The heterogeneous early illness courses of Korean patients with bipolar disorders – replication of the stage model

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Research Article

Keywords: bipolar disorder, mood disorders, staging, staging models, comorbidity

Posted Date: March 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1403711/v1

Abstract

Background

Clinical staging of bipolar disorder requires application of real-world data, as the next step in hypothesis. This study used the staging model to analyze the long-term course of BD in Korean patients based on clinical features and treatment responses to map the progression of bipolar illness from the early phase after the onset of illness.

Methods

A total of 136 patients diagnosed with BD-I (n = 62) or BD-II (n = 74) were recruited. Their progressive stages were retrospectively evaluated. The multi-state model was used to calculate the probability of progression to each stage. We calculated the hazard ratio of covariates expected to influence different courses of BD. Using the Alda score, we compared the long-term response to mood stabilizers depending on the current stage.

Results

Several sub-populations showed a varied course during the first five years after the onset of illness, with 41.5% remaining in stage 2 and 53% progressing to higher stages with shortening of time for transition. The profile of patients with BD-II differed profile from BD-I, suggesting biologically distinct groups. The group with Obsessive-compulsive Disorder (OCD) had higher risk in relation to both recurrent course (stage 3a or 3b) and malignant course (stage 3c or 4). Early age of onset, shorter lifetime duration, older age at the start of medication, and poor response to lithium affect long-term therapeutic outcomes.

Conclusions

The staging model encompasses early to recurrent and chronic courses of BD. The stage progression pattern differed in BD-Ⅰ and BD-Ⅱ patients from the early phase. Previous findings related to long-term course of BD enabled expansion of model parameters.

Background

Bipolar disorder (BD) is a chronic psychiatric disorder that is characterized by symptom recurrence and remission during patients' lifetime after the onset of the illness. Life-long treatment is inevitable in BD to prevent recurrence. Long-term treatment response and recurrence patterns vary depending on the patient, and the complexity of the illness hinders prediction of long-term prognosis.

A recent staging model shows the potential of understanding the course of complex illness such as BD based on a unified model. McGorry et al. (2006) proposed staging of mental disorders, and aimed to develop a transdiagnostic model. Berk et al. (2007) adapted the staging model to BD which is largely defined by the occurrence and recurrence of mood episodes. Kapczinski et al. (2014) proposed an alternative model based upon inter-episodic functional impairment and potential biomarkers. For this study, we applied the staging model proposed by Berk et al. (2007) We adopted this model to apply our clinical data on mood episodes and to gain insight for timely treatment decisions. We implemented modifications proposed by Kupka and Hillegers (2012) who defined initial depressive episodes without previous history of (hypo)manic episode as a prodromal stage of BD. In this study, we further refined the model by including psychiatric history of comorbid symptoms in the prodromal stage. Overall, based on the clinical staging model, several stages are proposed: stage 0, which is associated with genetic or clinical risk for developing BD; stage 1, prodromal symptoms; stage 2, the first episode; stage 3, recurrent episodes; and stage 4, chronic and unremitting illness. The stage model facilitates our understanding of the course of complex illness such as BD and identification of meaningful biomarkers that can be used in precision psychiatry.

Recent studies reported the application of stage models in analyzing the course of patients' illness clinically (van der Markt et al. 2019; de la Fuente-Tomás et al. 2020). However, it is still unclear how the stage model can be used in clinical evaluation and decision-making process in BD. Previous studies have certain limitations. First, they did not show how the stage model can be used in conjunction with previous findings associated with long-term bipolar illness including comorbid psychiatric conditions. Second, previous studies mainly included biased populations and predominantly patients with BD-I and ethnically western populations. Third, they did not report whether the stage was associated with long-term treatment responses. Additional studies are needed to determine the clinical utility of the stage model in BD treatment.

In this study, we applied the stage model to determine the course of long-term illness in Korean patients with BD. Accordingly, based on recurrence pattern, we retrospectively evaluated patients' long-term illness. Next, we explored the overall stage progression pattern after the onset of illness (stage 2). We also sought to determine the clinical features associated with pattern of bipolar illness progression. We also investigated if the patients’ current stage was associated with response to standard treatment.

Methods

Study participants

Patients who met the DSM-IV criteria for BD-I or BD-II and had received treatment at the Bipolar Disorder Clinic of the Samsung Medical Center, a tertiary-care university-affiliated hospital, were recruited between Sep 2019 and Sep 2021. The patients’ ages ranged from 18 to 55 years. Those who had evidence of neurological disorders or general medical conditions related to mental symptoms were excluded. A total

of 136 patients who met the above criteria and agreed to participate in the study were enrolled. The Institutional Review Board of the Samsung Medical Center approved this study (IRB no. 2021-01-084).

Clinical information

Information was collected via direct interview with patients, their available care-givers, and their physicians. Patients' medical records were also used as a supplementary information source by psychiatrists (JHB, DL, YC and KSH) and a psychologist (HWJ). The Korean version of the Diagnostic Interview for Genetic Studies (DIGS) (Joo et al. 2004) was used to confirm patients' diagnoses and disease history. All interviewers had at least two years of research experience using DIGS, and participated in several consensus meetings in order to improve inter-rater reliability. Based on the accumulated information, patients' diagnoses were re-established. Also, the course of illness, symptom profiles, lifetime co-occurrence of other DSM-IV axis I disorders, and past history of suicide attempts were evaluated.

