

Original Article

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Sex-specific risk profiles for suicide mortality in bipolar disorder: incidence, healthcare utilization and comorbidity

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Abstract

Background. Evidence on sex-specific incidence and comorbidity risk factors of suicide among patients with bipolar disorder is scarce. This study investigated the sex-specific risk profiles for suicide among the bipolar disorder population in terms of incidence, healthcare utilization and comorbidity.

Methods. Using data from the Taiwan National Health Insurance Research Database between 1 January 2000 and 31 December 2016, this nationwide cohort study included patients with bipolar disorder ($N = 46\,490$) and individuals representative of the general population ($N = 185\,960$) matched by age and sex at a 1:4 ratio. Mortality rate ratios (MRRs) of suicide were calculated between suicide rates of bipolar disorder cohort and general population. In addition, a nested case-control study (1428 cases died by suicide and 5710 living controls) was conducted in the bipolar disorder cohort to examine the sex-specific risk of healthcare utilization and comorbidities.

Results. Suicide risk was considerably higher in the cohort ($MRR = 21.9$) than in the general population, especially among women ($MRR = 35.6$). Sex-stratified analyses revealed distinct healthcare utilization patterns and physical comorbidity risk profiles between the sexes. Although female patients who died by suicide had higher risks of nonhypertensive cardiovascular disease, pneumonia, chronic kidney disease, peptic ulcer, irritable bowel syndrome, and sepsis compared to their living counterparts, male patients who died by suicide had higher risks of chronic kidney disease and sepsis compared to the living controls.

Conclusions. Patients with bipolar disorder who died by suicide had sex-specific risk profiles in incidence and physical comorbidities. Identifying these modifiable risk factors may guide interventions for suicide risk reduction.

Introduction

Suicide is a major public health concern and among the top 10 leading causes of death worldwide (World Health Organization, 2019). Notably, up to 90% individuals who complete suicide meet at least one diagnostic criterion for a psychiatric disorder (Gonda et al., 2012; Patel et al., 2018). Furthermore, studies have indicated that patients with bipolar disorder in both the West and the East have the highest risk of suicide among individuals with psychiatric disorders (Gonda et al., 2012; McIntyre et al., 2008; Miller & Black, 2020; Pan, Yeh, Chan, & Chang, 2020; Plans et al., 2019; Pompili et al., 2013; Schaffer et al., 2015).

Mortality studies in both the West and the East have demonstrated that the standardized mortality ratio (SMR) of death by suicide is greater for women with bipolar disorder compared to their male counterparts (Osby, Brandt, Correia, Ekblom, & Sparen, 2001; Pan et al., 2020). A nationwide cohort study conducted in Sweden reported that the SMRs of suicide for women to men are 20.9:15.0 (ratio: 1.39) in the bipolar disorder population (Osby et al., 2001). Another Taiwanese study involving two nationwide cohorts of individuals with bipolar disorder noted that SMRs of suicide for women to men were 16.9:12.4 (ratio: 1.36) and 20.5:12.3 (ratio: 1.67), respectively (Pan et al., 2020). These findings are contradictory to those from mortality studies on the general population, which suggest a higher risk of suicide mortality among men (Chen et al., 2011; Hedegaard, Curtin, & Warner, 2020; Kuo, Gunnell, Chen, Yip, & Chen, 2012). Moreover, the difference in the risk of suicide mortality between the sexes is also greater among patients with bipolar disorder than in patients with unipolar

depression (ratio: 1.20–1.29) (Osby et al., 2001; Pan et al., 2020). Taken together, evidence indicates that the risk of suicide mortality is substantially higher in women with bipolar disorder than in their male counterparts; thus, further investigation of the sex-specific risk factors is warranted.

