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Clinical profiles of subsequent stages in bipolar disorder: Results from the Dutch Bipolar Cohort

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Abstract

Introduction: The manifestation of bipolar disorder (BD) is hypothesized to be determined by clinical characteristics such as familial loading, childhood abuse, age at onset, illness duration, comorbid psychiatric disorders, addiction, treatment resistance, and premorbid cognitive functioning. Which of these are associated with a more severe course and worse outcome is currently unknown. Our objective is to find a combination of clinical characteristics associated with advancement to subsequent stages in two clinical staging models for BD.

Methods: Using cross-sectional data from the Dutch Bipolar Cohort, staging was applied to determine the progression of bipolar-I-disorder (BD-I; $N = 1396$). Model A is primarily defined by recurrence of mood episodes, ranging from prodromal to chronicity. Model B is defined by level of inter-episodic functioning, ranging from prodromal to inability to function autonomously. For both models, ordinal logistic regression was conducted to test which clinical characteristics are associated with subsequent stages.

Results: For model A, familial loading, childhood abuse, earlier onset, longer illness duration, psychiatric comorbidity, and treatment resistance were all predictors for a higher stage in contrast to addiction and cognitive functioning. For model B, childhood abuse, psychiatric comorbidity, cognitive functioning, and treatment resistance were predictors for a more severe stage, whereas age at onset, illness duration, and addiction were not.

Discussion/conclusions: Differences in clinical characteristics across stages support the construct validity of both staging models. Characteristics associated with a higher stage largely overlapped across both models. This study is a first step toward determining different clinical profiles, with a corresponding course and outcome.

KEYWORDS
bipolar disorders, mood episodes, profiles, staging, staging models

1 | INTRODUCTION

The clinical manifestation and course of bipolar disorder (BD) may be influenced by several patient characteristics. In earlier studies, familial loading,[1,2] childhood abuse,[3–5] age at onset,[6–10] illness duration,[11] comorbid psychiatric disorders,[9,12] addiction,[13,14] treatment resistance,[15–18] and cognitive functioning[19–21] have all been hypothesized to be associated with a higher likelihood of developing BD or a worse outcome. These factors appear to be interrelated in various ways; for example, an earlier onset of BD is associated with an increased rate of substance use disorders.[22] In combining all clinical characteristics, a multifold clinical profile emerges which varies to a large degree between patients. Understanding which of these characteristics contribute most to a more severe course of illness may lead to a better understanding of factors contributing to the functional outcome in patients with BD, thereby revealing options for early intervention and prevention.

The DSM-5 classification system differentiates various subtypes of BD without accounting for its long-term course and subsequent illness progression. It uses a binary approach, grouping those with an established disorder separately from those who do not (yet) qualify. It does not account for the wide range of clinical manifestations seen in clinical practice, with their largely varying courses and outcomes. Staging models do have the capacity to capture these different courses and outcomes, distinguishing prodromal symptoms from early, late, and chronic stages.

Various clinical staging models for BD have been introduced in recent years,[23–25] each using different measures to describe the illness progression. The model as proposed by Berk et al.[1] (Model A in this study) is largely defined by the occurrence and recurrence of mood episodes in a patient. It starts with stage 0, defined as being at risk for a severe mood disorder, due to e.g. familial loading or substance abuse. This is followed by a prodromal stage, in which symptoms do not yet fit the criteria for bipolar disorder. Stage 2 is the diagnostic threshold, including a major mood episode. Stage 3 involves recurrent mood episodes, and is subdivided into 3a, defined as recurrence of sub-threshold mood symptoms after a threshold mood episode; 3b, first relapse episode and 3c, multiple relapse episodes. Stage 4 consists of persistent and unremitting symptoms of an episode. Kapczinski et al.[2] (Model B in this study) employs an alternative staging model based on inter-episodic functional impairment. This model includes a latent stage and four clinical stages, defined as well defined periods of euthymia without overt psychiatric symptoms (stage I); inter-episodic symptoms (stage II); marked inter-episodic impairment in cognition and functioning with inability to work (stage III); and the inability to live autonomously owing to cognitive and functional impairment (stage IV). A third model is proposed by Duffy et al.[25], and focuses upon prodromal and early stages and the evolution of different illness trajectories. Since our sample includes patients with established BD type I, the staging model proposed by Duffy et al. was not applicable to our study.