Retrospective assessment of progressive illness using the stage model

The evaluation based on a direct interview has been described elsewhere (Baek et al. 2011; Yang et al. 2015; Baek et al. 2016). Based on clinical information, the study psychiatrists (JHB, DL, YC and KSH) and psychologists (HWJ and YL) with at least 2 years of clinical experience independently established the occurrence, duration and temporal sequence of stages each month after initial symptom development. Since our primary interest was at early clinical course of BD, we assessed illness progression in first 5 years after the onset of BD. The investigating psychiatrist and the clinician who saw each patient independently reviewed the information and arrived at a consensus regarding the pattern of stage progression. We also held regular consensus meetings to review the progression of each case.

In summary, the model consists of five stages, each divided into 4 sub-stages (i.e., A, B, C, and D). Stage 0 is defined as increased risk of severe mood disorder with familial loadings. Stage 1 is characterized by mild or non-specific symptoms including impulsivity, irritability, and major depressive episode. We modified staging model reported previously by van der Markt et al. (2019) by including comorbid symptoms fulfilling DSM- IV diagnostic criteria for psychiatric illness into stage 1. The diagnosis of BD is determined starting with stage 2. BD was further differentiated into recurrent episodes based on depressive, hypomanic, or manic/mixed symptoms. Stage 3a is defined as recurrence of subsyndromal depressive or manic symptoms after the onset of bipolar disorder. When the depressive, hypomanic, or manic episode recurs but fully remits for more than two months, it is considered as stage 3b. Stage 3c is characterized by incomplete remission of recurrent episodes, and persistent residual or subthreshold mood symptoms. Lastly, stage 4 includes multiple relapses of mood episodes without symptomatic and functional recovery for two years. When the first episode that qualifies for onset of BD occurs and lasts for two years, it is considered as chronic course, a fast transition from stage 2 to stage 4.

In general, patients enter higher stages as the disorder develops but course reversal also occurs following remission of symptoms after treatment. To distinguish re-entry into a specific stage after the first entry, backward transition from stage 4 to stage 3 was defined as stage 3', and stage 3c to stage b was defined as stage 3b'. In our model, subjects remained in the assigned stage after remission of the episode until transition to a consecutive stage.

Assessment of clinical characteristics

The rated variables cover age at onset and course of mood episodes, manifested symptoms, suicidality and comorbid psychiatric conditions on a lifetime basis. Age of first exposure to mood stabilizer or atypical antipsychotics, and age at onset were also explored. As age at first medication may differ from the age of BD onset, the duration of illness (DOI) was determined by subtracting the year of BD diagnosis from current age at the enrollment.

Psychiatric comorbid conditions including anxiety disorder, obsessive compulsive disorder and alcohol use disorder were evaluated due to their association with long-term clinical course. We additionally evaluated borderline personality traits, which were generally observed in BD (Saunders et al. 2021) and affected the course of overall illness (Riemann et al. 2017). We used Personality Assessment Inventory-Borderline scale (PAI-BPD; (Morey 1991)) to assess borderline personality characteristics in patients with BD. The PAI-BPD, including 24 items, was used to measure symptomatology of borderline personality disorder (M = 33.20, SD = 11.58). The scale includes subscales to assess affective instability, identity problems, negative relationships, and self-harm (Morey andHopwood 2006).

Assessment of response to long-term mood stabilizer treatment

We additionally compared the long-term effect of lithium depending on the patients' current stage. All patients received standardized treatment prescribed by their treating physicians based on the standard treatment guideline for BD (Goodwin 2009; Shin et al. 2013; Yatham et al. 2013; Ahn et al. 2017). Two psychiatrists (JHB and KSH) independently reviewed the charts retrospectively and interviewed patients. The long-term treatment response to mood stabilizers was evaluated using the Alda scale (Grof et al. 2002). The Alda scale comprises two subscales: The Alda A score evaluates the degree of improvement during the intervention, while the Alda B score assesses confounding variables that affect the outcome leaving medication effect aside (Lee et al. 2020). The total score is a composite score calculated by subtracting B from A.

Statistical analyses

A multi-state model was used to analyze the relationship between the proposed stages of BD (Keown-Stoneman et al. 2015). According to Markov assumption, the transition rate is independent of both the duration of remaining in the current state and the states visited prior to the current state (Keown-Stoneman et al. 2015). The mstate package in R statistical software (Rosseel 2012) was used to conduct this model in order to represent all the proposed stages instead of treating such stages as covariates.

We calculated the hazard ratio of covariates involved in different courses of stage progression using the Cox proportional-hazards model. We analyzed covariates involved in progression from stage 2 to stage 3a or stage 3b, and from stage 2 to stage 3c or stage 4. The following covariates were included: at least one parent with severe psychiatric illness, sex, working status, psychiatric comorbid conditions and cumulative scores of PAI-BPD. Due to variation in treatment history, we included age at onset, duration of illness (DOI), age first exposed to medication, and number of admissions to hospitalization in the analysis.

To compare long-term mood stabilizers, we classified the participants into three groups based on their current stage: early BD (stage 2; n = 64), recurrent group (including those in stage 3a and 3b; n = 31) and malignant course group (including those in stage 3c and 4; n = 41). We compared the basic demographic characteristics of groups. In addition, we compared the response to long-term mood stabilizers among groups. Linear regression analyses were conducted to adjust covariates that are known to be associated with mood stabilizer responses, i.e., alcohol use disorder, personality disorders, and higher lifetime number of hospital admissions (Grillault Laroche et al. 2020).

