A Retrospective Analysis of Risk and Protective Factors for Natural Death in Bipolar Disorder

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Objective: Many of the prior mortality studies on bipolar disorder have emerged primarily from the larger health service groups, with a tendency to focus on suicide alone. This study examines personal and clinical characteristics of bipolar patients in Taiwan in order to identify the factors associated with early natural death.

Method: Bipolar patients admitted to a psychiatric hospital in Taiwan between 1987 and 2002 were retrospectively followed through record linkage for cause of death. One living bipolar individual was matched to each deceased patient as a control subject for age, gender, and date of index admission. Clinical data and the results of laboratory examinations during the last period of hospitalization were obtained through a review of medical records.

Results: In a total of 60 natural deaths, the principal cause was circulatory disease (33.3%). Conditional logistic regressions revealed that the variables most strongly associated with natural deaths were years of antipsychotic treatment prior to the last visit (95% CI for odds ratio [OR] = 0.77 to 0.98), serum alanine aminotransferase levels (95% CI for OR = 1.02 to 1.25), and leukocyte counts (95% CI for OR = 1.01 to 2.50). Years of lithium treatment (95% CI for OR = 0.74 to 0.97) may be substituted for antipsychotic treatment as a protective factor.

Conclusions: Systemic inflammation and nonhepatic tissue damage during the acute phase of bipolar disorder may be risk factors for early natural death. Psychiatric treatment, including medication with antipsychotics or lithium, could be a factor in protecting against early natural death.

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Mortality is increased in most major psychiatric disorders.[1] In bipolar disorder, mortality is 2 to 4 times higher than the rate for the general population.[2] Although 18.9% of deaths in bipolar patients are due to suicide, the high suicide rate alone cannot fully account for such excess mortality[3]; thus, attention is directed toward the effects of comorbidity on mortality for certain physical diseases.[4] Nevertheless, as compared to the wide array of studies on suicide, studies on the risks and protective factors against excess/early natural death in bipolar disorder are very limited.

Although circulatory disorders and suicide account for the greatest number of excess deaths in bipolar disorder,[2,3,5,6] among those patients with mixed psychiatric diagnoses, an association has been found between underdiagnosis of medical comorbidity and an elevated risk of lower quality medical care and higher mortality rates.[7,8] The pathophysiology may vary in different psychiatric disorders,[9] and the relationships between natural causes of death and psychiatric disorders are quite subtle. Schneider et al.[10] suggested that biological variables contributed a major component of mortality from natural causes in bipolar disorder. Many of the prior studies on natural deaths in psychiatric disorders either have been limited by their sample size[10] or have had to use data collected by large health service groups with no assessment of conditions taking place through a systematic chart review.[11]

As regards protective factors, treatment with lithium has been associated with a reduction in mortality risk in bipolar disorder, particularly suicide[12,13]; however, the degree to which lithium may reduce mortality rates attributable to natural causes in bipolar patients remains unclear.[14] The existing reports on mortality-related issues in bipolar disorder have been conducted almost entirely among Western populations, in which the principal causes of mortality in psychiatric disorders, cardiovascular and respiratory diseases, may be explained by the high prevalence of smoking.[3,6,15] The mortality outcomes in bipolar disorder could therefore be complicated by the more than 30% comorbidity rate of alcohol/drug use disorders and by the at least 45% smoking rate among Western patients.[16]

In Taiwan, various approaches have consistently reported an approximate 10% comorbidity for alcohol/drug use disorders and a rate of less than 30% for smoking

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among bipolar patients.[17–19] Therefore, the factors contributing to natural death in bipolar disorder that emerge from such populations may be less contaminated by the use of substances and the consequent problems.

It has been proposed that activation of an inflammatory process may mediate the link between affective symptoms, myocardial infarction, and cardiac death.[20] We hypothesize that some biological factors may have an association with early natural death, particularly with regard to mortality from circulatory diseases. Since mortality risk is relatively specific for age, gender, and the follow-up period,[8,15,17,21] the aims of this gender- and age-controlled study are (1) to assess which combinations of clinical characteristics make an independent contribution to natural death and (2) to investigate whether psychiatric medication can reduce the risks of early natural death in bipolar disorder.