Both of the current staging models for bipolar disorder are clinical staging models, based on clinically observed phases of illness progression. Although these staging models need testing to determine their applicability and usefulness, they are also debated on a theoretical level. Mahli et al.[26] stated that current models are heavily influenced by the broad variation in clinical expression and are anticipating the uncovering of solid biomarkers to base a staging model on. Berk et al.[27] exploit a more hopeful approach by stating clinical staging to be useful on the basis of careful exploration of the current level of evidence on staging, suggesting forthcoming directions for further studies. The ISBD staging task force recently published a paper[28] to standardize the nomenclature on clinical staging of BD, in order to facilitate future research.

The influence of clinical characteristics on illness progression may be studied using staging models. In our current study, we are building on two previous studies[29,30] in which we verified the applicability of the two staging models by Berk et al.[23] and Kapczinski et al.[24] The current study investigates whether clinical profiles based on the characteristics found in previous studies, that is, familial loading, childhood abuse, age at onset, illness duration, comorbid psychiatric disorders, addiction, treatment resistance, and cognitive functioning are associated with illness progression as defined by the model from Berk et al.[23] and Kapczinski et al.[24]

2 | METHODS

2.1 | Study design

Data were acquired from the Dutch Bipolar Cohort (DBC), a large ongoing case-control study started in June 2011, in a collaboration between the University of California Los Angeles (UCLA) and the Dutch healthcare institutes of the University Medical Center Utrecht (UMC Utrecht), GGZ Altrecht, GGz inGeest, University Medical Center Groningen, Delta Center for Mental Health Care, Dimence, Parnassia (PsyQ) and Reinier van Arkel Group. DBC investigates genetic and phenotypic information of patients with bipolar disorder type I (BD-I), their first-degree relatives, and controls. Patient data were collected between June 2011 and April 2015. Patients were recruited via clinicians (19.2%), the Dutch BD patient association (15.8%), pharmacies (33.6%), advertisements (6.9%), self-referral (5%), participation in previous UMCU studies (4.5%), and miscellaneous (15.0%). Participants received a small allowance (40 euro) to cover expenses.

Inclusion criteria for all participants were: the diagnosis BD I, as verified by the Structured Clinical Interview for DSM-IV (SCID-I),[31] minimum age of 18, at least three biological grandparents of Dutch ancestry to acquire a homogeneous genetic sample, and a thorough understanding of the Dutch language. The study was approved by the medical ethical committee of the UMCU and all participants gave written informed consent.

The following additional cross-sectional data were acquired: Questionnaire for Bipolar Disorders (QBP, adapted from Leverich

et al.[32]) addressing demographics, BD illness history, family history, comorbidity, and current and past treatments. Composite International Diagnostic Interview (CIDI) was used to assess addiction and Structural Clinical Interview for DSM Disorders (SCID) was used to assess comorbidity. For neurocognitive functioning, the Dutch reading test for adults (Nederlandse leestest voor volwassenen – NLV) was used, estimating premorbid IQ. The assessments were administered by a SCID-I and Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997) trained UMCU research team, including bachelor-level psychology and medical students. The team was supervised by two clinical psychiatrists.

2.2 | Staging classification

All subjects were assigned to a stage from both model A and B using a decision flowchart (Figure 1).

For model A,[23] (sub)stages were allocated using a set number of items originating from the Questionnaire for Bipolar Disorder (QBP[32]). Patients were assigned to groups based on mood status in the previous year, distinguishing euthymia, current symptomatic (episode) with, or without recovery in the previous year (qualifying for stage 4). The total lifetime number of manic and depressive episodes was summed. In the case of a current mood episode, one additional mood episode was added to the lifetime total. Patients were allocated to stage 2 (one mood episode), stage 3a (one mood episode with current residual symptoms), stage 3b (two mood episodes), or stage 3c (multiple recurrent mood episodes). In our previous study on bipolar outpatients,[30] we found clustering in stage 3c of this model, which could be refined by subdividing subjects in this stage into subgroups with a maximum of 5 episodes, 6 to 10 episodes and more than 10 episodes, following cut-off points previously defined by Berk et al. and Magalhães et al.[33,34]

For model B,[24] subjects were assigned to a stage ranging from latent to stage IV, using a predetermined set of items from the Questionnaire for Bipolar Disorder (QBP,[32] Figure 1). Stages I to IV were assigned based on social, occupational, and psychological functioning (Global Assessment of Functioning (GAF) > or ≤ 80), current mood episode (yes or no), employment over the last year (yes or no), work limitations (present or not present), and limitations in functioning (present or not present).

2.3 | Clinical characteristics

2.3.1 | Familial loading

Familial loading was assessed for both parents using QBP items on family history of psychiatric disorders, relating to depressive disorder (item 31) bipolar disorder (item 32), and psychosis (item 33). These were merged into one categorical variable with the categories "no familial loading," "familial loading in one parent," and "familial loading in two parents."