Results

Basic sociodemographic characteristics of participants

The sociodemographic and clinical characteristics of 136 patients included in the analysis are presented in Table 1. Sixty-two subjects (45.6%) met the criteria for BD- I and 74 subjects (54.4%) met the criteria for BD- II. The sample includes both inpatients and outpatients. Forty subjects (29.9%) were never hospitalized, while others were hospitalized once (47, 35.1%), twice or more frequently (47, 35.1%).

Table 1
Sociodemographic and clinical characteristics of patients with BD (N = 136)

Characteristic	N (%)	Mean (SD)[range]
Gender		
male	40 (29.4%)	
female	96 (70.6%)	
Parental diagnosis of bipolar disorder	6 (4.4%)	
Marital status	34 (25.0%)	
Education level		
middle school	2 (1.5%)	
high school	22 (16.2%)	
some college	112 (82.4%)	
Working status, employed	96 (70.6%)	
Diagnosis		
BD-	62 (45.6%)	
BD-	74 (54.4%)	
Comorbidity		
Panic disorder	42 (31.1%)	
Alcohol-related disorders	14 (10.4%)	
Bulimia nervosa	12 (8.9%)	
GAD	11 (8.1%)	
OCD	9 (6.7%)	
Social phobia	9 (6.7%)	
Agoraphobia	8 (5.9%)	
Anorexia nervosa	2 (1.5%)	
Number of hospitalizations		
0	40 (29.9%)	

BD Bipolar Disorder, *GAD* Generalized Anxiety Disorder, *OCD* Obsessive-Compulsive Disorder

[a]self-reported

Characteristic	N (%)	Mean (SD)[range]
1	47 (35.1%)	
≥ 2	47 (35.1%)	
Age at onset, years		20.0 (7.0) [8.0–46.0]
Medication age, years		24.7 (7.4) [15.0–50.0]
Duration of illness, years		11.1 (7.7) [1.0–38.0]
PAI-BPD total score[a]		58.3 (14.0) [29.0–91.0]
BD Bipolar Disorder, *GAD* Generalized Anxiety Disorder, *OCD* Obsessive-Compulsive Disorder		
[a]self-reported		

The average age of onset, when a patient was first assigned to stage 2, was 20.0 (SD 7.0). First exposure to medication, mood stabilizer or antipsychotics, was delayed from disease onset in most cases, and the mean age was 24.7 years (SD 7.4). Table 1 lists psychiatric comorbidities, with the highest prevalence rates associated with panic disorder (31.1%), alcohol-related disorders (10.4%), and generalized anxiety disorder (8.1%).

Stage progression

Six patients (4.4%) reported familial loading of BD, which corresponds to the standard stage 0. The average duration spent at each stage was as follows: 6.6 years in stage 1(SD 6.9), 4.3 years in stage 2 (SD 6.5), 0.9 years in stage 3a (SD 3.7), 0.2 years in stage 3b (SD 1.2), 0.7 years in stage 3c (SD 2.0), and 0.4 years in stage 4 (SD 1.7).

Figure 1 shows the transition of the subjects throughout the model in 5 years after the onset of BD. The horizontal axis shows the years passed since the subjects' entry to stage 2. The vertical axis shows the cumulative probability of remaining in a certain stage: 41.5% of patients still remained in stage 2; 40.3% of patients reached stage 3; 17.0% remained in stage 3a, 4.0% stage 3b, and 19.3% in stage 3c, while 12.7% of patients advanced to stage 4. In total, 5.4% of patients regressed one stage, while 4.4% regressed from stage 3c to stage 3b, and 1.0% from stage 4 to stage 3.

Comparisons of stage progression between BD-I and BD-II

Figures 2A and B show the transition of patients with BD-Ⅰ (n = 62, 45.6%) and BD-Ⅱ (n = 74, 54.4%) five years after enrolling in stage 2. The disease course of patients with BD-Ⅰ (see Fig. 2A) reveals that 49.4% remained in stage 2, while 20.5% advanced to stage 3a, 7.8% to stage 3b and 18.3% to stage 3c. Finally, 3.9% of the patients progressed to stage 4. Among patients diagnosed with BD-Ⅱ, 33.9% remained in stage 2 (see Fig. 2B), while 12.6% reached stage 3a and 20.6% stage 3c. The rate of patients' advance to stage 4 was significantly higher in BD-Ⅱ than in BD-Ⅰ (3.9% in BD-I vs. 22.8% in BD-II, $p < 0.01$).

Furthermore, the reversal of course in two groups varied. When 5 years have passed from the onset of BD, probability of regression converged to zero for BD-Ⅰ patients while 1.8% of BD-Ⅱ patients regressed from stage 4 to stage 3, and 8.3% from stage 3c to stage 3b.

Cox hazard regression models to determine the clinical factors associated with stage progression

The Cox hazard regression model was used to calculate several covariates associated with stage progression (see Table 2). The hazard ratio indicates the increase in transition rate for an added variable within a group (van der Markt et al. 2019).