METHOD

Subjects

The source of patients was the Taipei City Psychiatric Center (TCPC), Taipei, Taiwan, a Taipei Medical University–affiliated psychiatric teaching hospital that provides comprehensive psychiatric services for 300 acute patients and 250 chronic patients. Since the methodology has already been described extensively elsewhere and successfully used in research on completed suicide in bipolar disorder,[17] it will only be briefly summarized here.

Multiple identifiers were used in the matching process to search for the deceased subjects, including name, age, gender, date of birth, and national identity numbers; the national identity number is unique for each citizen of Taiwan. A record linkage, in which a 1987–2002 roster of 2872 inpatients with mood disorders was electronically matched against data files held in the Taiwan Department of Health Death Certification System for certificates issued between January 1, 1987, and December 31, 2002, was utilized.

A case note form has been used since 1980 for all patients visiting the TCPC for the first time, while a separate form has been used for all inpatients. Both of these forms contain over 95 items that are structured to obtain specific and comprehensive information from patients regarding demographic characteristics and previous psychiatric history, along with details of any treatment at other hospitals, present illnesses, examinations of mental state, physical condition, alcohol/drug use problems, and family history.

Psychiatric diagnoses were based on DSM-III, DSM-III-R, or DSM-IV criteria, which were the diagnostic systems used in the hospital during the period of this study. Throughout the period, mood stabilizers (lithium, valproate, and carbamazepine) and antipsychotics were given to bipolar patients when clinically indicated. The sources of the data pertaining to the patient's hospitalization included standard interviews, serial clinical assessments, and direct observation by residents, nursing staff, and social workers. Following an overnight period of fasting, electrocardiography, chest x-rays, and blood tests, along with other metabolic measures, were routinely conducted on the morning after admission.

Data Collection

Information on each case, particularly psychiatric diagnoses, was carefully and independently reviewed by 2 members of the study research group, with strict DSM-IV diagnostic criteria being reapplied to each deceased patient in order to reconfirm the diagnoses and, in particular, to exclude the possibility of mood disorder due to general medical conditions.

All deceased patients with mood disorders who had exhibited at least 1 manic or mixed episode prior to December 31, 2002, were identified. As of that date, diagnoses of bipolar I disorder had been recorded on 126 deceased patients. While the determination/confirmation of the cause of death was based mainly on death certificates, as a result of reviewing patient charts, some additional deaths were found during the study period with familial confirmation having been available to the clinicians. A total of 60 patients diagnosed with bipolar I disorder (27 male and 33 female) who had died from natural causes were included in the study; the natural deaths included ICD-9 classes I–XVI.

Living Control Subjects

Each deceased patient was matched with 1 living patient with bipolar I disorder (as a control subject) based on age (± 2 years), gender, and the date of the index admission (± 3 years). However, no suitable living controls were available for 9 elderly deceased patients. The final study population comprised 51 deceased patients (24 male and 27 female) and their matched living controls, who provided their written informed consents for participation in the study.

In order to facilitate collection of data during the chart review, a specialized chart abstraction form was developed comprising 87 items. Data on all of the illness variables were recorded, from the first visit to the TCPC until the last visit, for both the deceased patients and the living controls. If any of the deceased patients had undergone several hospitalizations during the period of this study, the most recent event was considered to be the index hospitalization; however, the index hospitalization for the living controls was taken as the closest hospitalization to the index hospitalization of the matched case.

Onset of bipolar disorder was defined as symptoms necessitating hospitalization, or the first occurrence of affective symptoms causing severe impairment in the psychosocial functioning of the subject. Significant or se-

vere medical disease was extracted from case notes if it was potentially life-threatening without regular follow-up. All of the extracted data were double-checked to rule out potential individual errors. The exact consumption of all psychotropic drugs administered to each patient was calculated on an annual basis, from the year of the introduction until the year of the patient's death or emigration or the end of the observation period.