2.3.2 | Childhood abuse

A history of abuse was based on the QBP self-assessment items 38 (verbal), 39 (physical), and 40 (sexual). Childhood abuse was scored either as present (positive) or absent (negative). Endorsement included any self-reported child abuse, involving frequencies rarely, sometimes or often, during childhood or adolescence.

2.3.3 | Age at onset

The onset of the bipolar disorder was based on the earliest age as marked on self-assessment items QBP 37A (depressive symptoms) and 37B (manic symptoms).

2.3.4 | Illness duration

Illness duration was determined by subtracting age at onset from age at inclusion. This was a continuous variable.

2.3.5 | Comorbid psychiatric disorders

Lifetime and current comorbid axis-I psychiatric disorders were marked positive if one of the following SCID items was scored positively: schizophrenia (p47-49), schizophreniform disorder (p50–52), schizoaffective disorder (p53-55), delusional disorder (p56-57), brief psychotic disorder (p58-59), psychotic disorder due to a general medical condition (p60-61), substance-induced psychotic disorder (p62-63), psychotic disorder not otherwise specified (p64-65), panic disorder (p84-86), agoraphobia without panic disorder (p87-p88), social anxiety disorder (p89-p90), specific phobia (p91-92), obsessive-compulsive disorder (p91-92), post-traumatic stress disorder (p95-96), generalized anxiety disorder (p97), anxiety disorder due to medical condition (p98-p100), anxiety disorder related to substance abuse (p101-103), anxiety disorder not otherwise specified (p104-105) other DSM-IV disorders (p118-119).

2.3.6 | Addiction

When either substance abuse or dependence was scored in the Composite International Diagnostic Interview (CIDI), this item was marked positive.

2.3.7 | Treatment resistance

According to international guidelines for treatment of bipolar disorder, monotherapy is preferred as compared to polypharmacy. Therefore, polypharmacy has been used as an indicator for medication resistance. At inclusion, use of medication was grouped into