Table 2
Covariates that increased the risk of stage progression

Clinical factors	Hazard ratio	95% confidence interval	*P* value[a]
stage 2 to stage 3a/3b			
Comorbid OCD, yes	5.15	[1.44–16.92]	0.01[a]
Working status, unemployed	0.33	[0.11–0.97]	0.04[a]
Duration of illness, years	0.95	[0.89–1.02]	0.16
PAI-BPD total score	0.98	[0.95–1.01]	0.21
Comorbid alcohol-related disorders, yes	0.50	[0.07–4.05]	0.53
Comorbid panic disorder, yes	0.79	[0.33–1.87]	0.58
Comorbid GAD, yes	1.49	[0.33–6.84]	0.59
Sex, females	1.24	[0.53–2.93]	0.62
Parental diagnosis bipolar disorder	1.20	[0.15–9.83]	0.87
Duration of staying in stage 1, years	1.00	[0.93–1.07]	0.87
Age at start of medication, years	1.01	[0.90–1.12]	0.92
Age at onset, years	1.00	[0.90–1.11]	0.94
Comorbid BN, yes	0.00	[0.00-∞]	0.99
stage 2 to stage 3c/4			
Age at onset, years	0.80	[0.72–0.90]	< 0.001[a]
Age at start of medication, years	1.22	[1.10–1.36]	< 0.001[a]
Duration of illness, years	0.88	[0.80–0.96]	0.01[a]
Working status, unemployed	2.72	[1.28–5.79]	0.01[a]
Comorbid OCD, yes	5.73	[1.38–23.78]	0.02[a]
Comorbid BN, yes	2.97	[1.04–8.52]	0.04[a]
Comorbid alcohol-related disorders, yes	2.49	[0.98–6.34]	0.06

OCD Obsessive-Compulsive Disorder, *GAD* Generalized Anxiety Disorder, *BN* Bulimia Nervosa

[a]Significance $p \leq 0.05$.

Clinical factors	Hazard ratio	95% confidence interval	*P* value[a]
PAI-BPD total score	1.02	[1.00-1.05]	0.11
Comorbid GAD, yes	1.95	[0.73–5.18]	0.18
Duration of staying in stage 1, years	0.98	[0.92–1.04]	0.43
Parental diagnosis bipolar disorder	1.83	[0.34–9.67]	0.48
Comorbid panic disorder, yes	0.77	[0.37–1.60]	0.49
Sex, females	1.00	[0.45–2.24]	1.00
OCD Obsessive-Compulsive Disorder, *GAD* Generalized Anxiety Disorder, *BN* Bulimia Nervosa			
[a]Significance p $\leq$ 0.05.			

The group with OCD showed higher transition rate from stage 2 to stage 3a or stage 3b (HR = 4.92). Being unemployed also decreased the rate (HR = 0.33). Furthermore, we analyzed the influence of such factors on the progression from stage 2 to stage 3c or stage 4. Older age at onset, shorter DOI, older age at start of medication and being unemployed increased the rate. Subjects with comorbid OCD and bulimia nervosa had higher risk of progression to stage 3c or stage 4 (HR = 5.48, 2.85 and 2.51). There was no significant difference in transition rate to higher stages related to duration of years in prodromal state (stage 1).

Comparisons of clinical characteristics and long-term mood stabilizer responses depending on stages

We additionally classified the participants into three groups depending on the current stage: early BD group (those in stage 2; n = 64), recurrent group (including those in stage 3a and 3b; n = 31) and malignant course group (including those in stage 3c and 4; n = 41).

No significant differences were detected between groups regarding current age, age at onset, DOI, age first exposed to mood stabilizer or atypical antipsychotics and psychiatric comorbid conditions.

Of all participants included in the study, 57 subjects were treated with lithium, while 57 were treated with valproate. A significant difference was observed in Lithium Alda A (early BD group: mean 7.39, standard deviation (SD) = 1.34); recurrent BD group: mean = 6.21, SD = 1.63; malignant course group: mean 6.78, SD = 1.49; F = 4.10, p = 0.022) and total scores of groups (early BD group: mean = 4.35, SD = 2.15; recurrent group: mean = 2.07, SD = 2.50; malignant course group: mean = 2.74, SD = 1.79; F = 5.98, p = 0.004). The association remained significant even after controlling for age, sex, comorbid alcohol use disorder and comorbid borderline personality traits (F = 4.81, p = 0.012 for Alda A score; F = 7.30, p = 0.002 for total score) (Grillault Laroche et al. 2020).

Discussion

In this study, we applied the stage model to Korean patients with BD based on comprehensive clinical information obtained from diverse sources including chart review and direct interview with patients, their caregivers and treating physicians. This approach is both intuitive and applicable in clinical practice based on a series of symptoms in light of patient's own clinical evolution (Salagre et al. 2018).

The stage progression pattern in our study revealed several sub-populations with distinct progression patterns during the first five years after onset of bipolar illness, especially BD-I and BD-II. A prior study using the stage model (van der Markt et al. 2019) included patients with BD-I only. Our study finding corroborates previous findings that associated BD-II with chronic illness course and more frequent depressive episodes (Judd et al. 2003; Baek et al. 2011). This different clinical profile also supports differentiation of BD-I and BD-II (Gitlin andMalhi 2020; Karanti et al. 2020). In BD-II, a subset of patients reached stage 4 early in their course of illness, while others did not undergo relapse of episodes in 5 years. The interval (years) between episodes is widely distributed (Angst et al. 2005; Kurumaji et al. 2014), emphasizing heterogeneous features in the longitudinal course of BD-II.

