

Factors Associated with Non-Remission in Bipolar Disorder: The Multicenter Treatment Survey for Bipolar Disorder in Psychiatric Outpatient Clinics (MUSUBI)

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Purpose: The aim of this study was to identify factors associated with non-remission in bipolar disorder.

Patients and Methods: The multicenter treatment survey for bipolar disorder in psychiatric outpatient clinics (MUSUBI) study used a questionnaire administered at 176 clinics throughout Japan from September to October 2016. Clinic psychiatrists performed a retrospective medical record survey of consecutive cases with bipolar disorder. Patients were considered to be in remission if they met all of the following criteria: they were not in a mixed state, their manic or depressive symptoms were either borderline or nonexistent (corresponding to 2 or 1 points on the Clinical Global Impressions Scale, Bipolar Version), and their psychiatrists clinically considered them to be in remission. Enrolled patients were classified into remitters group and non-remitters group and demographic and clinical characteristics were contrasted between the groups. Non-remitters were compared with remitters, using a series of logistic regression analyses.

Results: A total of 3130 patients (1420 men; mean age: 50.3 years) were included in this study; 1307 patients (41.8%) were in remission. Of the remaining 1823 patients, 1260 (40.3%) had mild to severe depression, 261 (8.3%) suffered from manic or hypomanic episodes, and 302 (9.6%) were in a mixed state. Logistic regression analyses found the following eight factors to be significantly correlated with non-remission in patients with bipolar disorder: female gender, younger age, unemployed status, rapid cycling pattern, comorbid alcohol/substance abuse, poorer social function, lithium non-use, and antidepressant use.

Conclusion: The MUSUBI study, the largest nationwide investigation on bipolar disorder, identified eight clinically relevant factors associated with non-remission in bipolar patients. They have important clinical implications; further prospective studies are necessary to replicate these findings and to guide better managements for those in serious needs.

Keywords: bipolar disorder, non-remission, nationwide study, mood stabilizer, antipsychotics

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Introduction

Bipolar disorder is frequently a severe, recurrent, and debilitating psychiatric disorder.¹ Although several treatment-guidelines and meta-analyses on bipolar disorder have been published across the globe,²⁻⁷ the problem of non-response and non-remission has been ubiquitous in the real-world clinical settings. As such,

many individuals with bipolar disorders still suffer from troublesome symptoms, resulting in substantial financial, social, or work-related issues.⁸

Bipolar disorder is classified into bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified, for which different psychopharmacological treatment is recommended. In addition, the first-line medications are divided individually for acute mania phase, bipolar depression phase, and maintenance phase. Such a complexity constitutes the hurdles in conducting clinical research on bipolar disorders in a longitudinal manner. Only a few large-scale studies are available to guide clinical management (e.g., the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)⁹), and maintenance treatment is complicated in that the studies usually adopt an enrichment design;¹⁰ information is critically racking on what to do to who fail to show response or remission with standard treatments.

On the other hand, it is frequently challenging to distinguish bipolar disorder from unipolar depression; the average delay in diagnosis of bipolar disorder is reported to be 5–10 years after the symptoms begin.^{11,12} Even after an accurate diagnosis is made, it still remains a challenge to achieve complete remission of all symptoms with the currently available psychotropic medications, and symptoms may even become progressively more severe over time.^{13–15} It is thus of high clinical importance to extract factors associated with remission of bipolar disorder. According to the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study, patients who had a higher overall score on the Clinical Global Impression Scale, Bipolar Version for bipolar disorder (CGI-BP), who had depressive episodes in the year before, who had poor social functioning, and who were treated with typical antipsychotics or antidepressants were found to be less likely to achieve remission or recovery.¹⁶ However, while treatment response has usually expressed with a “relative” threshold (e.g., 50% decrease in the representative rating scales), the definition of remission in patients with bipolar disorder, albeit often arbitrarily expressed with an absolute threshold (e.g., a score of less than 7 on the Montgomery-Asberg depression rating scale¹⁸), has not been unequivocally established to date.¹⁷

With these backgrounds, the goal of this study was to perform a large-scale investigation of patients with bipolar disorder in order to identify factors associated with non-remission.

