Psychiatry and Clinical Neurosciences 2017; **71**: 716–724 doi:10.1111/pcn.12538

Regular Article

Risk factors for early cardiovascular mortality in patients with bipolar disorder

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Aim: We attempted to determine risk factors, particularly pathophysiological changes, for early cardiovascular mortality in bipolar disorder (BD).

Methods: A total of 5416 inpatients with bipolar I disorder were retrospectively followed through record linkage for cause of death. A total of 35 patients dying from cardiovascular disease (CVD; ICD 9: 401–443) before the age of 65 years were identified. Two living BD patients and two mentally healthy adults were matched with each deceased patient as control subjects according to age (±2 years), sex, and date (±3 years) of the final/index admission or the date of general health screening. Data were obtained through medical record reviews.

Results: Eighty percent of CVD deaths occurred within 10 years following the index admission. Conditional logistic regression revealed that the variables most strongly associated with CVD mortality were the leukocyte count and heart rate on the first day of the index hospitalization, as the deceased BD patients were compared with the living BD controls. Systolic pressure on the first day of the index hospitalization can be substituted for heart rate as another risk factor for CVD mortality.

Conclusion: It is suggested that systemic inflammation and sympathetic overactivity during the acute phase of BD may be risk factors for early CVD mortality.

Key words: bipolar disorder, cardiovascular disease, inflammation, mortality, sympathetic overactivity.

PATIENTS WITH BIPOLAR disorder (BD) have an elevated cardiovascular mortality risk and this mortality occurs 10 years earlier than it does in the general population.[1] Cardiovascular diseases (CVD) account for over one-third of mortality in patients with BD.[2,3] Cardiovascular risk in individuals with BD is multifactorial. The widely studied factors that increase cardiovascular risk in patients with BD include obesity, health behaviors (e.g., smoking, inappropriate diet, and physical inactivity),[4] adverse effects of long-term medication,[5] psychosocial functioning,[6] access to quality health care, and underlying pathophysiology.[7] Accordingly, metabolic syndrome involves several traditional cardiovascular risk factors that may partially explain the elevated CVD mortality risk in patients with BD.[8,9] BD is also associated with the inflammatory response system, which influences a spectrum of medical conditions, including CVD and type 2 diabetes, although this association has not been well articulated.[10,11]

Many of the prior studies on CVD mortality in patients with BD have been limited by their sample

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Received 9 November 2016; revised 9 May 2017; accepted 15 May 2017.

size or by using a population-based dataset without patients' clinical features through chart review.[12] Existing data support the association between BD and cardiovascular morbidity. However, it remains unclear if the increased mortality is mediated through traditional risk factors for cardiovascular disease or is related to unidentified and inherent mental illness pathophysiology.[4]

Furthermore, systemic inflammation during the acute phase of BD is considered a risk factor for early natural death, mainly CVD mortality.[3] Moreover, cardiac dysfunction in patients with BD during a manic phase is characterized by low heart-rate variability, reflecting autonomic dysfunction, which is also a strong and independent predictor of mortality in patients with acute myocardial infarction.[13] However, it remains unclear whether inflammatory activation and autonomic dysfunction contribute to the high cardiovascular mortality in patients with BD.

Because psychopathology involves potent physiological changes involving the autonomic nervous system, metabolic dysfunction, and inflammation,[3,13] it is hypothesized that a possible biological connection between psychopathological conditions and the CVD mortality risk may exist. To determine the pathophysiological predictors of early CVD deaths in patients with BD, we aimed to examine the generalizability of well-known risk factors for CVD mortality and to identify specific clinical characteristics as risk factors.

METHODS

All subjects in this study had been treated at Taipei Medical University Hospital, Taipei City Psychiatric Center, or Bali Psychiatric Center, which provide a total of 560 beds for acute patients and 604 beds for chronic patients in northern Taiwan. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. This study was approved by the institutional review board of each hospital. Since the methodology has already been described extensively elsewhere and successfully used in research on completed suicide[14] and natural death[3] in BD, it will only be briefly summarized here.