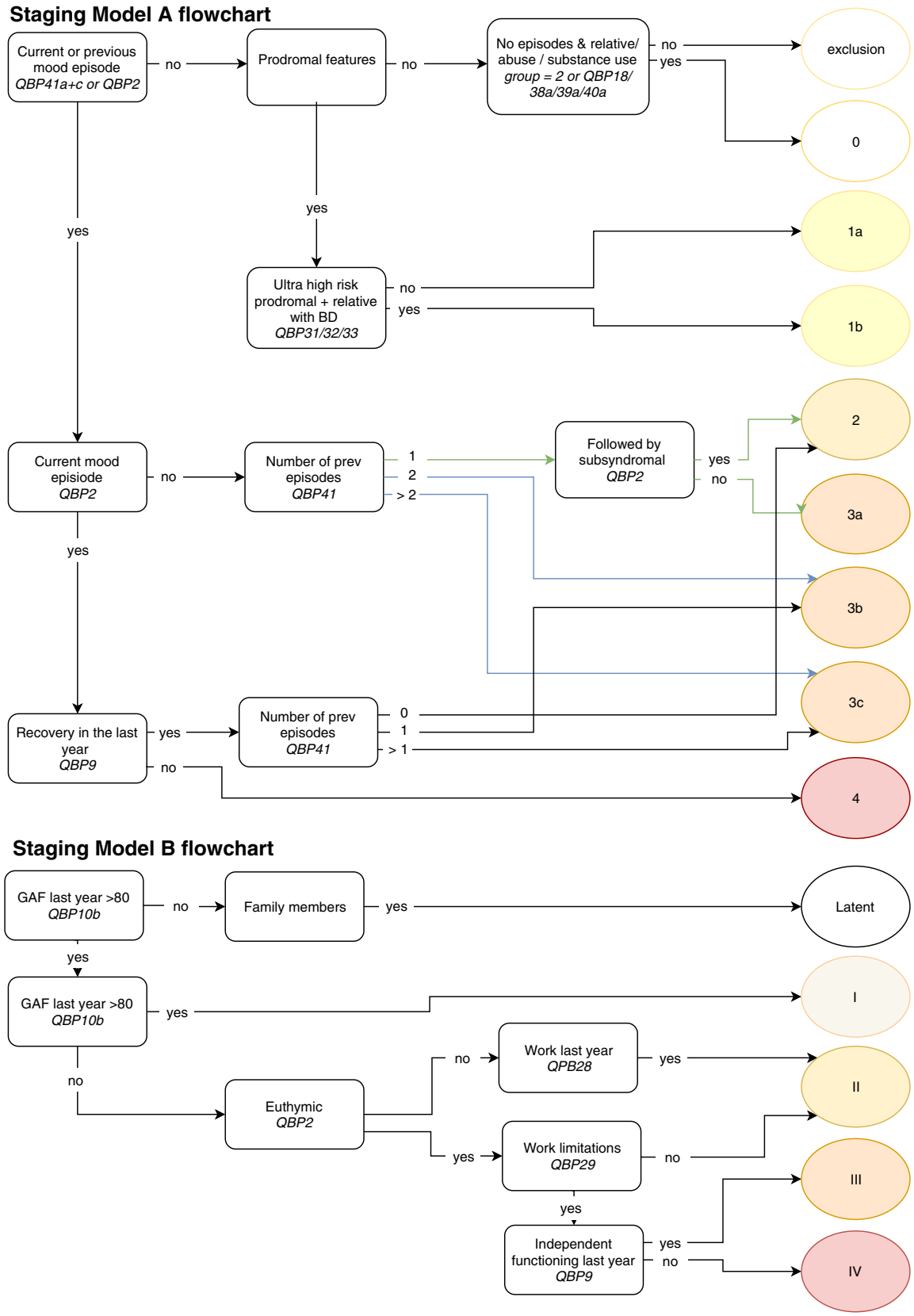

FIGURE 1 Flowcharts of two staging models

one of four classes; use of lithium, other mood stabilizers, antipsychotics, and antidepressants. The number of medication classes were considered to be an indicator of essential polypharmacy and therefore a measure for treatment resistance. This variable was subdivided into: no, one, two, three, or four medication classes.

2.3.8 | Premorbid cognitive functioning

The Dutch reading test for adults ("Nederlandse Leestest voor Volwassenen" – NLV) was used to determine the premorbid IQ, as a continuous score item. Subjects who indicated a diagnosis of dyslexia ($N = 9$) or who had an insufficient reading level ($N = 2$) were excluded because of its influence on the accuracy of the NLV.

2.4 | Statistical analysis

Variables were prepared for analysis and subsequently analyzed using SPSS 24.[35] Multicollinearity was tested for all variables by assessing distribution, homoscedasticity, and the variance inflation factor. The proportional odds assumption and the overall goodness of fit of the model were tested by calculating the Pearson and Deviance goodness-of-fit, Cox and Snell, Nagelkerke, and McFadden measures of R2, and the likelihood-ratio.

Ordinal logistic regression was performed separately for each variable for model A and B ($p < 0.10$), followed by backward elimination of variables with a p-value higher than 0.157, based on Sauerbrei et al.[36] Acquired at baseline, the following covariates were put into the model: types of medication, psychiatric comorbidity, addiction, childhood abuse, age at onset, illness duration, familial loading, and premorbid IQ. Missing data were omitted, in accordance with default settings for the ordinal logistic regression model in SPSS.

3 | RESULTS

3.1 | Demographic and clinical characteristics

The demographic and clinical characteristics were evaluated at baseline (Table 1). For 1217 out of 1396 subjects, data were available to assign a stage in model A; for model B, 1203 out of 1396 subjects qualified for stage assignment."

3.2 | Predictors for a higher stage

All variables fitted the proportional odds assumption, except for addiction. This was not at issue since this variable was eliminated from the model during backward elimination. The overall goodness of fit was adequate.

After the backward elimination procedure for staging model A, increased familial loading, the presence of childhood abuse, earlier