Materials and Methods

Study Design and Subjects

The multicenter treatment survey for bipolar disorder in psychiatric outpatient clinics (MUSUBI) is a cross-sectional study in which a questionnaire was administered at 176 clinics located across Japan from September to October 2016. Patients diagnosed with bipolar disorder according to the Tenth Revision of the International Classification of Diseases and Related Health Problems, 10th edition (ICD-10) and treated at the aforementioned clinics were included; patients with serious physical conditions such as terminal cancer or intractable diseases were excluded. Almost all psychiatrists involved in this study were psychiatric specialists certified by the Japanese Society of Psychiatry and Neurology, and/or designated psychiatrists certified by the Japanese Ministry of Health, Labour and Welfare.

Study Procedures

Clinic psychiatrists were asked to complete a questionnaire by performing a retrospective medical record survey of consecutive cases with bipolar disorder, beginning with the first patient who visited the clinic during the study period. The questionnaire included patient characteristics (age, gender, height, weight, academic background, and occupational status), comorbidities, psychiatric symptoms, course of the illness, the Global Assessment of Functioning (GAF) score, and details of pharmacological treatment. We mailed this questionnaire to each outpatient clinic in 20 copies and analyzed the responses.

This study focused on factors associated with remission (versus non-remission). Based on the proposal of the International Society of Bipolar Disorders, this study defined patients as being in remission if they met all three of the following criteria: they were not in a mixed state, their manic or depressive symptoms were either borderline or non-existent (corresponding to 2 or 1 points on the CGI-BP),¹⁷ and their psychiatrists clinically considered them to be in remission. Non-remitted patients comprised all the rest of bipolar patients and might have been in depressive, (hypo)manic and mixed state; we hereby term them remitters and non-remitters, respectively.

Statistical Analysis

SPSS version 25 (SPSS, IBM Corp, Armonk, NY, USA) was used for the analyses. All of the statistical tests were based on a two-sided significance level of 0.05 unless

otherwise specified. Demographic and clinical characteristics were analyzed using Mann–Whitney *U*-test or Kruskal–Wallis test for differences between remitters and non-remitters. For pharmacological treatment, comparisons were made among the following four groups: remission group, manic state group, depressive state group and mixed state group. Pearson's chi-square test was first used to compare the four groups, and then drugs with significant differences were analyzed using Mann–Whitney *U*-test for each pair of groups. A univariate logistic regression analysis was first performed to identify the demographic and clinical features of non-remitters. A multivariate logistic regression analysis was then performed for the features with a *p*-value of less than 0.001 in univariate analysis. The factors with a *p* value of 0.05 or less in the multivariate analysis were extracted as being significantly associated with non-remission.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Epidemiological Research. Prior to the initiation of the study, the study protocol was reviewed and approved by the institutional review board of the ethics committee of the Japanese Association of Neuro-Psychiatric Clinics (ID:

20160822). Since this was a retrospective medical record survey, informed consent was exempted but we instead released information on this research so that patients were free to opt out. To protect patients' personal information, a study-specific unique subject identification number was assigned to each patient for linkable anonymity.

Results

Demographic Characteristics

Completed questionnaires on 3213 patients with bipolar disorder were returned from 176 outpatient facilities participating in this study; response rate was 91.3%. Eighty-three patients, who missed much of the data on psychiatric symptoms or medications, were excluded, leaving a total of 3130 patients to be included in this study.

The demographic characteristics of the study sample are summarized in Table 1. The mean patient age was 50.3 years, and 45.4% of the patients were men. As for occupational status, 35.3% of the patients were working full time while 33.7% were unemployed. Regarding educational background, 37.1% of the patients were university graduates. The average body mass index was 23.4 kg/m². There were statistically significant differences between remitters vs non-remitters in terms of gender, age, and current work status.