Various factors have been found to be associated with suicide in patients with bipolar disorder. Although studies have observed heterogeneity in risk factors for suicide in individuals with bipolar disorder, common variables linked to the clinical characteristics of bipolar disorder have been identified. These include previous suicide attempts, earlier age at onset, the rapid-cycling subtype, and comorbidities (Gonda et al., 2012; McIntyre et al., 2008; Miller & Black, 2020; Pan et al., 2020; Plans et al., 2019; Pompili et al., 2013; Schaffer et al., 2015). Regarding comorbid risk factors, numerous studies have established associations between suicidality and psychiatric comorbidities in patients with bipolar disorder, including substance use disorder and alcohol use disorder (Cassidy, 2011; Dutta et al., 2007; Isometsa, 2014; Oquendo et al., 2010; Ostergaard, Nordentoft, & Hjorthoj, 2017), anxiety disorder (Kocabas, Sevincok, Memis, & Dogan, 2019; Simon et al., 2007b; Simon, Hunkeler, Fireman, Lee, & Savarino, 2007a), sleep disorder (Bertrand, Bourguignon, Beaulieu, Storch, & Linnaranta, 2020), and personality disorder (Coleman et al., 2017; Isometsa, 2014; Zimmerman et al., 2014). However, few studies have examined the relationship between physical comorbidities and suicide in patients with bipolar disorder (Fagiolini, Frank, Scott, Turkin, & Kupfer, 2005; Forty et al., 2014; Rosso et al., 2020) despite growing evidence on the multi-systemic nature of bipolar disorder (Leboyer et al., 2012). Given that comorbidities are factors that can be modified by clinical treatment, data on the risk of psychiatric and physical comorbidities presented a short period before suicide may provide insights for the development of interventions aimed at reducing the high suicide rate in individuals with bipolar disorder. Furthermore, knowledge on the comorbidity risk factors for suicide mortality in patients with bipolar disorder, as well as on the sex-specific profiles therein, can direct future research on the pathogenetic mechanisms underlying the sex-specific risk for suicide that has been noted in epidemiological studies (Osby et al., 2001; Pan et al., 2020).

As for this knowledge gap and clinical merits, herein we conducted a nationwide cohort study of individuals with bipolar disorder to investigate sex-specific patterns in healthcare utilization and risks of psychiatric and physical comorbidities in the 3-month period before suicide mortality.

Methods

Data sources

The data were collected from the Taiwan National Health Insurance Research Database (NHIRD). Launched in 1995, the National Health Insurance (NHI) program provides comprehensive and accessible medical care to nearly 98% of the national population, which numbers approximately 23 million. Containing the registration files and medical claims data of NHI beneficiaries, the NHIRD is maintained by the Health and Welfare Data Science Center. Data from the NHIRD have been used in numerous epidemiological studies, the reports of which have been published in various peer-reviewed journals (Chen et al., 2019; Hung et al., 2016; Kuo et al., 2013; Wu, Wang, Cheng, & Gau, 2011; Wu, Wang, Gau, Tsai, & Cheng, 2013).

The protocol of the present nationwide cohort study was approved by the Institutional Review Board of Taipei City Hospital. A waiver of informed consent was granted because of the deidentified and retrospective nature of the data.

Identification of bipolar disorder cohort

We selected patients from the NHIRD who were diagnosed as having a psychiatric disorder according to codes 290.x to 319.x in the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and codes F01–F99 in the *International Classification of Diseases, Tenth Revision* (ICD-10-CM) between 1 January 2000, and 31 December 2016 ($N = 10\,722\,613$; online Supplementary e-Fig. 1). We then excluded patients who received at least one psychiatric diagnosis of schizophrenia (ICD-9-CM code 295.**; ICD-10 codes F20.* and F25.*) over the same period ($N = 273\,751$). The final cohort comprised of patients with at least one psychiatric hospitalization with a discharge diagnosis of bipolar disorder (ICD-9-CM codes: 296.0–296.16, 296.4–296.81, 296.89, and 296.9; ICD-10 codes: F30.* and F31.*) between 1 January 2001, and 31 December 2016 ($N = 46\,490$).

In Taiwan, national cause-of-death statistics are classified on the basis of ICD-9-CM codes (for deaths before 31 December 2014) and *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes (for deaths after 1 January 2015). Therefore, according to the ICD-9-CM classification, the suicide codes were E950 to E959, and according to the ICD-10-CM classification, they were X60 to X84 and Y87.0. Each individual was electronically linked to the national mortality database from 1 January 2001, to 31 December 2016 (online Supplementary e-Fig. 1 in the Supplement). Of the 7757 individuals in the bipolar disorder cohort who died during the study period, 1428 died by suicide.

Nested case-control study

To examine the risk of healthcare utilization and comorbidities, we conducted a nested case-control study on the basis of risk set sampling (online Supplementary e-Fig. 1 in the Supplement). For each individual in the bipolar disorder cohort who died by suicide ($n = 1428$), four living patients from the same cohort were randomly selected as controls according to sex, age (± 5 years), and index year. To confirm that the comparison patients were alive before the corresponding index date (i.e. the date of the first diagnosis of bipolar disorder), we confirmed that each of those individuals had least one claims record after the corresponding index date. The suicide cases and living control patients comprised 1428 and 5710 individuals, respectively.