The national identity (ID) number is unique for each Taiwan resident. Multiple identifiers were used in the matching process to search for the deceased patients, including national ID, sex, and date of birth. A record linkage, in which a 1987–2008 roster of inpatients with mood disorders excluding major depression (ICD-9 codes 296.2x and 296.3x) was electronically matched with data from the Department of Health, Death Certification System in Taiwan recorded from 1 January 1987 to 31 December 2008. Psychiatric diagnoses were based on the DSM-III, DSM-III-R, or DSM-IV, which were the diagnostic systems used in these hospitals during this period. The cause of death was determined on the basis of records in death certificates. More than 70% of circulatory system deaths are attributable to coronary artery disease and cerebrovascular disease with the same pathogenesis – atherothrombosis.[15] Atherothrombosis is a common pathophysiological process of morbid or fatal clinical ischemic events affecting cerebral, coronary, or peripheral arterial circulation. Therefore, we included specific CVD categories in this study, namely coronary heart disease, cerebrovascular disease, congestive heart failure, CVD-associated hypertensive diseases, and CVD-associated hyperlipidemia. Patients who died of CVD (hypertensive and coronary heart diseases, ICD-9: 401–429; cerebrovascular diseases, ICD-9: 430–438; and vascular diseases, ICD-9: 440–443) were enrolled in the study. Information on each potential experimental participant, particularly psychiatric symptoms and history, was carefully and independently reviewed by two board-certified psychiatrists of our research group, with strict DSM-IV diagnostic criteria being reapplied to each deceased patient to confirm diagnoses along with history of rapid cycling and, in particular, to exclude the possibility of mood disorder due to general medical conditions.

All deceased patients who had experienced at least one manic or mixed episode before 31 December 2008 were included in the study. Patients were excluded if they had unclear chart documentation or premature discharge from the index hospitalization. The cut-off age for early death was 65 years because it is well accepted as the geriatric age and is economically relevant as the usual retirement age in developed countries. During the study period, 51 patients who later died of circulatory diseases were diagnosed with bipolar I disorder; 35 of these patients were younger than 65 years when they died and were included in the study. Each deceased patient was matched with two living patients with bipolar I disorder (as controls) according to age (birth year $\pm$ 2), sex, and the date of index admission ($\pm$3 years). Two mentally healthy adults who had visited Taipei Medical University Hospital for general health screening were matched according to sex, age (birth year $\pm$2), and the date of the health screening

examination (±3 years) to compare the results of laboratory and physical examination with those of the deceased patients. These healthy controls were screened for a history of DSM-IV axis I disorders by using a well-validated Chinese version of the General Health Questionnaire[16] and by reviewing medical records. The healthy controls gave their informed consent before participating in the study.

Data collection

A case note form was used for patients visiting these hospitals for the first time, and another form was used for inpatients. Both forms contain over 95 items structured to obtain specific and comprehensive information from patients regarding demographic characteristics, past and present illness, mental state examination, physical condition, alcohol/drug use problem, and family history. Data on patient hospitalization were obtained through personal interviews, serial clinical assessments, and direct observation by residents, nursing staff, and social workers. If the deceased patient had undergone several hospitalizations during the study period, the most recent event was considered the index hospitalization. The index hospitalization for the living controls was the hospitalization date nearest to the date of index hospitalization of the matched deceased patient. Initial findings were reviewed by a consensus panel of experienced investigators who specialized in major psychiatric-disorder-related research for verifying the accuracy and completeness of data for each subject.