Statistical Analysis

Group comparisons between deceased patients and living controls were made by χ^2 test with the Yates correction or Fisher exact test when explanatory variables were categorical, with the 2-tailed Student t test being used for continuous variables. The analysis reported here involves a conditional logistic regression equation fitted through stepwise model selection methods with the use of SPSS Base 10.0 software (SPSS, Chicago, Ill.). The potential independent variables with at least a moderate association with natural death ($p < .15$) were selected for entry into multivariate logistic regression models.

RESULTS

At the time of death, the mean age of the 60 deceased patients was 53.0 years (SD = 15.3, range, 24–83 years; women: 56.0 ± 14.9 years and men: 49.7 ± 15.4 years). A total of 37 deaths (61.7%) occurred within the first 6 months after the subjects' last psychiatric contact with the TCPC; of these, 27 deaths (45.0%) occurred within the first month after the last visit. A total of 31 deaths (51.7%) occurred within the first 2 years after the last admission. The mean ± SD interval from onset of bipolar disorder to death was 20.4 ± 13.6 years.

The most frequent cause of death among the 60 patients (33.3%) was circulatory diseases, including cardiovascular diseases (ICD-9 codes: 390–429, N = 14) and cerebrovascular diseases (ICD-9 codes: 430–438, N = 6), followed by respiratory diseases (ICD-9 codes: 460–519, N = 14), diseases of the digestive system (ICD-9 codes: 520–577, N = 8), neoplasm (ICD-9 codes: 140–239, N = 5), infectious diseases (ICD-9 codes: 11–42, N = 5), endocrine diseases (ICD-9 codes: 240–279, N = 3), and diseases of other systems (N = 5). Death from circulatory or respiratory diseases accounted for 56.7% (N = 34) of natural cause mortality.

Of the 60 deceased patients, a total of 20 (33.3%) were smokers (15 male and 5 female), while one third of the deceased patients (N = 20) and one third of the living controls (N = 17) had abnormal electrocardiography findings during the index admission. The proportion of deceased patients with leukocyte counts in excess of 7000/μL was slightly higher than that of the living controls, at 53.3% (N = 32) and 35.3% (N = 18), respectively ($\chi^2 = 3.62$, df = 1; p = .06). There was no difference in sociodemographic characteristics between the deceased patients and the living controls (Table 1). Furthermore, these 2 groups were both rated predominantly in the lower socioeconomic classes (Hollingshead class IV or V)[22] and lived with family members.

Table 1. Sociodemographic Characteristics of Patients With Bipolar I Disorder Dying From Natural Causes and Living Controls With Bipolar I Disorder

Characteristic	Deceased Patients (N = 51)	Living Controls (N = 51)
Marital status (married/widowed), N (%)	39 (76.5)	32 (62.7)
Living with family members, N (%)	42 (82.4)	45 (88.2)
Socioeconomic class (Hollingshead) IV or V at index admission, N (%)	48 (94.1)	44 (86.3)
Education ≥ 12 y, N (%)	22 (43.1)	28 (54.9)
Cumulative age at the end of 2002, mean ± SD, y	63.9 ± 16.6	59.9 ± 14.8

Among the categorical variables of the full history of the 51 deceased patients and the 51 living controls, a significantly higher proportion of deceased patients with residual symptoms could only be found in the last follow-up years (Table 2). Table 3 shows that the living controls had a significantly higher number of hospitalization events as well as more years of medication with antipsychotics and lithium, all of which were of relevance to psychiatric treatment. Of the physiological variables, the mean serum levels of thyroxine (T_4), aspartate aminotransferase (AST; formerly SGOT), and alanine aminotransferase (ALT; formerly SGPT) were significantly higher in the deceased patients than in the living controls.