TABLE 1 Descriptives

	Model A ($N = 1217$) Mean (SD) [range] or N(%)	Model B ($N = 1203$) Mean (SD) [range] or N(%)
Age in years	49.1 (12.2) [18.6–80.3]	49.2 (12.3) [18.6–78.3]
Sex, m/f	521/696 (42.8%/57.2%)	526/677 (43.7%/56.3%)
Education[a]		
Primary school	25 (2.1%)	24 (2.0%)
Secondary school	598 (49.5%)	597 (49.7%)
Higher education	585 (48.4%)	580 (48.3%)
Previous depressive episodes[b]		
0	26 (2.9%)	28 (3.2%)
1–5	568 (64.2%)	566 (64.3%)
6–10	156 (17.6%)	157 (17.8%)
11–20	93 (10.5%)	90 (10.2%)
>20	42 (4.8%)	40 (4.5%)
Previous manic/hypomanic episodes[b]		
0	0 (0%)	0 (0%)
1–5	855 (78.7%)	846 (78.6%)
6–10	138 (12.7%)	139 (12.9%)
11–20	65 (6.0%)	65 (6.0%)
>20	28 (2.6%)	27 (2.5%)
Familial loading[c]		
None	563 (50.5%)	566 (51.1%)
One parent	322 (28.9%)	320 (28.9%)
Two parents	229 (20.6%)	221 (20.0%)
Childhood abuse[d]		
None	501 (41.4%)	508 (42.3%)
Verbal	196 (16.2%)	187 (15.6%)
Physical	44 (3.6%)	46 (3.8%)
Sexual	75 (6.2%)	75 (6.2%)
Verbal + Physical	175 (14.5%)	170 (14.2%)
Verbal + Sexual	96 (7.9%)	94 (7.8%)
Physical + Sexual	11 (0.9%)	11 (0.9%)
Verbal + Physical + Sexual	112 (9.3%)	110 (9.2%)
Age at onset of mood symptoms[e]		
Depressive symptoms	24.4 (11.1) [0–70]	24.8 (11.3) [0–70]
Manic symptoms	28.9 (11.1) [2–64]	29.1 (11.3) [2–64]
Illness duration[f]	24.9 (12.8) [0–64.6]	24.8 (12.7) [0–64.6]
Psychiatric comorbidity[g]		

TABLE 1 (Continued)

	Model A (*N* = 1217) Mean (SD) [range] or N(%)	Model B (*N* = 1203) Mean (SD) [range] or N(%)
No comorbidity	774 (64.2%)	784 (65.9%)
Anxiety disorders	87 (7.2%)	83 (7.0%)
OCD	15 (1.2%)	14 (1.2%)
Psychotic disorders	6 (0.5%)	6 (0.5%)
PTSD	28 (2.3%)	27 (2.3%)
Other axis 1	271 (22.5%)	251 (21.1%)
Personality disorders	24 (2.0%)	25 (2.0%)
Addiction[h]	73 (13.1%)	77 (14.3%)
Medication[i]		
Any	1175	1155
Lithium	1084 (92.3%)	1064 (92.1%)
Valproic acid	332 (28.3%)	307 (26.6%)
Antipsychotics	875 (74.5%)	850 (73.6%)
Antidepressants	621 (52.9%)	600 (51.9%)
IQ[j]	106.4 (9.6)[69–130]	106.3(9.7)[69–130]

[a]QBP item 26 (highest completed education).
[b]SCID items A81 (number of depressions) A144 (number of manic episodes) and A162 (number of hypomanic episodes).
[c]QBP item 31a+d (depressive disorder) item 32a+d (bipolar disorder) and item 33a+d (psychosis).
[d]QBP item 38 (verbal abuse), 39 (physical abuse), and 40 (sexual abuse).
[e]QBP 37a (first symptoms of depression) +37b (first symptoms of hypomania or mania).
[f]Calculated as age subtracted with the age of first symptoms (the lowest of 37a and 37b).
[g]SCID p47-65, p84-119.
[h]CIDI.
[i]SCID p129.
[j]Dutch reading test for adults ("Nederlandse Leestest voor Volwassenen" – NLV).

onset, longer illness duration, the existence of psychiatric comorbidity, and increasing treatment resistance were all significantly associated with the higher stages (Table 2).

After the backward elimination procedure for staging model B, the presence of psychiatric comorbidity, childhood abuse, increased familial loading, lower premorbid IQ, and increasing polypharmacy as an indication for treatment resistance were all significantly associated with higher stages (Table 2). Addiction, illness duration, and an earlier age at onset were not significantly associated with progression to higher stages.

4 | DISCUSSION/CONCLUSION

Using data from over 1300 BD patients, we found that overlapping but not identical clinical profiles predicted the progression of BD in a staging model based on the number of episodes (model A) and interepisodic functional decline (model B). For model A, familial loading, childhood abuse, earlier onset, illness duration, psychiatric comorbidity, and treatment resistance were predictors for a higher stage; the presence of addiction and the IQ did not differ throughout the stages. For model B, childhood abuse, psychiatric comorbidity, lower IQ, and treatment resistance were predictors for a more severe stage, whereas age at onset, illness duration, and addiction were not. Although we have set out to study the contribution of clinical characteristics to the clinical profiles in relation to each other, we shall also discuss these characteristics individually (Figure 2).

In the prediction model for both staging models, familial loading for depression, bipolar disorders, and psychosis was associated with illness progression, defined as increasing the likelihood of reaching higher stages. It has been widely established that familial loading, especially with parental early-onset bipolar disorder, is one of the most consistent risk factors for developing BD,[1] but its influence on course and outcome is still understudied. Kohler-Forsberg[2] found that a family history of BD correlates with an earlier onset and a more severe course and outcome, including more hospitalizations, suicide attempts, and with sociodemographic markers such as lower education and lower household income.