Variables associated with suicide mortality

The demographic and clinical characteristics examined at the index date were sex, age, urbanization level, employment status, and Charlson comorbidity index (CCI) score. Urbanization was categorized into five levels specific to Taiwan, with levels 1, 2, 3, 4, and 5 representing highly urbanized areas, moderately urbanized areas, townships, subrural areas, and rural areas, respectively. Calculated according to ICD-9-CM codes, the CCI scores were categorized as 0, 1, or ≥ 2 physical comorbidities. The variables concerning health care utilization within 3 months of suicide were the number of hospitalizations, emergency room

visits, outpatient visits, and outpatient specialist visits. Physical comorbidities present in the 3-month period before suicide were categorized as cardiovascular diseases, cerebrovascular diseases, metabolic diseases, respiratory diseases, and others (online Supplementary e-Tables 1 and 2 in the Supplement). In view of evidence for a dose–response association of infection with suicide risk (Lund-Sorensen et al., 2016), we included sepsis as a variable to represent severe systemic infection. Sepsis was defined according to the Angus sepsis abstraction criteria (Angus et al., 2001).

Statistical analysis

In this study, we calculated the mortality rate ratios (MRRs) as an index for estimating the risk of suicide in the bipolar disorder population. Because the MRR was defined as the ratio of suicide rate between the bipolar disorder cohort and the general population, we randomly matched the patients with bipolar disorder with individuals from the general population by age (± 0 years) and sex at a 1:4 ratio between 1 January 2001, and 31 December 2016 (online Supplementary e-Fig. 1 in the Supplement). We calculated the survival (contributed) time of each member of the bipolar disorder cohort starting from the index date to death by suicide or to the end of the study (i.e. 31 December 2016). The crude incidence of suicide was computed by dividing the number of incident cases by the person-year contribution. Subsequently, the MRRs for suicide were calculated as the ratio of suicide rates between the bipolar disorder and comparison cohorts representing the general population. The 95% confidence intervals (CIs) of the MRRs were estimated using Poisson regression models. Between-sex differences in suicide incidence were examined using the Gehan's generalized Wilcoxon test (Lee, 1992).

In the nested case–control study, we conducted conditional logistic regression analyses to explore the sex-stratified risks of healthcare utilization and comorbidities between patients with bipolar disorder who died by suicide and their living counterparts. Multivariable regression analysis was performed through backward variable selection on two models, one of physical comorbidities and the other of psychiatric comorbidities. Variables with a significant association ($p < 0.05$) were retained. All statistical analyses were conducted using SAS for Windows, version 9.4 (SAS Institute, Cary, NC, USA). Considering the multiple comparisons in our study, we further performed sensitivity analysis using a conservative approach. Variables in the multivariable regression analyses were retained if they had a p value < 0.01 (online Supplementary e-Fig. 3 in the Supplement).

Results

Suicide incidence by sex

As expected, the incidence of suicide in the general population was greater among men (25.7 per 100 000 person-years) than among women (11.6 per 100 000 person-years) (online Supplementary e-Table 3 in the Supplement). By contrast, suicide incidence in the bipolar disorder cohort was slightly higher among the women (411.9 per 100 000 person-years) than among the men (400.2 per 100 000 person-years). Survival curves of the cumulative incidence of suicide between male and female patients (online Supplementary e-Fig. 2 in the Supplement) revealed no significant sex differences.

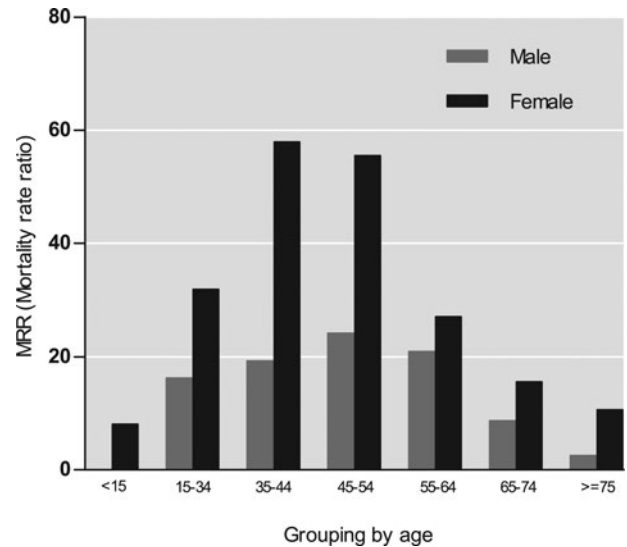


Fig. 1. Sex- and age-stratified mortality rate ratios of suicide in patients with bipolar disorder and the general population.

Notably, the MRR of suicide in the bipolar disorder cohort was 21.9 times higher than that in the general population (online Supplementary e-Table 3 in the Supplement). Sex-stratified analyses showed that the MRR of suicide was 35.6 (95% CI 29.1–45.3) and 15.6 (95% CI 13.3–18.4) in the female and male patients, respectively. In addition, the gap of MRRs between the female and male patients consistently existed across each age interval, with the greatest one in the age interval from 35 to 54 years (Fig. 1).