The duration of transition shortened as patients reach higher stages. In our study, the number of years spent in later stages 3 and 4 was less than a year. This transition was faster in later stages than in the previous study (van der Markt et al. 2019), while the progression in earlier stages (1 and 2) was even slower. A previous study by Park and colleagues also reported that cumulative episodes contributed to increased recurrence (Park et al. 2018). Salvatore et al. (2014) clustered antecedents into early, intermediate, and late (prodromal) phases, and found that the mean latency among phases was reduced gradually. The mean latency between early and intermediate antecedent phases was 4.7 ± 6.9 years, and between first-episode symptoms and syndrome was 8.4 ± 14.4 weeks. Only late (prodromal) behavioral dysfunctions anticipated later mania from other (mixed, depressive, or nonaffective) major psychotic episodes (Salvatore et al. 2014). The acceleration also suggests that early BD and malignant groups manifest different illness course, which highlights the need for considering current stage in planning treatment strategies.

Notably, several studies showed different rates of stage progression patterns reflecting the progression of illness during 5 years after the onset of BD, a time frame for early intervention of the targeted population. In a previous study by van der Markt et al. (van der Markt et al.), 85% of subjects experienced stage progression in 5 years, with 7% remaining at the same stage. The rate of stage progression in our study was lower than in the previous study (53% in our study versus 85% in the study by van der Markt and colleagues, $p < 0.0001$), while substantial number of patients stayed in stage 2(41.5% vs. 7%, $p < 0.0001$). Because our study population was recruited from a BD clinic, timely and appropriate treatment might delay the progression of illness. These findings suggest the need for using a stage model in clinical practice as a prophylactic intervention against recurrent episodes.

Treatment can alter the disease course, progression and regression. Early onset and delayed medication were significant factors leading to chronic course of BD in our study, which was in line with previous

studies involving subjects with cycle acceleration (Finseth et al. 2014). In a study using the stage model based on recurrent episodes, earlier age at onset and treatment with fewer psychotropic medications during patients' lifetime were associated with higher stages (Kamali et al. 2021). Joslyn et al. (2016) also found that early age of onset is associated with factors that can negatively impact long-term outcomes. Chronic BD was shorter in duration possibly due to rapid transition. The association of gender and increased risk of stage progression was not replicated in our study (van der Markt et al. 2019). Identification of individual factors for personalized care requires assessment and adjustment of clinical interventions.

Other elements should be considered as they represent stage-specific markers (McGorry et al. 2006; Salagre et al. 2018). Previous studies have included mood symptoms such as prodromal subsyndromal depressive or manic symptoms or specific bipolar onset (van der Markt et al. 2019). In our study, we included psychiatric comorbid conditions as covariates associated with long-term bipolar illness (Singh andZarate 2006). As expected, early BD with comorbid OCD, alcohol-related disorders, or bulimia nervosa showed increased rate of transition to higher stages. Furthermore, we identified distinct factors associated with recurrent (stage 3a/3b) or malignant course (stage 3c/4). Recurrent BD is associated with better prognosis as it includes remission of episodes, whereas malignant BD is characterized by residual state without complete remission, even though these two courses have recurrent episodes in common (Judd et al. 2008). An interesting finding is that unemployment increased the risk of malignant course, but lowered the risk of episodes following remission. We can speculate that severe impairment or loss of function occurs in individuals later in the course of established BD. However, the state of being unemployed, which indicates the current work situation, may not suggest inability to work. Kapczinski et al. (2009) included psychosocial functioning as an index of illness progression.

The stage model not only enhances our understanding of BD, but also sheds light on treatments with differential value across stages. Previous studies reported mixed results involving treatment response. A study by Berk et al. (2017) pooled 12 BD studies and identified that patients in the earliest phases of the illness had a more favorable response to treatment. However, staging was not a significant factor in antidepressant response in a randomized trial (Magalhães et al. 2012). Staging did not moderate the randomized treatment effect of lithium vs. quetiapine (Kamali et al. 2021). Our study showed that current stage was associated with long-term mood stabilization in response to lithium therapy. The discrepancy in results may be attributed to the sample population. In our study, both average duration of illness and mean age were nearly 10 years earlier than in previous studies. Our sample consists of a diverse range of patients in early to chronic courses of illness. Application of this model in treatment decisions and prognosis requires determination of stage-specific pharmacological treatment.

The present study has strengths in using real world clinical data actually observed by treating physicians repeatedly. We obtained data not only from patients' recall or electronic health records, but regular consensus meetings to improve reliability of stage definition for enhanced conceptualization and measurement of staging (Tremain et al. 2020).

Our study has several limitations. First, the small sample size might affect the study findings. Second, there could be a recall bias regarding patients' early illness. The participants in our study were in relatively earlier course of illness compared with those in previous study, suggesting limited recall bias. In addition, we tried to re-formulate patients' course of illness using all available information sources and repeated contacts with patients themselves, their caregivers and their treating physicians. Third, all patients were recruited and treated at the BD specialized clinic, which suggests difficulty in generalizing the study findings. Fourth, we only applied the stage model based on recurrent episodes. A recent study that integrates diverse information including laboratory data and cognitive function in the defining stage (de la Fuente-Tomás et al. 2020) showed fair validity. Descriptions of clinical stages of BD still need operationalization or consensus on terminology. For instance, whether a mixed episode meets the criteria for a certain stage can be disputed, leading to systemic error.

Within these limitations in mind, this study demonstrated the feasibility of application of the stage model based on real-world data involving Korean patients with BD. Our findings suggest that clinical staging can be used to integrate diverse courses of BD. Exacerbation of BD and resistance to treatment provide insight into illness progression at a group level ranging from early to recurrent and chronic conditions. Known variables that aggravate prognosis were confirmed, and additional variables and biomarkers are reflected in this framework.