A history of childhood abuse was strongly related to the progression of BD in both models. This is in line with earlier studies on childhood abuse.[3–5] In their meta-analysis, Agnew-Blais et al.[3] described the association between childhood maltreatment and a greater number of manic and depressive episodes as well as an increased risk of rapid cycling in BD, which is in accordance with our finding for model A. They also found an increased rate of psychiatric comorbidity and substance misuse disorders as well as an earlier age at onset in bipolar individuals who experienced childhood abuse.

Applying age as a continuous variable, earlier age at onset was associated with illness progression for model A, but not for model B. This suggests that an early age at onset is associated with a higher number of mood episodes, but not necessarily with worse functioning. A meta-analysis by Joslyn et al.[37] showed that an early age at onset, defined as an onset before 18, was associated with a worse outcome including a longer delay to treatment, greater severity of depression, and higher levels of comorbid anxiety and substance use. Several studies suggest early onset to be correlated with more frequent recurrences[38–40] and a higher rate of unremitting illness[39,40] compared to adult onset. Both Perlis et al.[40] and Lish et al.[38] found a higher rate of functional impairment in early onset patients. According to Lish et al. functional impairment could be diminished by effective treatment. They also found that an early age at onset appears to be clinically correlated with comorbid psychiatric illness,[38] suggesting mutual reinforcement. Illness duration was associated with illness progression for model A, but not for model B, suggesting an association with the number of mood episodes, but not with functioning. The influence of illness duration on the number of mood episodes has been described in various publications, suggesting an increasing sensitization for the development of mood episodes (kindling hypothesis).[41] Our finding for model B is in line with a study

TABLE 2 Ordinal logistic regression

		Model A			Model B		
Coefficient		**OR**	**CI**	***p***	**OR**	**CI**	***p***
Univariate model results							
Familial loading	1 parent	1.73	1.35–2.23	<0.01*	1.74	1.34–2.26	<0.01*
	2 parents	1.40	1.06–1.86	0.02*	1.54	1.15–2.07	<0.01*
Childhood abuse	present	2.05	1.66–2.53	<0.01*	2.12	1.70–2.64	<0.01*
Age at onset	years	0.94	0.93–0.95	<0.01*	0.98	0.97–0.99	<0.01*
Illness duration	years	1.06	1.05–1.07	<0.01*	1.01	1.00–1.02	0.15
Psychiatric comorbidity	present	2.31	1.85–2.88	<0.01*	2.26	1.79–2.85	<0.01*
Addiction	present	0.86	0.55–1.35	0.52	1.14	0.73–1.78	0.58
Treatment resistance	1 type	0.80	0.43–1.47	0.47	0.68	0.37–1.25	0.22
	2 types	0.65	0.37–1.14	0.13	0.92	0.53–1.59	0.76
	3 types	1.39	0.79–2.43	0.25	1.51	0.87–2.60	0.14
	4 types	2.67	1.50–4.78	<0.01*	1.92	1.08–3.40	0.03*
IQ	score	1.01	1.00–1.02	0.24	0.99	0.98–1.00	0.02*
Multivariate model with backward elimination							
Familial loading	1 parent	1.35	1.04–1.75	0.03+	1.55	1.12–2.03	<0.01+
	2 parents	1.00	0.75–1.34	0.99	1.34	0.99–1.83	0.06+
Childhood abuse	present	1.46	1.16–1.85	<0.01+	1.80	1.41–2.30	<0.01+
Age at onset	years	0.97	0.96–0.84	<0.01+			
Illness duration	years	1.04	1.03–1.05	<0.01+			
Psychiatric comorbidity	present	1.69	1.32–2.15	<0.01+	1.94	1.51–2.50	<0.01+
Treatment resistance	1 type	0.91	0.48–1.74	0.78	0.80	0.41–1.54	0.50
	2 types	0.83	0.46–1.49	0.53	1.15	0.64–2.08	0.64
	3 types	1.81	1.00–3.26	0.05+	1.88	1.04–3.40	0.04+
	4 types	3.00	1.63–5.52	<0.01+	2.20	1.18–4.09	0.01+
IQ	Score				0.98	0.97–1.00	<0.01+
		*p <.10 significant +p <.157 significant Wald 72.92 sig.000 Pseudo R-Square Cox and Snell.247 Nagelkerke.262 McFadden.100			*p <.10 significant +p <.157 significant Wald 10.597 sig.005 Pseudo R-Square Cox and Snell.108 Nagelkerke.122 McFadden.052		

Note: Outcomes of the ordinal logistic regression with the following reference categories: familial loading: no parents; childhood abuse: no childhood abuse; psychiatric comorbidity: absent; addiction: absent; treatment resistance: no medication.

by Reinares et al.,[19] who found functional impairment not related to illness duration. This suggests a large variation in the acquisition and functional expression of cumulative neuropathological damage.