Demographic and clinical characteristics of the bipolar disorder cohort

Table 1 presents the demographic and clinical characteristics of the patients in the nested case–control study. No significant differences in urbanization level were observed between groups. The patients who died by suicide were likely to have been employed and to have more physical comorbidities at the index date. With stratification for sex, the male patients who died by suicide did not have a higher risk of physical comorbidities than their living counterparts (online Supplementary e-Table 4 in the Supplement). By contrast, the female patients who died by suicide had more physical comorbidities than the living controls (online Supplementary e-Table 5 in the Supplement).

Healthcare utilization by sex in the bipolar disorder cohort

Both the male and female patients who died by suicide were more likely to have sought medical attention in the 3-month period before death than their living counterparts (Table 2). Sex-stratified analysis revealed distinct patterns of healthcare utilization between the female and male patients. Although the female patients who died by suicide were more likely than their living counterparts to have visited specialists in internal medicine and neurology, the male patients who died by suicide were more likely to have visited specialists in physical rehabilitation clinics relative to their living controls. In addition, sex-stratified analysis revealed that higher proportions of the female patients who died by suicide have received respiratory and anti-diabetic medications

Table 1. Demographic and clinical characteristics of suicide cases and living controls in bipolar disorder cohort at index date

Characteristics	Suicide cases (N = 1428)	Living controls (N = 5710)	Crude risk ratio ^a	95% CI	p
	n (%)	n (%)			
Sex					
Male	677 (47.4)	2706 (47.4)	Reference		
Female	751 (52.6)	3004 (52.6)	–	–	–
Age, years					
15–34	514 (36.0)	2057 (36.0)	Reference		
35–44	377 (26.4)	1485 (26.0)	–	–	–
45–54	282 (19.8)	1206 (21.1)	–	–	–
55–64	163 (11.4)	599 (10.5)	–	–	–
65–74	69 (4.8)	271 (4.8)	–	–	–
≥ 75	23 (1.6)	92 (1.6)	–	–	–
Urbanization ^b					
Level 1	654 (45.8)	2619 (45.9)	Reference		
Level 2	413 (28.9)	1516 (26.6)	1.09	0.95–1.25	0.218
Level 3	79 (5.5)	393 (6.9)	0.80	0.62–1.04	0.095
Level 4	119 (8.3)	446 (7.8)	1.07	0.86–1.33	0.564
Level 5	163 (11.4)	736 (12.9)	0.88	0.73–1.07	0.208
Employment					
No	593 (41.5)	2744 (48.1)	Reference		
Yes	835 (58.5)	2966 (51.9)	1.33	1.18–1.50	<0.001
Charlson comorbidity index score					
0	991 (69.4)	4201 (73.6)	Reference		
1	247 (17.3)	834 (14.6)	1.29	1.09–1.51	0.003
≥ 2	190 (13.3)	675 (11.8)	1.24	1.03–1.49	0.025

^aEstimated through univariate conditional logistic regression.

^bLevels of urbanization were specific to Taiwan, with levels 1, 2, 3, 4, and 5 representing highly urbanized areas, moderately urbanized areas, townships, subrural areas, and rural areas, respectively.

than those of their living counterparts, which was not found in the male patients (online Supplementary e-Tables 6 and 7).

Psychiatric and physical comorbidities by sex in the bipolar disorder cohort

Table 3 presents data on the risk of psychiatric and physical comorbidities in the 3-month period before suicide in patients with bipolar disorder (for detailed information, see online Supplementary e-Tables 8 and 9 in the Supplement). Several physical and psychiatric comorbidities were identified. Figure 2 shows the sex-stratified risks of specific physical and psychiatric comorbidities within 3 months of suicide in patients with bipolar disorder (for detailed information, see online Supplementary e-Tables 10–13 in the Supplement). The multivariable regression analysis indicated sex-specific risk profiles in the physical comorbidities. Specifically, the female patients who died by suicide had a higher risk of nonhypertensive cardiovascular disease, pneumonia, chronic kidney disease, peptic ulcer, irritable bowel syndrome, and sepsis but a lower risk of hyperlipidemia than their living counterparts. On the contrary, the male patients who died by suicide had higher risks of only two physical

conditions, namely chronic kidney disease and sepsis, than the living controls. As for the psychiatric comorbidities, both female and male patients who died by suicide respectively experienced high risks of alcohol use-related disorders, substance use-related disorders, anxiety disorder, sleep disorder, and personality disorder than those of their living controls.