Table 1 Demographic Characteristics

Variables	Total	Non-Remitters	Remitters	p value
N	3130	1823	1307	
Male gender n (%)	1420 (45.4)	763 (41.9)	657 (50.3)	<0.001
Age (years): mean±SD	50.3±13.9	48.9±13.3	52.2±14.4	<0.001
Current work status: n (%)				<0.001
Unemployed	1054 (33.7)	690 (37.8)	364 (27.9)	
Full-time manager	186 (5.9)	88 (4.8)	98 (7.5)	
Full-time worker	918 (29.3)	457 (25.1)	461 (35.3)	
Part-time worker	294 (9.4)	165 (9.1)	129 (9.9)	
Housewife	497 (15.9)	305 (16.7)	192 (14.7)	
Student	34 (1.1)	20 (1.1)	14 (1.1)	
Employment of the disabled	90 (2.9)	65 (3.6)	25 (1.9)	
Educational background: n (%)				0.082
Special support education school	10 (0.3)	5 (0.3)	5 (0.4)	
Junior high school	146 (4.7)	85 (4.7)	61 (4.7)	
High school, vocational school	1394 (44.5)	844 (46.3)	550 (42.1)	
Junior college, technical college	271 (8.7)	173 (9.5)	98 (7.5)	
University	1059 (33.8)	588 (32.3)	471 (36.0)	
Master's degree or higher	102 (3.3)	62 (3.4)	40 (3.1)	
Body Mass Index (kg/m ²): mean±SD	23.4±3.9	23.4±3.9	23.4±3.8	0.681

Clinical Characteristics

There were 1307 patients (41.8%) in remission on a cross-sectional basis. Of the remaining 1823 patients who comprised the non-remission group, 1260 (40.3%) had mild to severe depression, 261 (8.3%) suffered from manic or hypomanic episodes with a score in the CGI-BP of 3 or more, and 302 (9.6%) were in a mixed state. A total of 329 patients (10.5%) had bipolar disorder with a rapid cycling characteristic.

The clinical characteristics of the patients are summarized in Table 2. The mean age at the onset of the first episode was 34.7 years. Our sample included 610 patients (19.5%) with coexisting psychiatric disorders, 31.0% with physical complications, and 5.3% with alcohol/substance abuse. There were statistically significant differences between the groups in terms of age of onset, comorbidity of personality disorders, comorbidity of pervasive developmental disorders, rapid cycling pattern, comorbidity of alcohol/substance abuse, and social function. Lithium use was more frequent among remitters but psychopharmacological treatment was more extensive among non-remitters.

Pharmacological Treatment

Almost all of the patients had been receiving any psychopharmacological treatment. The results, in relation to mood states, are detailed in Table 3. Many patients across the four groups were treated with lithium. Lithium was used significantly more frequently in the remission group than in the depressive state group (53.9% vs 41.5%, respectively; $P<0.001$). On the other hand, lamotrigine was administered significantly more frequently in the depressive state group and the mixed group than in the remission group (28.6% and 23.2% vs 20.1%, respectively; $P<0.001$ and $P=0.017$). While more than 20 antipsychotic drugs were available in Japan at the time of this survey, Table 3 lists only representative ones. Aripiprazole was the most commonly prescribed antipsychotic, and was administered frequently in the depressive state group and the mixed state in particular. Furthermore, a total of 1291 patients (41.2%) were receiving various types of antidepressant drugs; 155 patients (5.0%) were treated with tricyclic antidepressants and 120 patients (3.8%) were treated only with antidepressants in the absence of mood stabilizers or antipsychotics. Of the 1260 patients in the

Table 2 Comparison of Remitters vs Non-Remitters

Variables	Total	Non-Remitters	Remitters	p value
N	3130	1823	1307	
Age of onset (years): mean \pm SD	34.7 \pm 12.5	33.5 \pm 12.0	36.2 \pm 13.0	<0.001
Personality disorders: n (%)	181 (5.8)	148 (8.1)	32 (2.4)	<0.001
Pervasive developmental disorders: n (%)	207 (6.6)	148 (8.1)	59 (4.5)	<0.001
Alcohol/substance abuse: n (%)	167 (5.3)	133 (7.3)	34 (2.6)	<0.001
Physical comorbidity: n (%)	968 (30.9)	557 (30.6)	411 (31.4)	0.601
Rapid cycling: n (%)	329 (10.5)	264 (14.5)	65 (5.0)	<0.001
Social function: n (%)				<0.001
Global Assessment of Functioning 81–100	1008 (32.2)	203 (11.1)	805 (61.6)	
Global Assessment of Functioning 61–80	1407 (45.0)	972 (53.3)	435 (33.3)	
Global Assessment of Functioning 41–60	606 (19.4)	550 (30.2)	56 (4.3)	
Global Assessment of Functioning 1–40	87 (2.8)	81 (4.4)	6 (0.5)	
Pharmacological treatment: n (%)	3104 (99.2)	1811 (99.3)	1293 (98.9)	0.147
Mood stabilizers: n (%)				
Lithium	1488 (47.5)	783 (43.0)	705 (53.9)	<0.001
Valproic acid	893 (28.5)	533 (29.2)	358 (27.4)	0.259
Carbamazepine	149 (4.8)	97 (5.3)	52 (4.0)	0.082
Lamotrigine	744 (23.8)	481 (26.4)	263 (20.1)	<0.001
Antipsychotics: n (%)	1692 (54.1)	1081 (59.3)	611 (46.7)	<0.001
Antidepressants: n (%)	1291 (41.2)	828 (45.4)	463 (35.4)	<0.001
Anxiolytics: n (%)	1133 (36.2)	739 (40.6)	394 (30.2)	<0.001
Hypnotics: n (%)	1886 (60.3)	1213 (66.5)	673 (51.5)	<0.001