Comorbid psychiatric disorders were associated with illness progression for both models. Krishnan[6] published a review on psychiatric comorbidity in BD and found a strong association between the combined prevalence of BD and anxiety disorders, attention-deficit/hyperactivity disorder, eating disorders, cyclothymia, and axis II personality disorders. According to Duffy et al.,[7] anxiety symptoms often precede the diagnosis of BD. The most prevalent comorbid psychiatric disorders for BD are anxiety disorders.[8,9] Comorbid anxiety disorders led to a worse outcome on several domains of BD including illness severity, euthymia, and proportion of the year spent ill.[10] Levander et al.[9] and Kolodziej et al.[8] found comorbid anxiety disorders especially prevalent among BD subjects with co-occurring substance use disorders.

Addiction to any type of substance (in accordance with the DSM-IV diagnosis for substance abuse or – dependence) was not found to be associated with illness progression for either model. The most common type of substance abuse in BD is alcoholism.[14] Post et al.[13] studied drug abuse and found cocaine, amphetamines, phencyclidine, and use of various other drugs associated with chronicity of BD (comparable to stage 4 in model A). A meta-analysis by Messer et al. found that substance use in patients with BD was related to the

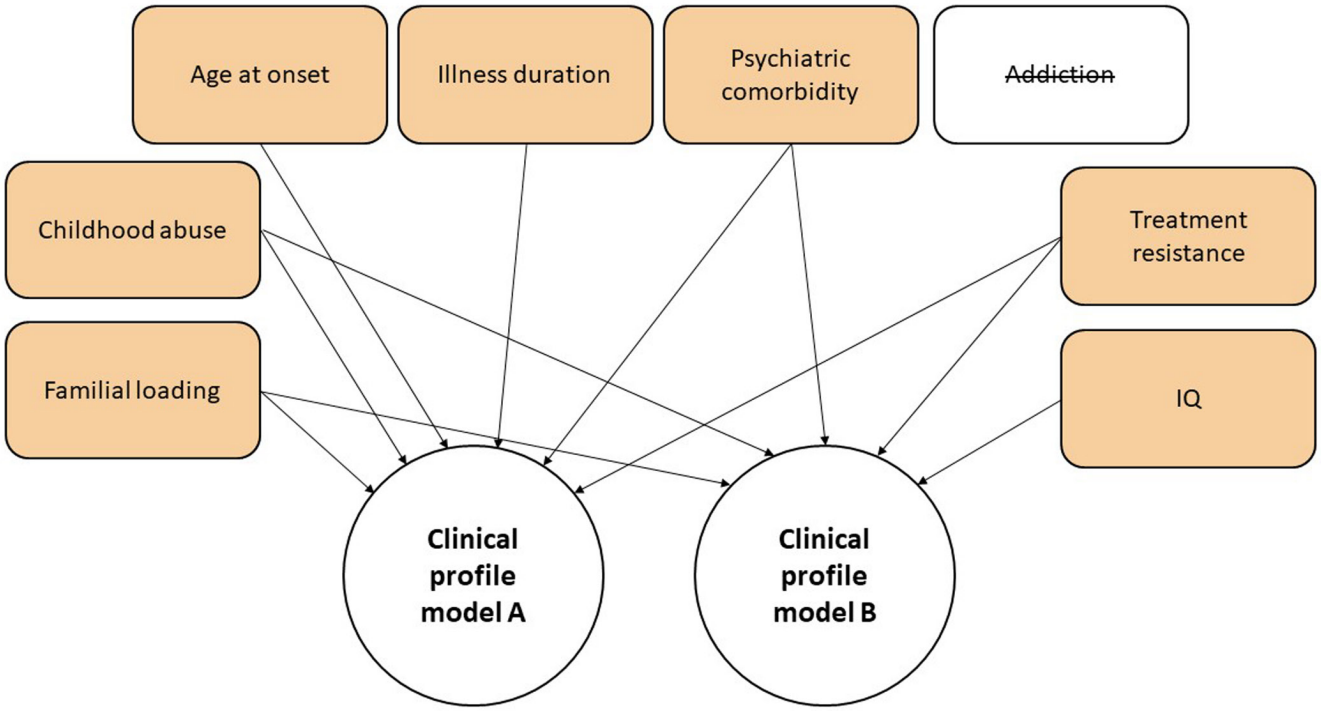

FIGURE 2 Clinical characteristics

number of manic episodes. Due to selection bias in our cohort, we may not have found this in our sample, being a selection of euthymic out-patients, with a willingness to participate in an academic study.