Conservative sensitivity analysis ($p < 0.01$) revealed that four physical conditions were retained in the multivariable regression analysis of the female patients who died by suicide (online Supplementary e-Fig. 3 in the Supplement). By contrast, no physical conditions were retained for the male patients. The psychiatric comorbidity risk profiles remained similar except for the anxiety disorder retained for the male patients.

Discussion

To the best of our knowledge, this is the first nationwide population-based cohort study to examine the incidence of suicide and the risk of physical and psychiatric comorbidities that occur within a short period before suicide in patients with bipolar disorder. The MRR of suicide was 2.28 times higher in female patients with bipolar disorder (35.6, 95% CI 27.4–49.5)

Table 2. Sex-Stratified Healthcare Utilization in the 3-Month Period Before Suicide Mortality in Bipolar Disorder Cohort

Characteristics	Suicide Cases (N = 1428)	Living Controls (N = 5710)			
Men	N = 677 (47.4%)	N = 2706 (47.4%)	Crude risk ratio ^a	95% CI	P
	Mean (SD)	Mean (SD)			
Number of hospitalizations					
Total	0.49 (0.82)	0.22 (0.60)	1.73	1.54–1.95	< .001
Nonpsychiatric	0.22 (0.54)	0.11 (0.45)	1.52	1.30–1.78	< .001
Psychiatric	0.27 (0.58)	0.11 (0.38)	2.22	1.84–2.68	< .001
Number of emergency room visits					
Total	0.91 (2.11)	0.32 (1.27)	1.31	1.22–1.40	< .001
Nonpsychiatric	0.06 (0.28)	0.03 (0.23)	1.77	1.25–2.51	.001
Psychiatric	0.84 (2.03)	0.30 (1.20)	1.31	1.22–1.42	< .001
Number of outpatient visits					
Total	8.55 (7.74)	6.45 (7.31)	1.04	1.02–1.05	< .001
Nonpsychiatric	5.41 (6.72)	4.60 (6.38)	1.02	1.01–1.03	.003
Psychiatric	3.14 (2.99)	1.84 (2.41)	1.20	1.16–1.24	< .001
Women	N = 751 (52.6%)	N = 3004 (52.6%)			
	Mean (SD)	Mean (SD)			
Number of hospitalizations					
Total	0.59 (0.85)	0.18 (0.50)	2.53	2.22–2.87	< .001
Nonpsychiatric	0.28 (0.59)	0.08 (0.32)	2.86	2.37–3.45	< .001
Psychiatric	0.30 (0.59)	0.11 (0.37)	2.46	2.07–2.92	< .001
Number of emergency room visits					
Total	1.18 (1.97)	0.41 (1.12)	1.48	1.38–1.58	< .001
Nonpsychiatric	0.06 (0.35)	0.03 (0.22)	1.51	1.13–2.00	.005
Psychiatric	1.12 (1.91)	0.38 (1.07)	1.50	1.40–1.61	< .001
Number of outpatient visits					
Total	12.25 (9.28)	8.68 (7.54)	1.05	1.04–1.06	< .001
Nonpsychiatric	7.91 (8.13)	6.33 (6.71)	1.03	1.02–1.04	< .001
Psychiatric	4.35 (3.41)	2.35 (2.61)	1.27	1.23–1.31	< .001
Men	N = 677 (47.4%)	N = 2706 (47.4%)	Crude risk ratio ^a	95% CI	P
	n (%)	n (%)			
Proportion of outpatient specialist visit					
General practitioner	629 (92.9)	2298 (84.9)	2.44	1.77–3.36	<.001
Internal medicine	181 (26.7)	635 (23.5)	1.20	0.98–1.46	0.072
Surgery	264 (39.0)	960 (35.5)	1.17	0.98–1.40	.081
Orthopedics	100 (14.8)	249 (9.2)	1.72	1.34–2.21	< .001
Psychiatry	90 (13.3)	259 (9.6)	1.45	1.12–1.87	.005
Neurology	537 (79.3)	1534 (56.7)	3.22	2.60–3.99	< .001
Physical rehabilitation	64 (9.5)	214 (7.9)	1.23	0.91–1.66	.180
Dermatology	49 (7.2)	122 (4.5)	1.64	1.17–2.31	.005
Traditional medicine	62 (9.2)	238 (8.8)	1.05	0.78–1.40	.765
	100 (14.8)	361 (13.3)	1.13	0.89–1.44	.325

(Continued)

Table 2. (Continued.)