Table 3 Psychotropics According to Mood State

	Remission (Re)	Manic State (Ma)	Depressive State (De)	Mixed State (Mi)	p value		
n	1307	261	1260	302	Re vs Ma	Re vs, De	Re vs Mi
Mood stabilizers: n (%)							
Lithium	705 (53.9%)	134 (51.3%)	523 (41.5%)	126 (41.7%)	0.442	<0.001	0.083
Valproic acid	358 (27.4%)	89 (34.1%)	339 (26.9%)	105 (34.8%)	0.028	0.448	<0.001
Carbamazepine	52 (4.0%)	20 (9.3%)	58 (4.6%)	19 (6.3%)	0.009	0.54	0.02
Lamotrigine	263 (20.1%)	51 (19.5%)	360 (28.6%)	70 (23.2%)	0.83	<0.001	0.017
Antipsychotics: n (%)							
Aripiprazole	194 (14.8%)	38 (14.6%)	314 (24.9%)	60 (19.9%)	0.906	<0.001	0.001
Olanzapine	150 (11.5%)	35 (13.4%)	188 (14.9%)	46 (15.2%)	0.377	0.023	0.007
Quetiapine	136 (10.4%)	38 (14.6%)	155 (12.3%)	45 (14.9%)	0.051	0.219	0.002
Risperidone	49 (3.7%)	13 (5.0%)	50 (4.0%)	11 (3.6%)	0.351	0.897	0.729

depressive state group, 659 (52.3%) were receiving antidepressant treatment, 124 (9.8%) were treated with tricyclic antidepressants, and 59 (4.7%) received only antidepressants.

Factors Associated with Non-Remission

After the patients were classified into remitters and non-remitters, a univariate logistic regression analysis was performed on all demographic and clinical characteristics. Of these, 15 with a p-value of less than 0.001 were identified as candidate factors that were correlated with non-remission.

A multivariate logistic regression analysis was then performed on the following 15 factors: female, younger age, unemployed status, earlier age of onset, comorbidity of personality disorders, comorbidity of pervasive developmental disorders, rapid cycling pattern, comorbidity of alcohol/substance abuse, poorer social function, lithium non-use, lamotrigine use, antipsychotic use, antidepressant use, anxiolytic use, and hypnotic use. As shown in Table 4, the following eight factors were found to be significantly correlated with non-remission in Japanese outpatients with bipolar disorder: female gender, younger age, unemployed status, rapid cycling pattern, comorbidity of alcohol/substance abuse, poorer social function, lithium non-use, and antidepressant use.

Discussion

This is the first multicenter nationwide study, to the best of our knowledge, an effort to characterize the current status on treatment of bipolar disorder in Japan. The strength of the study is that as many as 3130 outpatients with bipolar disorder were included and, along with the STEP-BD, it is

one of the largest clinical studies on this illness. The participants in this study were more likely to have graduated from university than the general population in Japan, and a similar trend was seen in the STEP-BD sample vs the US general population.¹⁸ MacCabe et al suggested that bipolar disorder may be associated with a high intelligence quotient or excellent school performance,¹⁹ and the results may support such theory. Furthermore, both this study and the STEP-BD study showed that the percentage of full-time workers was lower than the general population, and conversely the percentage of unemployed people was higher.¹⁸ According to Kessler et al, a greater employment loss