Following an overnight period of fasting, the laboratory examination of blood and other metabolic measures of inpatients was routinely conducted once on the morning after admission. The following variables were examined: present psychiatric illness, family history, medication history, and results of physical and laboratory examinations at the index hospitalization. The 2008 sex-specific version of the Framingham Risk Score[17] was calculated according to age, sex, smoking history, hypertension treatment, systolic blood pressure, serum total cholesterol levels, and high-density lipoprotein levels at the index hospitalization. The four main vital signs were routinely monitored by nursing staff every morning after admission. Based on the hospital's standard procedure, heart rate was routinely determined according to the radial pulse measured during a 1-min recording at rest, and then blood pressure was checked every morning. Resting electrocardiography (ECG) was obtained using a simultaneously recorded 12-lead machine with automatic measurements of parameters. The QT interval corrected for the heart rate (QTc) was calculated using Bazett's formula (Bazett's correction). A prolonged QTc interval was ≥440 ms in men and ≥450 ms in women.[18]

Statistical analyses

Two-group comparisons were made by using the χ^2-test with Yates correction or Fisher's exact test for categorical explanatory variables or using the two-tailed Student's *t*-test for continuous variables. The variables significantly associated with the outcome ($P < 0.05$) were entered into the multivariate regression model. Conditional logistic regression models were applied to examine any interaction between potential risk factors and mortality by using SPSS Statistics 17.0 for Windows (SPSS, Chicago, IL, USA). Given the exploratory nature of this study, the univariate analyses are presented without Bonferroni corrections.

RESULTS

At the time of death, the mean age of the 35 deceased patients was 47.2 ± 11.7 years. Twenty-eight deaths (80.0%) occurred within 10 years after the last admission. Twenty-six (74.3%) patients died of hypertensive and coronary heart diseases, eight (22.9%) died of cerebrovascular diseases, and one (2.9%) died of other vascular disease. No significant difference was observed in sociodemographic characteristics, rates of cigarette smoking habit or lowest socioeconomic class, personal and family histories pertaining to the index hospitalization, medical morbidities, abnormal ECG findings, or prolonged QTc values between the deceased and the living control BD groups (Table 1).

The mean values of the leukocyte count, body mass index (BMI), systolic pressure, and heart rate on day 1 of the index hospitalization were significantly higher in the deceased patients than in the living controls (Tables 2,3). The mean heart rate value obtained from ECG of the deceased patients during the index hospitalization was higher than that of the living controls with a marginal statistical significance (Table 2). The deceased patients and

Table 1. Demographic characteristics of patients with bipolar I disorder dying from cardiovascular causes and living controls with bipolar I disorder by comparisons of categorical variables

Characteristics	Deceased patients $n = 35$ n (%)	Living controls $n = 70$ n (%)	χ^2	P
Male	16 (45.7)	32 (45.7)	0.00	1.00
Education ≤ 12 years	29 (82.9)	52 (74.3)	0.96	0.79
Married or widowed	14 (40.0)	33 (47.1)	1.19	0.61
Social class V	29 (82.9)	47 (67.1)	1.32	0.50
Living with family members	27 (77.1)	62 (88.6)	1.12	0.63
History of rapid cycling	11 (31.4)	14 (20.0)	1.68	0.20
Abnormal ECG finding at the index admission	20 (60.6)	35 (50.0)	0.75	0.39
Prolonged QTc[†] on ECG	7 (20.0)	8 (11.6)	1.39	0.49
Comorbid alcohol use disorders during lifetime	9 (25.7)	24 (34.3)	–0.80	0.37
Cigarette smoking habit	17 (48.6)	34 (48.6)	0.00	1.00
History of first-degree relative with mood disorders	9 (25.7)	12 (17.1)	1.51	0.47
Significant concurrent medical morbidity				
Cardiovascular diseases	7 (20.0)	15 (21.4)	0.24	0.62
Brain and cerebrovascular diseases[‡]	5 (14.3)	2 (2.9)		0.07
Endocrine	11 (31.4)	20 (28.6)	0.09	0.91
Gastrointestinal system[‡]	5 (14.3)	13 (18.6)		0.58

[†]Rate-corrected QT interval.
[‡]Fisher's exact test.
ECG, electrocardiogram.

living controls did not show a significant difference in the Framingham Risk Score.

