] Although glucocorticoids have exhibited gastroprotective effects under conditions of acute stress,[25] an animal model showed the opposite effect under conditions of chronic stress.[26] Consequently, BDs can increase the risk of PUDs. Studies have demonstrated chronic inflammation among BDs,[22–24] DM,[27,28] HTN,[29] hyperlipidemia,[30,31] cirrhosis,[32] anxiety,[33,34] COPD,[35] and cerebrovascular diseases.[36,37] The immune reaction associated with proinflammatory cytokines could induce neuroinflammation.[38] In addition, chronic inflammation, a type of chronic stress, may

**TABLE 4.** Adjusted HR of Peptic Ulcer Associated With Number of Used Hospital Care Service Per Year Due to Bipolar in Study Period

| Variables | N | Event | Adjusted HR† (95% CI) |
|---|---|---|---|
| Nonbipolar | 84,240 | 11,987 | 1.00 |
| Number of used hospital care service per year | | | |
| ≤5 | 7525 | 1165 | 1.16 (1.08–1.24)*** |
| 5–11 | 5924 | 1020 | 1.23 (1.14–1.33)*** |
| 11–17 | 4764 | 1124 | 1.81 (1.68–1.95)*** |
| >17 | 2847 | 1050 | 3.61 (3.34–3.91)*** |
| *P* value for trend | | | <0.0001 |

CI = confidence interval, HR = hazard ratio.
† Adjusted HR: multivariable analysis including for age, sex, comorbidities history, and antidepressants treatment by Cox proportional hazard regression model. Hospital care service including outpatient and hospitalized services.
*** $P < 0.001$.

disturb the HPA axis and induce hypercortisolemia and neuroinflammation through a proinflammatory response.[39–41] HPA axis dysfunction has been reported to increase the risk of PUDs under conditions of chronic stress.[26]

Goodwin et al[42] reported an association between anxiety disorders and PUDs, but this association weakened after adjustment for nicotine and alcohol dependence, suggesting that comorbid dependence on nicotine and alcohol may partially explain their observations. A study showed that high levels of alcohol consumption can induce adverse systemic effects such as reduced immune defense.[43] Furthermore, heavy alcohol intake causes damage to the stomach lining, and alcohol-related illnesses mostly occur in people who drink substantial amounts of alcohol. However, our data suggest that regardless of alcohol-related illnesses, the patients with BDs exhibited a higher risk of PUDs than that of the non-BD patients (Table 3), suggesting that comorbid dependence on alcohol does not explain why patients with BDs exhibited a higher risk for subsequent PUDs.[42] We have used COPD adjustment for replacing nicotine abuse. There were several reasons for COPD adjustment. First, COPD is a chronic inflammatory disease. Second, cigarette smoke is the most important risk factor of COPD, and it also induces the chronic inflammation. Because of the lack of information on healthy behaviors in NHIRD, we considered COPD instead of cigarette smoke in the Cox proportional hazard regression.[44,45]

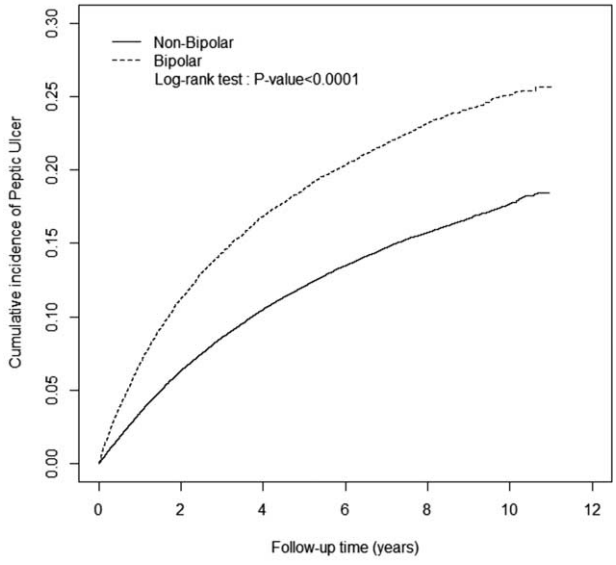


**FIGURE 1.** Cumulative incidence of peptic ulcer diseases among non-BD (solid line) and BD (dashed line) cohorts. BD = bipolar disorder.

We checked if BDs are the risk factor to develop PUDs. Therefore, we used the case–control study including the population-based cohort of patients having BDs with matched controls of comorbidity. It is the strength of this study. Nonetheless, some limitations of this study could be judged to read these findings in this study: first, we diagnosed BDs according to ICD-9-CM codes only using the NHIRD. Therefore, the data of BDs' severity could not be measured to judge the risk factor for the subsequent PUDs. Second, the causal–effect association between the 2 diseases could not be evaluated by the chronological order. But we should consider the possible relationship between PUDs and BDs. Third, the NHIRD lacks a lot of possible confounding factors (such as socioeconomic status, lifestyle, and family history), which might be regarded to be associated with BDs and PUD. Fourth, it is very difficult to accurately divide the subgroups of these depression patients from the BDs cohort by ICD-9 codes only (supplementary table, http://links.lww.com/MD/A339). Fifth, severe PUD is usually combined with many complications (such as bleeding, obstruction, and perforation). In order to perform differentiated diagnoses between gastritis and PUD, we have to use the endoscopic examinations to check gastric tissues. But these invasive procedures usually were refused by these patients or resulted in severe complication (such as bleeding and perforation).[46]

In conclusion, we propose that patients with BDs exhibit a significantly increased risk for developing PUDs. According to our data, we suggest that following a diagnosis of BD, clinical practitioners could notice the occurrence of PUDs and associated prevention. Further prospective clinical studies investigating the relationship between BDs and PUDs are warranted.

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