Table 4 Factors Associated with Non-Remission

Candidate Factors	p value	Odds Ratio	95% Confidence Interval
Female gender	0.001	1.364	1.137–1.637
Younger age	0.028	0.99	0.981–0.999
Unemployed	<0.001	1.592	1.283–1.975
Earlier onset	0.591	1.003	0.993–1.012
Personality disorders	0.295	1.283	0.804–2.047
Pervasive developmental disorders	0.291	0.817	0.561–1.189
Rapid cycling	0.008	1.556	1.12–2.162
Alcohol/substance abuse	<0.001	2.221	1.432–3.445
Poorer social function	<0.001	6.949	5.887–8.204
Lithium non-use	<0.001	1.488	1.235–1.793
Lamotrigine	0.227	1.144	0.92–1.424
Antipsychotics	0.594	0.951	0.789–1.145
Antidepressants	0.02	1.25	1.035–1.51
Anxiolytics	0.279	1.157	0.888–1.508
Hypnotics	0.093	1.263	0.961–1.66

was noted in bipolar disorder than in major depressive disorder.²⁰ In addition, their study showed that more severe and persistent depressive episodes in bipolar disorder were associated with employment disadvantage,²⁰ which is consistent with the results of a meta-analysis that indicated the course of illness affected work status, irrespective of years of education.²¹

Concerning the cross-sectional prevalence of each phase of bipolar disorder in this study, about 40% of the patients were in remission or a depressive state, while fewer than 10% were in a manic or mixed state. Judd et al investigated the long-term natural history of the symptomatic status of bipolar I and II disorders, and found that in these two conditions, depressive (31.9% and 50.3%, respectively) and euthymic (52.9% and 46.1%, respectively) symptoms were much more dominant than manic/hypomanic (9.3% and 1.3%, respectively) and cycling/mixed (5.9% and 2.3%, respectively) symptoms.^{22,23} The proportions of the disease states in our 3130 patients were generally consistent with the previous research, which might guarantee generalizability of study results although this study failed to distinguish bipolar subtypes.

Lithium was found to be the most commonly utilized drug in all phases of bipolar disorder, which is consistent with the recommendations of the Japanese guidelines.²⁴ According to the evidence-based Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder, lithium has a level 1 recommendation for treatment of acute mania and the maintenance phase, and a level 2 recommendation for treatment of acute depression.² This reflects the notion that the effectiveness of lithium is well established as an initial treatment that usually continues to the maintenance phase of the illness in bipolar disorder.²⁵ Further, lithium may be effective for patients with mixed state although the evidence is currently insufficient.²⁶ Although 41.7% of mixed state patients were treated with lithium in this study, there might have been in more remission cases should more patients would have been treated with lithium. Lamotrigine was the next most frequently prescribed drug in the depressive phase in this study. Lamotrigine is recommended for acute depression by the JSMD 2017 and CANMAT/ISBD 2018 guidelines,² but a recent multiple-treatments meta-analysis of bipolar depression does not endorse the drug due to its high risk of switching and less robust efficacy.⁷ Like lithium, quetiapine is recommended by the guidelines for all phases,^{2,3} but it was used infrequently in this study. This may be because quetiapine was

off-label for bipolar disorder at the time of this survey and is contraindicated for those with diabetes mellitus in Japan. Meanwhile, aripiprazole was the most frequently utilized antipsychotic drug despite the fact that most guidelines on bipolar disorder do not recommend it for acute depression.^{2-4,24} This may be because it is infrequently difficult to distinguish between bipolar depression and unipolar depression;^{11,12} aripiprazole is the only antipsychotic agent that is covered by insurance for unipolar depression in Japan. Finally, both antidepressant monotherapy prescription and tricyclic antidepressant use were relatively infrequent, which is reassuring and consistent with the guidelines.^{2-4,24} To interpret the results more precisely, however, it is important to be aware of the fact that there are many types of antidepressants and antipsychotics available, and a combination therapy within each category or across categories is also often clinically adopted.