Treatment resistance, defined as the need for polypharmacy, predicted higher stages for both models. A recent systemic review by Hui et al.[15] found predictors for a good response to lithium to be earlier absence of psychotic symptoms, a family history of bipolar disorder, and a later age at onset. The number of mood episodes showed a week negative relation with the number of mood episodes prior to lithium, but the total number of mood episodes before inclusion was not assessed as a predictor for lithium response. Several studies have shown that initial good responders may turn treatment-resistant after recurrent mood episodes; for lithium[16] and olanzapine,[17] this point has been shown to lie at around ten mood episodes. Polypharmacy due to treatment resistance is in line with our finding for model A. Our result for model B is in line with the findings by Goi et al.,[18] who analyzed treatment resistance for a staging model showing resemblance to model B. Goi et al. found monotherapy to be more prevalent in stage I and two-drug combinations more common in stage II. Subjects in stage III and IV mostly required combinations of three or more drugs.

Premorbid cognitive functioning, defined as IQ, was not a clinical indicator for model A, in contrast to model B, suggesting that a lower premorbid IQ is associated with poorer functioning but not with the lifetime number of mood episodes. This finding for model A is in line with four studies reviewed by Robinson and Ferrier,[20] showing only the one by El-Badri et al.[42] to report a negative relation between IQ and total number of mood episodes. Our finding for model B is in line with Martino et al.,[21] finding diminished functioning to be associated with an increasing number of mood episodes, though less for subjects with a higher premorbid IQ. Reinares et al.[19] found a higher verbal IQ to be associated with better functioning, defined in the SF-36 questionnaire as the ability to work and function socially.

4.1 | Limitations

Our study has several limitations. Both models are based on clinical parameters since there are no validated neuropathological biomarkers for BD. Both models are designed to be directly applied to current patients instead of an existing database. Therefore, the fit between these models and the use in clinical settings may only be approximated. Both models are unsuitable for capturing subtle differences in disease progression since passing from one clinical stage to another indicates a major shift in illness progression and therefore each stage contains a broad range of clinical severity.

A possible limitation of staging model B is that psychosocial functioning may be rated differently depending on the cultural context. E.g., independent functioning will be evaluated differently in a society where it is more common to live with family members as compared to living alone, and work demands may largely differ for each country. The sample may also be less representative for patients with non-Dutch origin since one of the inclusion criteria was to have at least three biological grandparents of Dutch ancestry. The reported number of previous mood episodes may be subject to recall bias, which may lead to some inaccuracy in assigning the stage in model A.

With this study, we have identified largely overlapping clinical profiles for both clinical staging models. Common predictors for progression in both models were familial loading, childhood abuse, psychiatric comorbidity, and treatment resistance. Specific for model A were earlier onset and longer illness duration, for model B cognitive functioning. For both models, addiction to substances was not a predictive factor. Most of these clinical factors have been associated with illness progression, but never in combination with each other and never in the context of a staging model. Additional research is needed to further test these clinical profiles in different types of patient data and to identify additional markers like biomarkers and BD episode specifiers such as psychotic symptoms, anxiety, suicidality, and catatonia. Future studies could benefit from a machine learning approach. Although these techniques have some methodological challenges, both Librenza-Garcia et al.,[43] and Passos et al.,[44] have addressed luring perspectives for improvements in diagnosis, personalized treatment, and prognosis orientation. So far, only Mwangi et al.[45] combined MRI-based machine learning with staging, using the number of manic episodes. "Early stage" included BD-I patients, reporting less than 3 lifetime manic episodes without hospitalization, "intermediate stage" included 3–10 manic episodes, and "late stage" covered more than 10 lifetime manic episodes including hospitalizations. Patients with BD-II were categorized as a separate stage and so were the controls. BD-I patients could be accurately distinguished from controls on the basis of severity of the illness and extent of the structural brain abnormalities.

The profiles in our current study could be a first step toward understanding what drives the progression of BD. Ultimately, this may lead to the discovery of different clinical profiles with different predicted outcomes, which may be of clinical use for preventing illness progression in BD.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data not available due to ethical restrictions. Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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