The healthy control group had significantly lower mean BMI values (24.5 ± 3.2 kg/m^2, $t = -2.55$, $P = 0.04$) and ECG heart rate measurements (66.2 ± 10.0 b.p.m., $t = 6.42$, $P < 0.001$) than the deceased BD group (data not shown). According to the associations identified in all univariate analyses of the deceased patients and the healthy controls (Table 3), three variables remained significantly predictive of increased risk for CVD mortality in BD patients: hemoglobin level (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.37–0.83, $P = 0.014$), leukocyte count (OR, 1.56; 95%CI, 1.17–2.08, $P = 0.003$), and heart rate (OR, 1.08; 95% CI, 1.03–1.13, $P = 0.001$).

To assess the simultaneous impact of several potential risk factors for early CVD mortality, a conditional logistic regression analysis was conducted on the basis of preliminary univariate associations identified in the preceding analyses (Tables 1–3). Results of a multivariate logistic regression are displayed in Table 4. The mean values of BMI on day 1 and the discharge day were relatively similar; therefore, only the BMI on day 1 of the index hospitalization was included in the model. In the regression model, only one risk factor (leukocyte counts) was significant at the 0.05 level.

Further statistical analysis was carried out and yielded two explanatory models for predicting early CVD mortality that was highly significant overall. The greatest predictive validity of CVD mortality was provided by leukocyte counts (OR, 1.25; 95% CI, 1.03–1.53; $P = 0.025$) and heart rate on day 1 of the index hospitalization (OR, 1.04; 95%CI, 1.00–1.08; $P = 0.038$). Furthermore, the predictive validity of early CVD mortality was also provided by leukocyte counts (OR, 1.23; 95%CI, 1.01–1.49; $P = 0.04$) and systolic pressure on day 1 of the index hospitalization (OR, 1.03; 95%CI, 1.00–1.06; $P = 0.038$).

DISCUSSION

The strength of this study is that two types of control subjects were recruited and relatively valid laboratory data along with physiological variables, such as the leukocyte count, ECG, and vital signs, were

Table 2. Clinical characteristics and measurement of patients with bipolar I disorder dying from cardiovascular causes and living controls with bipolar I disorder by comparisons of continuous variables

Characteristics	Deceased patients n = 35 Mean (SD)	Living controls n = 70 Mean (SD)	t	P
Illness variables				
Age at onset (years)	25.6 (9.7)	24.4 (7.7)	0.68	0.50
Age at first psychiatric visit to TCPC, TMUH, or BPC	28.3 (9.2)	27,2 (8.1)	0.51	0.62
Age at first psychiatric admission (years)	30.4 (12.6)	29.0 (11.2)	0.60	0.55
Age at index admission (years)	41.5 (12.6)	40.7 (11.7)	0.34	0.73
Age at last psychiatric visit (years)	43.8 (12.2)	46.2 (12.3)	−0.87	0.38
Total affective episodes	10.6 (6.6)	10.4 (6.6)	0.12	0.90
Total hospitalizations	5.5 (4.6)	5.9 (4.1)	−0.37	0.71
Duration of medication before last visit (years)				
Lithium	5.2 (6.2)	6.5 (5.7)	−1.08	0.29
Valproate	0.7 (2.3)	1.2 (2.6)	−0.92	0.36
All antipsychotics	8.7 (7.7)	7.3 (7.4)	0.88	0.38
Typical antipsychotics	8.3 (7.2)	6.9 (6.9)	0.91	0.37
Atypical antipsychotics	0.7 (1.6)	0.4 (1.1)	0.93	0.36
Body mass index of the index hospitalization (kg/m^2)				
Day 1	26.6 (5.8)	24.1 (3.5)	2.26	0.03
Discharge day	26.9 (5.9)	24.7 (3.7)	2.25	0.03
Systolic pressure of index hospitalization (mmHg)				
Day 1	129.7 (18.9)	121.8 (13.9)	2.19	0.03
Day 2	124.0 (20.2)	118.6 (14.0)	1.40	0.17
Day 3	124.1 (17.8)	120.1 (16.0)	1.15	0.25
Discharge day	120.8 (12.6)	115.0 (16.3)	1.80	0.08
Diastolic pressure of index hospitalization (mmHg)				
Day 1	83.5 (14.9)	79.5 (10.4)	1.43	0.16
Day 2	79.7 (10.3)	76.3 (9.8)	1.67	0.09
Day 3	80.0 (11.5)	78.9 (10.6)	0.46	0.65
Discharge day	77.4 (8.4)	74.2 (11.4)	1.41	0.16
Pulse pressure of index hospitalization (mmHg)				
Day 1	46.2 (15.3)	42.5 (10.6)	1.27	0.21
Day 2	44.2 (13.1)	42.1 (11.0)	0.86	0.35
Day 3	44.2 (12.5)	41.2 (10.9)	0.33	0.79
Discharge day	43.5 (9.6)	39.9 (9.4)	1.73	0.08
Heart rate (b.p.m.)				
Day 1	92.7 (14.5)	87.1 (11.3)	2.15	0.03
Day 2	93.8 (12.6)	88.6 (13.9)	1.86	0.07
Day 3	92.2 (12.5)	87.6 (14.8)	1.58	0.12
Discharge day	85.2 (11.1)	84.7 (12.3)	0.20	0.84
ECG measurements				
Heart rate (b.p.m.)	83.8 (18.7)	77.0 (15.1)	1.71	0.09
QRS duration (ms)	94.5 (20.5)	101.5 (154.0)	−0.24	0.85
QT interval (ms)	352.1 (43.2)	367.0 (44.9)	−1.34	0.16
QTc (Bazett's) (ms)	414.7 (33.6)	411.9 (30.8)	0.41	0.69
Framingham risk score	3.9 (4.1)	4.3 (4.6)	−0.45	0.68