Characteristics	Suicide Cases (N = 1428)	Living Controls (N = 5710)			
Women	N = 751 (52.6%)	N = 3004 (52.6%)			
	n (%)	n (%)			
Proportion of outpatient specialist visit	738 (98.3)	2826 (94.1)	3.59	2.03–6.34	<.001
General practitioner	214 (28.5)	880 (29.3)	0.96	0.80–1.15	0.664
Internal medicine	365 (48.6)	1201 (40.0)	1.44	1.22–1.70	<.001
Surgery	112 (14.9)	339 (11.3)	1.37	1.09–1.72	.007
Gynecology	171 (22.8)	645 (21.5)	1.08	0.89–1.31	.436
Orthopedics	117 (15.6)	343 (11.4)	1.43	1.14–1.80	.002
Psychiatry	685 (91.2)	2073 (69.0)	4.96	3.78–6.51	<.001
Neurology	82 (10.9)	252 (8.4)	1.34	1.03–1.74	.030
Physical rehabilitation	54 (7.2)	174 (5.8)	1.26	0.92–1.73	.152
Dermatology	86 (11.5)	372 (12.4)	0.92	0.71–1.17	.485
Traditional medicine	184 (24.5)	650 (21.6)	1.18	0.97–1.42	.092

^aEstimated through univariate conditional logistic regression.
Abbreviation: SD, standard deviation

Table 3. Multivariate conditional logistic regression of the risk of psychiatric and physical comorbidities in the 3-month period before suicide mortality in patients with bipolar disorder

Characteristics	Suicide cases (N = 1428) n (%)	Living controls (N = 5710) n (%)	Adjusted risk ratio ^a	95% CI	p
Model for physical comorbidity					
Nonhypertensive cardiovascular disease	129 (9.0)	360 (6.3)	1.37	1.11–1.70	0.004
Pneumonia	59 (4.1)	106 (1.9)	2.03	1.45–2.85	<0.001
Chronic kidney disease	11 (0.8)	61 (1.1)	1.84	1.21–2.81	0.004
Connective tissue disease	28 (2.0)	72 (1.3)	1.60	1.02–2.50	0.040
Sepsis	25 (1.8)	31 (0.5)	2.45	1.42–4.25	0.001
Model for Psychiatric comorbidity					
Alcohol use-related disorder	147 (10.3)	321 (5.6)	1.78	1.43–2.22	<0.001
Substance use-related disorder	123 (8.6)	180 (3.2)	2.27	1.77–2.91	<0.001
Anxiety disorder	334 (23.4)	897 (15.7)	1.34	1.15–1.56	<0.001
Sleep disorder	507 (35.5)	1328 (23.3)	1.59	1.39–1.82	<0.001
Personality disorder	138 (9.7)	220 (3.9)	2.35	1.86–2.97	<0.001

^aFor detailed information, refer to online Supplementary e-Tables 8 and 9 in the Supplement.

*Variables for which the p value in the conditional logistic regression analysis was <0.05 were retained and included in the final model.

than in the male patients with bipolar disorder (15.6, 95% CI 12.7–19.5). The MRRs of suicide were greater among female patients with bipolar disorder across their entire lifespan, with the peak between the ages of 35 and 44 years (57.9, 95% CI 33.6–169.8) and the ages of 35 and 54 years (55.5, 95% CI 29.9–234.3). In the present context, MRRs may be more valid than the SMRs used in other studies (Osby et al., 2001; Pan et al., 2020) for estimating suicide risk in patients with bipolar disorder, given the advantage of comparable follow-up periods between the cohort and comparison groups. Nationwide cohort

studies (Osby et al., 2001; Pan et al., 2020) and a systematic review (Tondo, Isacson, & Baldessarini, 2003) have reported SMRs for suicide of approximately 12.3–15.0 for men and 16.9 to 21.1 for women with bipolar disorder. In line with these findings, the MRRs obtained in the present nationwide cohort study confirm that suicide risk was greater among the female patients with bipolar disorder than among the male patients, which is contrast to that of the general population.

In the current study, several physical comorbidities were associated with suicide in patients with bipolar disorder. The