In a comparison between those patients who died from cardiovascular diseases (N = 14) and all other deceased patients, no significant differences were revealed in either the leukocyte counts or the serum levels of AST, ALT, and T_4 (data not shown); however, in those patients who died from cardiovascular diseases, the mean serum levels of AST and ALT were significantly higher than those of the living controls (AST: 34.6 ± 18.8 U/L vs. 19.3 ± 11.8 U/L; $p < .05$ and ALT: 45.3 ± 28.4 U/L vs. 16.9 ± 9.9 U/L; $p < .05$, respectively). There were no differences between the serum levels of AST and ALT in those patients who had died from liver diseases (N = 5) and those of either the living controls or the other deceased patients (N = 46) (data not shown).

In order to assess the simultaneous impact of several potential risk factors for natural death, a conditional logistic regression analysis was conducted based upon the preliminary univariate associations identified in the preceding analyses (Tables 2 and 3). The duration of psychopharmacologic treatment, along with the serum levels of ALT and the leukocyte counts in the acute phase, yielded 2 explanatory models for predicting natural death outcomes that were, overall, highly significant (Tables 4 and 5). The greatest predictive validity of natural death

Table 2. Clinical Characteristics of Patients With Bipolar I Disorder Dying From Natural Causes and Living Controls With Bipolar I Disorder by Comparisons of Categorical Variables

	Deceased Patients (N = 51)		Living Controls (N = 51)		
Characteristic	N	%	N	%	p
Mania as the first episode	26	51.0	27	52.9	NS
History of rapid cycling	14	27.5	18	35.3	NS
History of depressive episode	34	66.7	39	76.5	NS
History of first-degree relative with bipolar disorder	10	19.6	11	21.6	NS
Residual syndrome in the last follow-up year[a]	27	52.9	17	33.3	< .05
Abnormal ECG finding at the index admission	17	33.3	17	33.3	NS
Significant concurrent medical disease					
Cardiovascular	18	35.3	21	41.2	NS
Endocrine	17	33.3	19	37.3	NS
Hepatobiliary tract	15	29.4	11	21.6	NS
Malignance	4	7.8	3	5.9	NS
Hepatitis B virus carrier	14	27.5	7	13.7	< .1
Cigarette smoking	19	37.3	21	41.2	NS
Comorbid alcohol use disorders	11	21.6	13	25.5	NS
Comorbid other substance use disorders	1	2.0	2	3.9	NS

[a] $\chi^2 = 4.00$, df = 1.
Abbreviations: ECG = electrocardiogram, NS = not significant.

Table 3. Clinical Characteristics of Patients With Bipolar I Disorder Dying From Natural Causes and Living Controls With Bipolar I Disorder by Comparisons of Continuous Variables

	Deceased Patients (N = 51)		Living Controls (N = 51)			
Characteristic	Mean	SD	Mean	SD	t	p
Illness variable						
Total hospitalizations	4.6	3.4	6.5	4.2	–2.54	< .025
Total episodes	10.1	6.9	11.4	5.9	–0.98	NS
Age at onset, y	30.9	13.5	31.0	12.8	0.02	NS
Age at index admission, y	47.0	12.9	49.0	13.6	–0.75	NS
Age at last hospital visit, y	48.8	13.4	53.2	14.2	–0.61	NS
Duration of medication prior to last visit, y						
Antipsychotics	4.4	4.8	7.5	7.2	–2.85	< .025
Lithium	3.0	3.9	6.2	5.7	–3.26	< .0025
Antidepressants	0.4	1.0	1.1	2.9	–1.42	NS
Physiological variables at index hospitalization						
Body mass index, kg/m^2	23.72	4.51	23.67	4.60	0.02	NS
Fasting blood sugar, mg/dL	122.5	78.0	103.0	22.5	1.71	.09
Serum AST, U/L	30.2	19.9	20.9	16.2	2.56	< .025
Serum ALT, U/L	33.9	25.5	20.5	9.8	3.48	< .001
Serum uric acid, mg/dL	6.37	1.99	6.51	2.44	–0.32	NS
Serum cholesterol, mg/dL	181.3	40.1	172.6	34.7	1.15	NS
Thyroxine, mg/dL	8.8	2.5	7.6	2.0	2.73	< .0075
Leukocytes, $\times 10^3/\mu L$	7.61	3.25	6.62	1.67	1.92	.06

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, NS = not significant.

outcomes was provided by the duration of antipsychotic treatment, serum ALT levels, and leukocyte counts (Table 4).