ALT, alanine aminotransferase, formerly SGPT; AST, aspartate aminotransferase, formerly SGOT; BPC, Bali Psychiatric Center; ECG, electrocardiogram; TCPC, Taipei City Psychiatric Center; TMUH, Taipei Medical University Hospital.

Table 3. Results of laboratory examination of patients with bipolar I disorder dying from cardiovascular causes, living controls with bipolar I disorder at the index hospitalization, and healthy controls

	Deceased patients(A) n = 35 Mean (SD)	Living controls(B) n = 70 Mean (SD)	A vs B t	Healthy controls(C) n = 70 Mean (SD)	A vs C t
Fasting blood sugar (mg/dL)	103.2 (20.1)	98.4 (24.1)	1.01	91.1 (20.8)	2.57**
Blood urea nitrogen (mg/dL)	12.4 (4.9)	11.3 (3.9)	1.20	13.8 (3.6)	−0.81
Creatinine (mg/dL)	1.0 (0.3)	1.1 (1.0)	−0.67	0.8 (0.2)	3.42***
Uric acid (mg/dL)	7.2 (2.6)	6.5 (2.4)	1.27	5.9 (1.7)	2.71**
AST (U/L)	27.6 (14.0)	25.4 (15.2)	0.71	25.7 (14.7)	1.05
ALT (U/L)	27.5 (16.9)	30.5 (41.3)	−0.41	32.8 (41.3)	−0.65
Cholesterol (mg/dL)	178.7 (33.3)	171.5 (38.3)	0.93	194.8 (37.0)	−2.20*
Triglyceride (mg/dL)	125.9 (51.5)	133.1 (68.3)	−0.41	124.0 (70.2)	−0.10
Sodium (mg/dL)	143.9 (3.9)	140.2 (17.1)	1.23	142.0 (2.9)	0.84
Thyroxine (T_4) (mg/dL)	8.2 (2.5)	7.4 (2.8)	1.49	7.3 (3.0)	0.44
Leukocytes, $\times 10^3/\mu L$	8.1 (2.6)	7.1 (2.0)	2.22*	6.0 (1.7)	4.78****
Erythrocytes, $\times 10^6/\mu L$	4.6 (0.6)	4.7 (1.4)	0.25	4.9 (0.5)	−2.25*
Hemoglobin (g/dL)	13.5 (1.6)	14.2 (3.8)	0.91	14.5 (1.3)	−3.78****
Platelets, $\times 10^3/\mu L$	253.0 (76.8)	234.8 (71.4)	0.99	237.4 (63.1)	0.89

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.025$.
****$P < 0.005$.
ALT, alanine aminotransferase, formerly SGPT; AST, aspartate aminotransferase, formerly SGOT.

examined for all subjects. Age and sex are important risk factors for CVD morbidity and mortality;[17] therefore, age and sex were controlled in the present study to explore other CVD risk factors linked with BD.