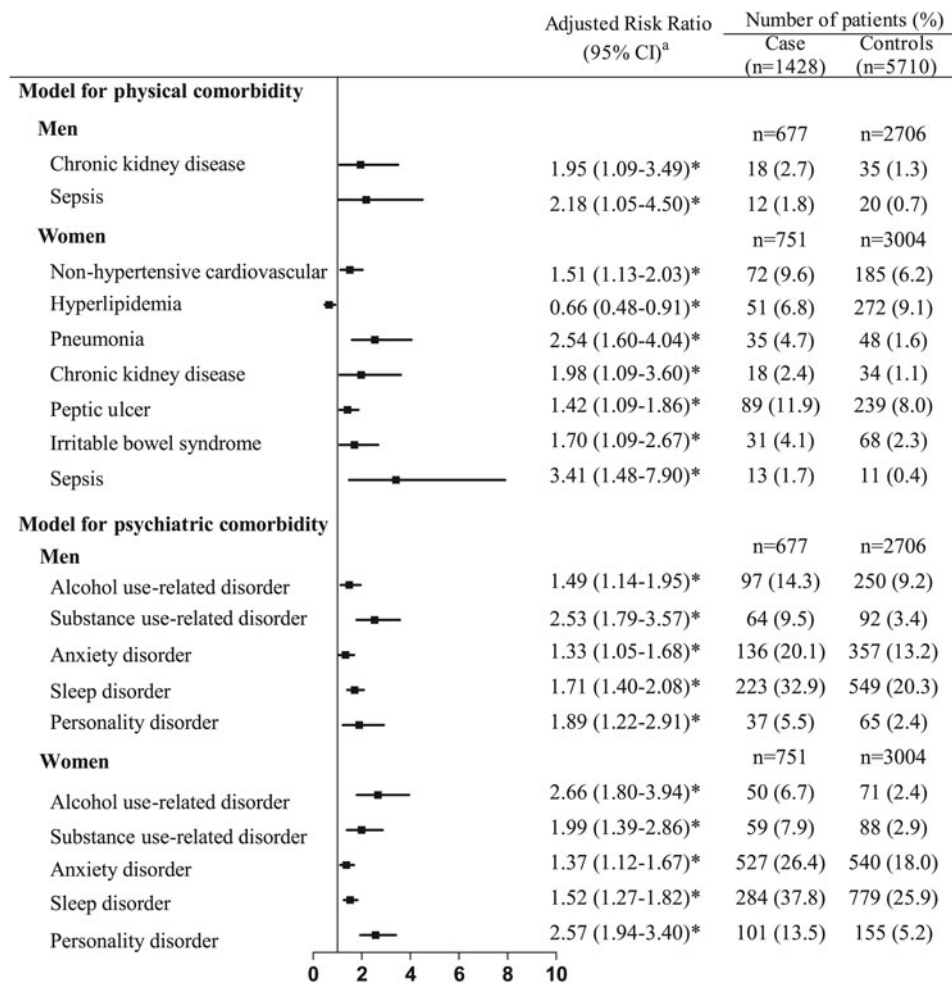


Fig. 2. Sex-stratified risks of physical and psychiatric comorbidities in the 3-month period before suicide mortality in patients with bipolar disorder. *Variables for which the *p* value from the conditional logistic regression analysis was < 0.05 were retained and included in the final model. ^aFor detailed information, refer to online Supplementary e-Tables 10–13 in the Supplement.

mechanisms underlying these associations may be complex. Studies have demonstrated that physical comorbidities are associated with a more severe disease course (i.e. of bipolar disorder), involving more intense symptoms of depression and anxiety, greater mood instability, more frequent rapid-cycling mood episodes, and poorer response to psychotropic medications (Dargel *et al.*, 2018; Forty *et al.*, 2014; Kemp *et al.*, 2010; Kemp *et al.*, 2014). Mediating factors linking physical conditions to an aggravated course of bipolar disorder include the psychological stress of physical illness, maladjustment to work or household responsibilities due to physical disability, and the alternation of pathophysiological mechanisms involving counterregulatory hormones, proinflammatory response, and the gut microbiome (Dargel *et al.*, 2018; Evans *et al.*, 2017; McIntyre *et al.*, 2006). Notably, several studies have observed that major depressive episodes are a critical risk factor for suicide in individuals with bipolar disorder, as indicated by the fact that most suicides in this patient population occur during the depressive phase (Kessing, 2004; Valtonen *et al.*, 2007, 2008). Furthermore, the rapid-cycling subtype of bipolar disorder is associated with a higher risk of suicide attempts and lethality than the non-rapid-cycling subtype (Coryell *et al.*, 2003; Gao *et al.*, 2009). Taken together, evidence suggests that physical comorbidities may increase the

vulnerability of patients with bipolar disorder and thereby contribute to increased suicidality.

Notably, the risks of nonhypertensive cardiovascular disease, pneumonia, peptic ulcer, chronic kidney disease, irritable bowel syndrome, and sepsis were elevated within the 3 months before suicide in women with bipolar disorder. By contrast, only chronic kidney disease and sepsis were associated with suicide in the male patients. The sex-specific risks of physical comorbidities in individuals with bipolar disorder who complete suicide remain unclear, but studies have suggested that women with bipolar disorder are more susceptible to inflammatory and metabolic disruptions than are their male counterparts (Baskaran, Cha, Powell, Jalil, & McIntyre, 2014), which may in turn increase their risk of developing psychiatric and physical comorbidities (Crump, Sundquist, Winkleby, & Sundquist, 2013; Patel *et al.*, 2018). For a clearer understanding of the nature of sex-specific risks in psychiatric and physical comorbidities among patients with bipolar disorder who die by suicide, the mediating factors associated with suicide risk and sex-specific comorbidities in individuals with bipolar disorder must be examined.