DISCUSSION

Several clinical characteristics typical of bipolar disorder, as described in the DSM-IV,[23] are manifested in both the living controls and the deceased patients, including a mean age at onset of 31 years, a positive rate of bipolar disorder in first-degree relatives (20%), a prior depressive episode in 71.6% of cases, and a history of rapid cycling exhibited in about 30% of cases. Thus, this study does appear to be representative of a bipolar patient group commonly seen by clinicians elsewhere.

A common limitation of mortality studies is that data obtained from death certificates may be inaccurate and may thus tend to attribute death by classification under certain causes of death (e.g., heart failure), which may mask other types of underlying causes (such as diabetes mellitus or cancer).[24] The most common competing conditions are respiratory, circulatory, and malignant diseases,[25] all of which are potentially fatal but etiologically independent conditions arising simultaneously within an individual.[21] As the present sample was a heterogeneous group of patients dying from any natural cause, this study

Table 4. Conditional Logistic Regression of Factors for Natural Death: Model 1[a]

Variable	Adjusted OR	95% CI for OR	p
Years of antipsychotic treatment	0.87	0.77 to 0.98	< .025
Serum ALT level	1.13	1.02 to 1.25	< .025
Leukocyte count	1.58	1.01 to 2.50	< .05

[a]Goodness of fit, $\chi^2 = 20.33$, df = 4; p = .0004.
Abbreviations: ALT = alanine aminotransferase, CI = confidence interval, OR = odds ratio.

Table 5. Conditional Logistic Regression of Factors for Natural Death: Model 2[a]

Variable	Adjusted OR	95% CI for OR	p
Years of lithium treatment	0.85	0.74 to 0.97	< .025
Serum ALT level	1.08	1.01 to 1.15	< .025
Leukocyte count	1.38	0.94 to 2.04	< .098

[a]Goodness of fit, $\chi^2 = 19.81$, df = 4; p = .0002.
Abbreviations: ALT = alanine aminotransferase, CI = confidence interval, OR = odds ratio.

was designed to identify, from various natural causes, the common risk factors of mortality in patients of mixed age with bipolar disorder.

Bipolar mania may be accompanied by a state-dependent pathophysiologic alteration in immunomodulatory systems.[9,26] Laboratory data on the subjects analyzed in this study revealed their physical conditions at hospitalization for the acute phase, mostly manic or mixed episodes. Therefore, given the potential for variation in pathophysiology during the opposite polarities of affective episodes and the subsequent remission of bipolar patients, our findings should be interpreted cautiously.

The present study has raised 3 major findings. First, the duration of either antipsychotic or lithium treatment is a significant factor in reducing the risk of natural death in patients with bipolar disorder. The medication taken by the subjects of this study could not be controlled. The living controls had a similar mean number of affective episodes and mean age at onset of illness and last psychiatric visit as the deceased patients, but had a significantly higher number of admissions and years of medication, which may indicate that the living controls were more compliant and received better medical care and that the reduction in mortality may be a consequence of appropriate treatment. Furthermore, residual affective symptoms were manifested more in the deceased patients in the final year of follow-up. Taken together, the present findings support the hypothesis that psychiatric treatment, particularly pharmacotherapy, may lead to improvements not only in psychopathologic outcomes,[27] but also in the general health of bipolar patients. A further way to prevent early natural deaths in bipolar disorder is therefore to engage in vigorous treatment of the illness.