The present study has two major findings. First, the elevated leukocyte counts in patients with BD in acute affective episodes are more associated with CVD mortality than traditional cardiovascular risk factors, such as smoking, BMI, and hyperlipidemia. Our early work showing that elevated leukocyte counts potentially predict premature natural mortality in patients with BD[3] supports the present finding. The total leukocyte count is a marker of systemic inflammation and has been shown to be a predictor of coronary heart disease progression and in patients with pre-existing vascular diseases.[19] Furthermore, the leukocyte count is vital for stratifying risks in patients with myocardial infarction and can be used as a universal marker for predicting 1-year mortality after any treatment.[20] Immune dysfunction appears to be a mediator of the association between BD and CVD.[11] Furthermore, chronic inflammation is observed in patients with bipolar

Table 4. Conditional logistic regression of factors for cardiovascular mortality of bipolar I disorder

	Adjusted OR	95%CI for OR	P
Leukocyte count	1.23	1.001–1.51	0.049
Heart rate on day 1 of index hospitalization	1.04	1.00–1.08	0.052
Systolic pressure on Day 1 of index hospitalization	1.01	0.98–1.04	0.55
Body mass index on Day 1 of index hospitalization	0.998	0.99–1.01	0.79

Goodness of fit, $\chi^2 = 8.79$, d.f. = 1, $P = 0.003$. CI, confidence interval; OR, odds ratio.

depression or mania from the acute phase to full remission.[21,22] Therefore, our findings may provide additional evidence that systematic inflammation is a possible risk factor for early CVD mortality in patients with BD.

Second, increased heart rate or systolic pressure on the first day of the index hospitalization may be another risk factor for early circulatory mortality in BD. An elevated heart rate increasing the mechanical stress on the heart and the arterial wall, particularly in middle-aged adults, has been associated with cardiovascular mortality.[23] The heart rate acts as an indicator of sympathetic nervous system activity and depends on the balance between vagal and adrenergic tones.[24] Therefore, a high heart rate in the acute phase of BD may be due to autonomic imbalance. Systolic pressure is mainly determined by the arterial compliance and total peripheral resistance, and it is a more effective predictor of coronary heart disease and congestive heart failure than the diastolic pressure, particularly in patients aged at least 50 years.[25] The heart rate and systolic pressure of patients with BD in the acute phase may increase with sympathetic activity and severity of manic phase. However, some of the present bipolar subjects might suffer from depressive episode with higher sympathetic activity but not increasing heart rate and systolic pressure.[26] Therefore, symptomatic severity cannot account for increased heart rate and systolic pressure. Under the assumption that the illness severity during the acute phase in the deceased patients and living controls was comparable, sympathetic overactivity superior to greater symptom severity may be another explanation for the significant elevation in the heart rate and systolic pressure observed in the deceased patients. Disappearance of the significant elevation of heart rate and systolic pressure from the second day of acute hospitalization may partially contribute to the effects of medication on both the psychopathology and cardiovascular system.

Taking our findings together, patients with BD who exhibit more inflammatory load and sympathetic overactivity may be susceptible to circulatory morbidity and mortality. The inflammatory reflex ensures that the autonomic nervous system regulates the inflammatory response in real time as it controls the heart rate and other vital functions.[27] Therefore, a dysfunctional inflammatory reflex may be a potential cause of elevated leukocyte counts and sympathetic activity in the acute phase of these deceased BD patients. A known association between a high inflammation level and heart rate[28] supports this finding.