Conclusion

The present study provided additional evidence that distinct courses of bipolar disorder appear in five years after the onset of illness. In addition, the stage progression pattern differed in BD-□ and BD-□ patients from the early phase. Psychiatric history of comorbid symptoms, resistance to treatment aggravated prognosis, and further studies are needed to expand the clinical staging to map the progression pattern of bipolar illness.

Abbreviations

BD
Bipolar disorder
BD-I
Bipolar I disorder
BD-II
Bipolar II disorder
OCD
Obsessive-compulsive Disorder
DIGS
Diagnostic Interview for Genetic Studies
DOI
Duration of illness

PAI-BPD
Personality Assessment Inventory-Borderline scale
GAD
Generalized Anxiety Disorder
BN
Bulimia Nervosa.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Samsung Medical Center approved this study (IRB no. 2021-01-084).

Consent for publication

Not applicable.

Availability of data and material

The dataset that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research was supported by the Original Technology Research Program for Brain Science through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (No. 2019M3C7A1030624).

Authors' contributions

JHB designed the overall study. YL, HWJ, YJC reviewed the data and conducted the rating. YL wrote the initial manuscript and conducted the statistical analysis. All authors reviewed the manuscript and participated in the revision process.

Acknowledgments

The authors thank Jinseob Kim (Zarathu Co., Ltd, Seoul, Republic of Korea) for statistical advice.

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References

1. Ahn SW, Baek JH, Yang SY, Kim Y, Cho Y, Choi Y, et al. Long-term response to mood stabilizer treatment and its clinical correlates in patients with bipolar disorders: a retrospective observational study. Int J Bipolar Disord. 2017;5(1):24.
2. Angst J, Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. J Affect Disord. 2005;84(2-3):149-57.
3. Baek JH, Kim JS, Kim MJ, Ryu S, Lee K, Ha K, et al. Lifetime Characteristics of Evening-Preference and Irregular Bed-Rise Time Are Associated With Lifetime Seasonal Variation of Mood and Behavior: Comparison Between Individuals With Bipolar Disorder and Healthy Controls. Behav Sleep Med. 2016;14(2):155-68.
4. Baek JH, Park DY, Choi J, Kim JS, Choi JS, Ha K, et al. Differences between bipolar I and bipolar II disorders in clinical features, comorbidity, and family history. J Affect Disord. 2011;131(1-3):59-67.
5. Berk M, Conus P, Lucas N, Hallam K, Malhi GS, Dodd S, et al. Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disord. 2007;9(7):671-8.
6. Berk M, Post R, Ratheesh A, Gliddon E, Singh A, Vieta E, et al. Staging in bipolar disorder: from theoretical framework to clinical utility. World Psychiatry. 2017;16(3):236-44.
7. de la Fuente-Tomás L, Sierra P, Sanchez-Autet M, Arranz B, García-Blanco A, Safont G, et al. A clinical staging model for bipolar disorder: longitudinal approach. Transl Psychiatry. 2020;10(1):45.
8. Finseth PI, Morken G, Malt UF, Andreassen OA, Vaaler AE. Risk factors of cycle acceleration in acutely admitted patients with bipolar disorder. Acta Psychiatr Scand. 2014;130(5):388-96.
9. Gitlin M, Malhi GS. The existential crisis of bipolar II disorder. Int J Bipolar Disord. 2020;8(1):5.
10. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition–recommendations from the British Association for Psychopharmacology. J Psychopharmacol.

2009;23(4):346-88.

11. Grillault Laroche D, Etain B, Severus E, Scott J, Bellivier F. Socio-demographic and clinical predictors of outcome to long-term treatment with lithium in bipolar disorders: a systematic review of the contemporary literature and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Int J Bipolar Disord. 2020;8(1):40.
12. Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, et al. Is response to prophylactic lithium a familial trait? J Clin Psychiatry. 2002;63(10):942-7.
13. Joo EJ, Joo YH, Hong JP, Hwang S, Maeng SJ, Han JH, et al. Korean version of the diagnostic interview for genetic studies: Validity and reliability. Compr Psychiatry. 2004;45(3):225-9.
14. Joslyn C, Hawes DJ, Hunt C, Mitchell PB. Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review. Bipolar Disord. 2016;18(5):389-403.
15. Judd LL, Schettler PJ, Akiskal HS, Coryell W, Leon AC, Maser JD, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Arch Gen Psychiatry. 2008;65(4):386-94.
16. Judd LL, Schettler PJ, Akiskal HS, Maser J, Coryell W, Solomon D, et al. Long-term symptomatic status of bipolar I vs. bipolar II disorders. Int J Neuropsychopharmacol. 2003;6(2):127-37.
17. Kamali M, Pegg S, Janos JA, Bobo WV, Brody B, Gao K, et al. Illness stage and predominant polarity in bipolar disorder: Correlation with burden of illness and moderation of treatment outcome. J Psychiatr Res. 2021;140:205-13.
18. Kapczinski F, Dias VV, Kauer-Sant'Anna M, Frey BN, Grassi-Oliveira R, Colom F, et al. Clinical implications of a staging model for bipolar disorders. Expert Rev Neurother. 2009;9(7):957-66.
19. Kapczinski F, Magalhães PV, Balanzá-Martinez V, Dias VV, Frangou S, Gama CS, et al. Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force Report. Acta Psychiatr Scand. 2014;130(5):354-63.
20. Karanti A, Kardell M, Joas E, Runeson B, Pålsson E, Landén M. Characteristics of bipolar I and II disorder: A study of 8766 individuals. Bipolar Disord. 2020;22(4):392-400.
21. Keown-Stoneman CD, Horrocks J, Darlington GA, Goodday S, Grof P, Duffy A. Multi-state models for investigating possible stages leading to bipolar disorder. Int J Bipolar Disord. 2015;3:5.
22. Kupka RW, Hillegers MH. [Staging and profiling in bipolar disorders]. Tijdschr Psychiatr. 2012;54(11):949-56.
23. Kurumaji A, Narushima K, Ooshima K, Yukizane T, Takeda M, Nishikawa T. Clinical course of the bipolar II disorder in a Japanese sample. J Affect Disord. 2014;168:363-6.
24. Lee J, Baek JH, Lee D, Ahn SW, Yang SY, Choi Y, et al. Defining phenotypes of long-term lithium and valproate response, including combination therapy: a modified application of the Alda scale in patients with bipolar disorders. Int J Bipolar Disord. 2020;8(1):36.
25. Magalhães PV, Dodd S, Nierenberg AA, Berk M. Cumulative morbidity and prognostic staging of illness in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Aust N Z