Second, the elevated leukocyte counts during the acute affective episode may increase the risk of early natural death from all causes in bipolar patients, independent of smoking and the risk factors from other cardiovascular diseases. Among this group of Asian bipolar patients, the increased mortality rates from circulatory and respiratory diseases as the leading causes of natural death concur with the findings of the previous reports on Western patients[3,6]; however, the prevalence of such diseases does increase with age. Despite our having an age-matched control group, the large age range in our subjects may result in some difficulties in interpreting the findings of our study. In this bipolar study, the major cardiovascular risk factors,[28] including concurrent hypertension, serum cholesterol level, obesity (body mass index), smoking, and abnormal ECG findings during the index hospitalization, have failed to reveal any association with mortality from natural causes.

An association between elevated leukocyte counts (> 7000/μL) and all-cause mortality has been repeatedly observed among various populations.[29,30] The total leukocyte count is one marker of systemic inflammation. Over half of the deceased subjects in this study had leukocyte counts in excess of 7000/μL, a rate which was higher than that of the living controls. The present results may therefore indicate an association between systemic inflammation and increased risk of mortality from natural causes in bipolar disorder. Since the use of mood stabilizers and symptomatic severity may have distinct effects on leukocyte counts,[9,31] the measurement of other immunoinflammatory parameters may provide a more accurate mechanism for analyzing such an association.

Third, the elevation of serum ALT level can be considered an additional risk factor of natural death in bipolar disorder. ALT is found primarily in the liver, and liver disease is an important cause of increased ALT and AST activity. A simultaneous release of lactate dehydrogenase (LDH) and AST has been reported in newly admitted manic patients, presumably as a result of release from muscles in association with agitation.[32] Since the serum levels of LDH and creatine kinase were not measured, we are unable to determine whether the elevation of ALT and AST is indicative of disruption of myocytes or cell damage in other tissues. However, patients dying from cardiovascular diseases had significantly higher serum ALT and AST levels than the living controls. Both ALT and AST are widely distributed throughout the body, and any abnormal elevation of ALT and AST is a surrogate marker of cardiac dysfunction.[33] Furthermore, liver disease was not the main cause of natural death among the subjects of the present study; thus, the elevation of serum AST and ALT levels in our deceased patients cannot be fully explained by abnormal liver function. Nonhepatic factors, including myogenic (especially cardiac) factors, may be potential causes of elevated ALT activity in bipolar disorder.

We acknowledge a number of major methodological shortcomings in the present study. First, the use of formerly hospitalized patients as a sample in this study may have led to Berkson's bias, i.e., a selection of severely ill patients with concurrent physical diseases or comorbid psychiatric disorders. Second, prior to referral for psychiatric care, concurrent physical diseases are often missed during physical examination; thus, certain somatic disorders that may have been present may not have been identified by chart review. Third, death by natural causes is often entered in the death certificate for official use in Taiwan so as to avoid any potential stigma associated with suicide; thus, the possibility of recruiting suicide victims in this study cannot be completely excluded. Fourth, the differences in the quality of medical care received by patients may substantially affect the mortality of the same disease entity. In this study, only the number of admissions and years of medication were considered as the 2 parameters for analyzing the effects of medical care on natural death. Fifth, a retrospective study such as this, based on information contained from case notes, does have its limitations in terms of data accuracy and validity; however, more than half of the patients died within 2 years following the index hospitalization, which increased the validity of the data from chart reviews. Finally, with the possibility of changes in name and other personal identifiers, which would obviously result in recording errors, missed linkages may have occurred.

In conclusion, systemic inflammation and nonhepatic tissue damage may be component factors in the risk of early natural death; however, psychiatric treatment, especially medication and adequate prophylaxis, may bring about a reduction in the risk of early natural death in the long term. In order to reduce the risk of early natural death, there is a need for further investigation into bipolar disorder, with a large sample size. Such a study would need to focus on the differences in pathophysiologic change during illnesses among subgroups in the same age range and with the same medical diseases.

Drug names: carbamazepine (Carbatrol, Equetro, and others), lithium (Eskalith, Lithobid, and others).

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