The Framingham Risk Score has been used to predict the 10-year risk of fatal cardiac events in the general population,[29] but it fails to predict the mortality risk of the BD patients in this study. Although 80% of the deceased patients died within 10 years following the index admission, their mean Framingham Risk Score at the time of index admission was comparable to those of the living controls. The mean values of the 10-year Framingham Risk Score and BMI for the present deceased patients are close to those of a large population-based sample in Taiwan (4.7 scores and 24.1 kg/m^2, respectively) with the mean age of 47.8 years. The deceased patients did not exhibit any remarkable ECG-related abnormalities, including QTc interval prolongation. This result supports that there is no consistent association between prolonged QTc interval and cardiovascular mortality or morbidity in the general population.[30] Therefore, performing ECG is unable to detect the risk of cardiac mortality reliably. The pathophysiology of cardiovascular disease associated with BD may differ from that in the general population.[31] Our findings support that BD with an excessive risk of new-onset CVD is not fully explained by traditional CVD risk factors[32] and provide additional evidences that physiological changes of BD may increase the risk of early CVD mortality. Comparisons with mentally healthy controls found that lower hemoglobin level could be an additional risk factor for circulatory mortality in BD. Strong evidence suggests that patients with anemia have increased mortality with cerebrovascular disease.[33] The prevalence of anemia among chronic psychiatry patients is higher than the general population.[34] Regular measures of hemoglobin of bipolar patients may be necessary to reliably detect associations between anemia and CVD mortality.

This study has some methodological limitations. First, one-fifth of the deaths occurred more than 10 years after the last admission. The leukocyte count was measured only once at the beginning of the index hospitalization; therefore, determining whether systemic inflammation is a state or trait phenomenon remains difficult. Second, before referral for psychiatric admission, concurrent physical diseases may be neglected by psychiatrists in outpatient clinics. Certain CVD risk factors or somatic diseases may have been present but are not identified in the chart review. Third, death

certificates may be incorrectly attributed to certain categories of causes of death (e.g., heart failure), masking other types of underlying causes (e.g., diabetes mellitus, obstructive pulmonary diseases, and cancer). Moreover, neither validation nor adjudication of the circulatory mortality was performed and a limited number of events was observed. Fourth, using formerly hospitalized patients as a sample may have led to Berkson's bias, which is a selection bias toward severely ill patients with current physical diseases or comorbid psychiatric disorders. Furthermore, there is likely considerable variability in our methodology in clinical care. However, less than 3 years is estimated between mean age at illness onset and mean age at first psychiatric visit at any hospital of this study. Both BD groups manifested typical age at onset, which is during the 20s, according to the literature. Furthermore, additional information from family members may make our data more reliable. The average of 5.5–5.9 hospitalizations in the present BD groups and information available from family members make the identification of recurrent episodes between two admissions reliable in both BD groups. Fifth, medication used by the people included in the study could not be controlled for. Although the medication statuses throughout the lifetime of a patient were comparable between the patient groups, cardiovascular and metabolic effects of long-term medication involving antipsychotics or lithium may confound the results of ECG (e.g., QTc) and routine laboratory examinations upon admission. Finally, there were limited data available for prediction and lack of systematic collection of such data in the exploratory study. In conclusion, systemic inflammation and sympathetic overactivity during the acute phase of BD are considered as additional risk factors for CVD mortality. We suggest that bipolar-illness-related pathophysiological factors partially contribute to CVD mortality. Further investigation should focus on the inflammatory reflex of patients with BD. This would help to prevent early circulatory morbidity and mortality.

ACKNOWLEDGMENTS

This study was supported by grants from the National Science Council, Taiwan (NSC98-2314-B-038-020-MY3). The authors thank Miss Ying-Fang Wang for her assistance in data collection.

DISCLOSURE STATEMENT

None of the authors have conflicts of interest, financial or nonfinancial, regarding the content described in this paper.

AUTHOR CONTRIBUTIONS

S.Y.T. was the principal investigator, designed the study, and wrote the first draft of the manuscript. C.H.L. and C.J.K. undertook statistical analyses and helped with numerous revisions of the manuscript. S.Y.T., P.H.C., K.H.C., and S.H.H. collected the clinical information and reviewed references. All authors participated in interpreting data and contributed to revision of the manuscript and have approved the final version.

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