J Psychiatry. 2012;46(11):1058-67.

26. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry. 2006;40(8):616-22.
27. Morey LC. Personality Assessment Inventory. Odessa, FL: Psychological Assessment Resources; 1991.
28. Morey LC, Hopwood CJ. The personality assessment inventory and the measurement of normal and abnormal personality constructs. In: Strack S, editor. Differentiating Normal and Abnormal Personality. 2nd ed. New York, NY: Springer Publishing Company; 2006. p. 451-72.
29. Park DY, Do D, Chang L, Shah S, Yuen LD, Hooshmand F, et al. Episode accumulation associated with hastened recurrence and delayed recovery in bipolar disorder. J Affect Disord. 2018;227:657-64.
30. Riemann G, Weisscher N, Post RM, Altshuler L, McElroy S, Frye MA, et al. The relationship between self-reported borderline personality features and prospective illness course in bipolar disorder. Int J Bipolar Disord. 2017;5(1):31.
31. Rosseel Y. lavaan: An R package for structural equation modeling. J Stat softw. 2012;48(2):1-36.
32. Salagre E, Dodd S, Aedo A, Rosa A, Amoretti S, Pinzon J, et al. Toward Precision Psychiatry in Bipolar Disorder: Staging 2.0. Front Psychiatry. 2018;9:641.
33. Salvatore P, Baldessarini RJ, Khalsa HM, Vázquez G, Perez J, Faedda GL, et al. Antecedents of manic versus other first psychotic episodes in 263 bipolar I disorder patients. Acta Psychiatr Scand. 2014;129(4):275-85.
34. Saunders KEA, Jones T, Perry A, Di Florio A, Craddock N, Jones I, et al. The influence of borderline personality traits on clinical outcomes in bipolar disorder. Bipolar Disord. 2021;23(4):368-75.
35. Shin YC, Min KJ, Yoon BH, Kim W, Jon DI, Seo JS, et al. Korean medication algorithm for bipolar disorder: second revision. Asia Pac Psychiatry. 2013;5(4):301-8.
36. Singh JB, Zarate CA, Jr. Pharmacological treatment of psychiatric comorbidity in bipolar disorder: a review of controlled trials. Bipolar Disord. 2006;8(6):696-709.
37. Tremain H, Fletcher K, Murray G. Number of episodes in bipolar disorder: The case for more thoughtful conceptualization and measurement. Bipolar Disord. 2020;22(3):231-44.
38. van der Markt A, Klumpers UM, Draisma S, Dols A, Nolen WA, Post RM, et al. Testing a clinical staging model for bipolar disorder using longitudinal life chart data. Bipolar Disord. 2019;21(3):228-34.
39. Yang F, Gardner CO, Jr., Bigdeli T, Gao J, Zhang Z, Tao M, et al. Clinical features of and risk factors for major depression with history of postpartum episodes in Han Chinese women: A retrospective study. J Affect Disord. 2015;183:339-46.
40. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)

collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013;15(1):1-44.