Several psychiatric comorbidities have been shown to be associated with suicide in patients with bipolar disorder (Schaffer *et al.*, 2015). The present sex-stratified analysis revealed that the

male and female patients who died by suicide had comparable psychiatric comorbidity risk factors. The findings suggest that although the high psychiatric burden of bipolar disorder contributed to the substantially higher rate of suicide in patients with this condition relative to that in the general population, this burden cannot entirely explain the gap of suicide risk between female and male patients with bipolar disorder.

We also observed a sex-specific pattern of visits to outpatient specialists. As mentioned, the female patients who died by suicide were more likely to have sought care at internal medicine and neurology clinics than their living counterparts. Considering that nonhypertensive cardiovascular disease, pneumonia, peptic ulcer, chronic kidney disease, irritable bowel syndrome, and sepsis are common conditions in internal medicine, this sex-specific pattern of healthcare utilization supports the premise that women with bipolar disorder who die by suicide tend to have more physical comorbidity risk factors than do their male counterparts. However, our analysis was based on diagnostic codes; information on the severity and progression of physical conditions was not available. Therefore, we could not determine whether more visits to the medical departments reflect a better somatic care in our patients. Numerous studies have indicated that relative to the general population, patients with bipolar disorder tend to have fewer opportunities to receive medical procedures for cardiovascular diseases after initial hospital admission (Ayerbe et al., 2018; Laursen, Munk-Olsen, Agerbo, Gasse, & Mortensen, 2009). The untreated cardiovascular disease and its related risk factors are likely to be associated with the abnormalities in brain structure and function (McWhinney et al., 2021; Naiberg et al., 2016b; Naiberg, Newton, Collins, Bowie, & Goldstein, 2016a), therefore aggravating mood symptoms and increasing suicide risk among individuals with bipolar disorder. Given that comorbidities are clinically modifiable risk factors, further research is warranted to examine the association between the effectiveness of somatic healthcare and the risk of suicide in the bipolar disorder population.

Strengths and limitations

The large and nationally representative sample was a strength of the current study. Furthermore, the NHIRD contains detailed information on healthcare utilization and the diagnostic codes of beneficiaries covered by the NHI, thus allowing us to examine the risk of multiple types of psychiatric and physical comorbidities in the 3-month period before the suicide mortality.

Nevertheless, this study has several limitations. First, no information was obtained from face-to-face psychiatric interviews or laboratory examinations to confirm the psychiatric or physical diagnoses. To increase diagnostic validity, we included only patients who had at least psychiatric hospitalization and a discharge diagnosis of bipolar disorder. The accreditation standards of hospitals contracted with the NHI program mandate that diagnoses be made by board-certified psychiatrists. Thus, the accuracy of the diagnostic coding in the current study was acceptable.

Second, we could not preclude the possibility that some of the patients who died by suicide were misclassified as having died of other causes, such as accidental death (typically for reasons concerning social stigma or insurance benefits). Furthermore, we were unable to track the mortality status of patients who emigrated during the study period.

Third, to enroll a larger sample with a long follow-up period, we applied a shorter washout period of 1 year. Nevertheless, our sample may have included patients who were living before 2000 and received continual treatment after 2001. Future studies should recruit only incident patients.

Conclusion

This nationwide population-based cohort study observed that women with bipolar disorder were more likely than men with bipolar disorder to die by suicide across all age intervals. Sex-stratified analyses revealed distinct healthcare utilization patterns and physical comorbidity risk profiles between the sexes. Further research is therefore necessary to elucidate the pathogenetic mechanisms underlying the sex-specific risks of suicide and of physical comorbidities. Given that the comorbid risk factors identified in this study are clinically modifiable, to reduce suicide rates, future studies should investigate the effectiveness of integrated mental and somatic health care in the bipolar disorder population.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S003329172100307X>

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Author contributions. PH Chen, CH Pan, and CJ Kuo conceived and designed the study. CJ Kuo acquired the data. SS Su performed the statistical analysis. PH Chen and CJ Kuo drafted the manuscript. HM Chang and YL Chen made critical revisions to the manuscript for important intellectual content. SY Tsai and CC Chen provided administrative and technical support and supervised the study.

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