Bipolar disorder is a highly recurrent disease; 70–90% of patients are reported to relapse within 5 years.¹ Alternatively, it is of high clinical relevance to identify factors associated with remission. However, clinical trials of maintenance therapy for bipolar disorder are usually short for this often chronic condition, are not necessarily consistent in methodology and may be somewhat biased through an enrichment design. In the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, it was pointed out that clinical studies on the long-term treatment of bipolar disorder have used various primary outcomes.⁴ A number of other factors have been inconsistent as well, such as inclusion criteria, observation periods, and definitions of remission and recovery, all making it difficult to draw firm conclusions.^{4,27} Thus we believe that although this study consisted of a retrospective chart review, the results have important clinical implications. A naturalistic Taiwanese study found that comorbid substance use disorders, earlier age at onset, and greater manic symptom severity were statistically significant predictors of a longer time to achieve remission in bipolar mania.²⁸ Another prospective 5-year follow-up study from Denmark found that non-remission in bipolar disorder increased with younger age, co-morbid anxiety, and suicidal ideation.²⁹ While both of the previous studies included hundreds of patients, a strength of this work is that it explored factors associated with remission status in over 3000 outpatients with bipolar disorder. The eight factors we found in this study have substantial clinical relevance in a quest for remission status in bipolar patients and the findings are expected to be incremental to the existing literature on

bipolar disorder in the Asian region. An important finding is that non-use of lithium was associated with non-remission. Lithium non-use might be a result of excessive fear of its side effects. Clinicians are required to well balance the risks and benefits of lithium treatment in bipolar disorder.

There are several limitations on this study that should be acknowledged to better interpret the results. First, since this was a retrospective chart study, the identified factors associated with non-remission in bipolar disorder may not necessarily establish causation. This would be considered as the most outstanding limitation of this work. Well-designed prospective studies are necessary to identify factors that are causally related to remission status. Second, it is possible that missing information on the clinical variables limited the analysis. However, only 83 cases (out of 3213 patients: 2.6%) were excluded because of missing data. Third, the characteristics of this study may limit generalizability to other populations. This study of the Japanese outpatients with bipolar disorder included slightly more females than males, but the incidence of bipolar disorder has been reported to be equal not only between genders but also across different cultural and ethnic groups.^{30,31} Moreover, the average age of onset of mood disturbance was 34.7 y.o. in this study, whereas it was 17.4 y.o. in the STEP-BD study.¹⁸ Fourth, in this study, remission was arbitrarily based on the impression of the evaluators; it would have been more precisely defined with assessment scales such as the Hamilton Depression Rating Scale or the MADRS and the Young Mania Rating Scale (YMRS).¹⁷ But it would contrarily have been impractical for clinic psychiatrists to perform these assessment scales in daily clinical practice. Fifth, due to lack of data that were not included in the survey, this study failed to analyze several factors identified in previous studies as potentially affecting remission status, such as the number of previous episodes, impulsivity, adherence and time to respond to treatment drugs.^{32–35} Sixth, this study did not distinguish bipolar I disorder from bipolar II disorder and the dose of medications was not considered. Seventh, neuromodulation treatments such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) may be effective for refractory bipolar disorder.^{36,37} However, ECT is a treatment performed in a hospital in Japan; this study was conducted at outpatient psychiatric clinics. In addition, TMS is not approved for bipolar disorder in Japan. Finally, as is always problematic for this kind of retrospective chart

reviews, there are many possible biases and unmeasured confounders.

Conclusion

To the best of our knowledge, this survey is the largest nationwide investigation thus far on the remission status of patients with bipolar disorder conducted in Japan. Data from more than 3000 outpatients indicated that in real-world clinical settings, not all treatment selections conform to bipolar disorder treatment guidelines. Most importantly, this study suggests that the following eight factors are associated with non-remission in patients with bipolar disorder: female gender, younger age, unemployed status, rapid cycling pattern, comorbidity of alcohol/substance abuse, poorer social function, non-use of lithium, and antidepressant use. They have important clinical implications and further prospective interventions as well as observational studies are necessary to replicate these findings in order to inform better managements for those in serious needs.

Consent for Publication

Since this study was a retrospective medical record survey, informed consent was exempted but we instead released information on this research so that patients were free to opt out.

Data Sharing Statement

The datasets of the current study are available from the corresponding author on reasonable request.

Ethics and Consent Statement

This study protocol was reviewed and approved by the institutional review board of the ethics committee of the Japanese Association of Neuro-Psychiatric Clinics (ID: 20160822).

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Author Contributions

All authors designed this study. Dr. Tsuboi analyzed the data and wrote the first draft of the manuscript. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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