Figures

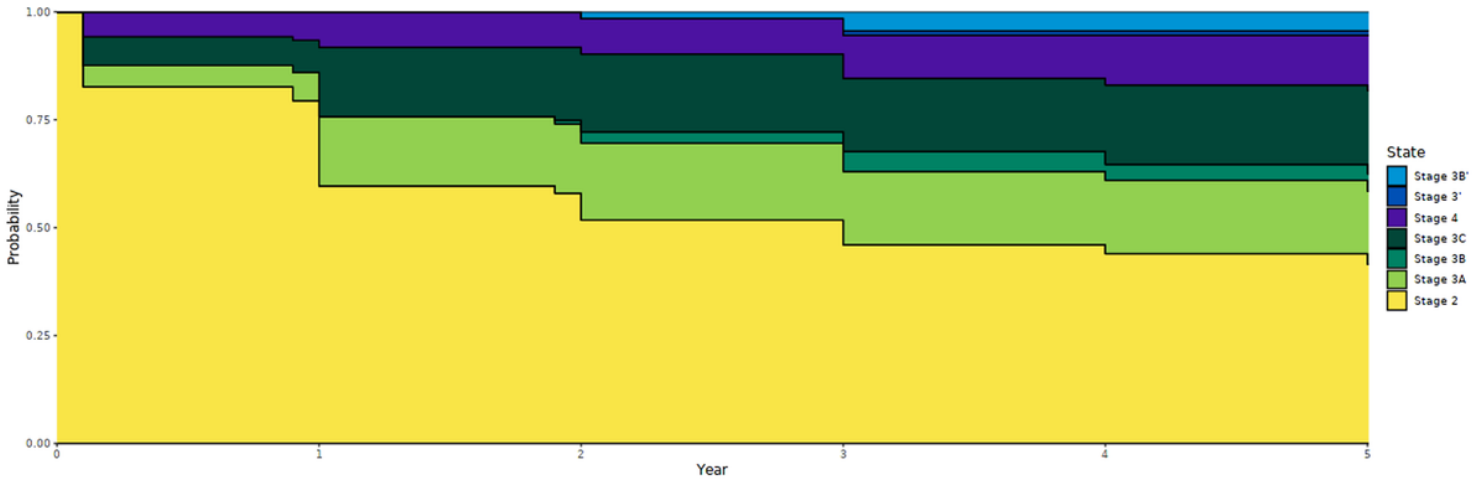

Figure 1

Probability of different stages in the first 5 years after onset of BD (N = 136)

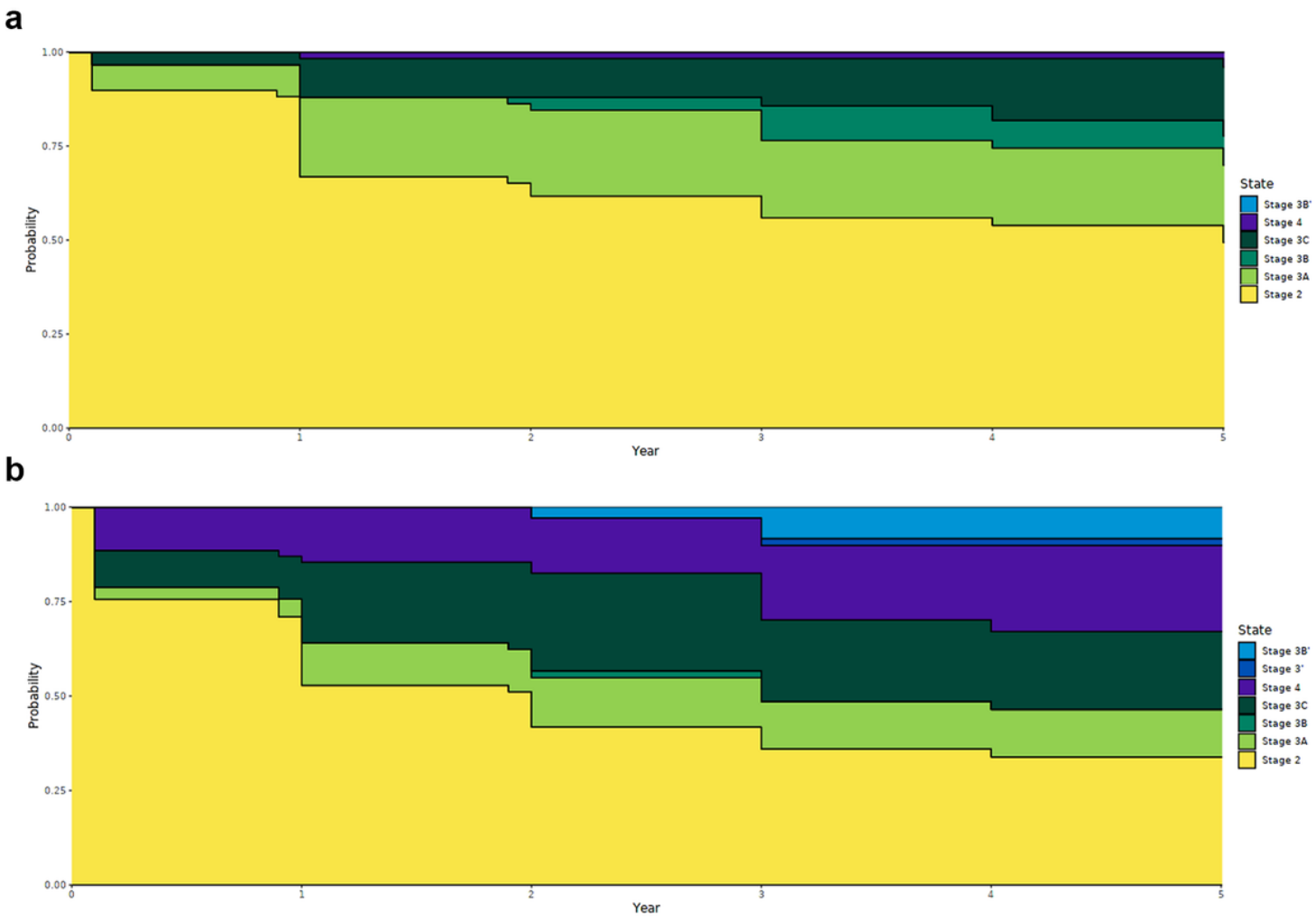

Figure 2

(A) Probability of different stages among patients with BD-I (N = 62). (B) Probability of different stages among patients with BD-II (N = 74)