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## Clinical predictors of recurrences in bipolar disorders type 1 and 2: a FACE-BD longitudinal study

Etain B <sup>1,2,3,4</sup>, Bellivier F <sup>1,2,3,4</sup>, Olié E <sup>4,5</sup>, Aouizerate B <sup>4,6</sup>, Aubin V <sup>4,7</sup>, Belzeaux R <sup>4,8</sup>, Courtet P <sup>4,5</sup>, Dubertret C <sup>4,9</sup>, Schwan R <sup>4,10</sup>, Roux P <sup>4,11</sup>, Polosan M <sup>4,12</sup>, Leboyer M <sup>4,13</sup>, Godin O <sup>4, 14</sup>.

On behalf of the FondaMental Advanced Center of Expertise for Bipolar Disorders (FACE-BD)

1. Université de Paris, Paris, France,
2. AP-HP, Groupe Hospitalo-universitaire AP-HP Nord, DMU Neurosciences, Hôpital Fernand Widal, Département de Psychiatrie et de Médecine Addictologique, Paris, France
3. INSERM UMRS 1144, Paris, France
4. Fondation FondaMental, Créteil, France
5. Department of Emergency Psychiatry and Acute Care, CHU Montpellier, INSERM U1061, Montpellier University, Montpellier, France,
6. Centre Hospitalier Charles Perrens, F-33076 Bordeaux, France; Université de Bordeaux ; Centre Hospitalier Charles Perrens, Laboratoire NutriNeuro (UMR INRA 1286), Université de Bordeaux, F-33076 Bordeaux, France;
7. Pôle de Psychiatrie, Centre Hospitalier Princesse Grace, Monaco,
8. Pôle de Psychiatrie, Assistance Publique Hôpitaux de Marseille, Marseille, France; INT-UMR7289,CNRS Aix-Marseille Université, Marseille, France
9. AP-HP, Groupe Hospitalo-universitaire AP-HP Nord, DMU ESPRIT, Service de psychiatrie et addictologie, Hôpital Louis Mourier, Colombes, France and Inserm U894, Université de Paris, Sorbonne Paris Cité, Faculté de médecine, France.
- 10.Université de Lorraine, CHRU de Nancy et Pôle de Psychiatrie et Psychologie Clinique, Centre Psychothérapique de Nancy, Nancy, France
- 11.Centre Hospitalier de Versailles, Service Universitaire de psychiatrie d'adulte et d'addictologie, Le Chesnay, EA 4047 HANDIRESP, UFR des Sciences de la Santé Simone Veil, Université Versailles Saint-Quentin-en-Yvelines, Versailles, France, Equipe « PsyDev », CESP, Université Paris-Saclay, Inserm, 94807, Villejuif, France.
- 12.Université Grenoble Alpes, CHU de Grenoble et des Alpes, Grenoble Institut des Neurosciences (GIN) Inserm U 1216, Grenoble, France ;
- 13.INSERM U955, équipe de psychiatrie translationnelle, Créteil, France, Université Paris-Est Créteil, DHU Pe-PSY, Pôle de Psychiatrie des Hôpitaux Universitaires H Mondor, Créteil, France
- 14.Sorbonne Universités, UPMC Univ Paris 06, UMR\_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique; INSERM, UMR\_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, F-75013 Paris, France.

### Corresponding Author

Professeur Bruno ETAIN

Centre Expert Troubles Bipolaires,

Département de Psychiatrie et de Médecine Addictologique,

Hôpital Fernand Widal, 200, rue du Faubourg Saint Denis, 75010 Paris Cedex, France

Email : [bruno.etain@inserm.fr](mailto:bruno.etain@inserm.fr)

## **ABSTRACT**

**OBJECTIVE:** To examine which characteristics predict the time to a first mood recurrence at three years in Bipolar Disorder type I (BD-I) and type II (BD-II).

**METHODS:** Individuals with BD were followed up to 3 years. Turbull's extension of the Kaplan-Meier analysis for interval-censored data was used to estimate the cumulative probability of recurrence over time. Separate models were performed according to BD subtype to determine which baseline factors were predictive of recurrences and were adjusted for age, gender and educational level.

**RESULTS:** We included 630 individuals with BD-I and 505 with BD-II. The first recurrence of any polarity occurred earlier in BD-II ( $p=0.03$ ). The first depressive recurrence occurred earlier in BD-II ( $p<0.0001$ ), whereas the first (hypo)manic recurrence occurred earlier in BD-I ( $p=0.0003$ ). In BD-I, the clinical variables that were associated to the time to a first mood recurrence were depressive symptoms, lifetime rapid cycling, global activation and the number of psychotropic medications at baseline. In BD-II, the time to a first recurrence was associated with a younger age at onset of BD and a higher number of lifetime mood episodes. The Areas Under the Curve for both models were moderate.

**CONCLUSION:** Predictors of recurrences showed few specificities to BD-I or BD-II. The ability to predict recurrences in BD based on socio-demographic and clinical variables remained too moderate for a transfer in daily practice. This study highlights the need for further studies that would include other types of predictors, such as molecular, cognitive or neuro-imaging ones, to achieve an accurate level of prediction of recurrences in BD.

**Key Words:** bipolar disorder, subtype, recurrence, prediction, longitudinal study

## INTRODUCTION

Bipolar Disorder (BD) is a highly recurrent disease and a significant part of its prognosis, burden, direct and indirect costs depend on the frequency and severity of mood recurrences. As an example, the NESARC (National Epidemiologic Survey on Alcohol and Related Conditions) study including 909 patients with BD type I showed that mood recurrences were associated with greater risk for new onset suicidality, psychiatric comorbidity, disability, unemployment, and poor functioning during follow-up (Peters et al., 2016). The prediction of mood recurrences in BD is thus a challenge to characterize the risk for a subsequent episode and to tailor the care plan including, for example, a more intensive follow-up, the selection of (combinations of) drugs and psychosocial interventions, with the ultimate goal of preserving the functioning and quality of life of individuals.

Earlier studies found that the recurrence risk of BD was about 0.4 episodes/year (Angst et al., 2003). A familial study suggested that the episode frequency was smoothly distributed over the range of 0.02–20.2 episodes/year, with a peak around 0.6 episodes/year for mania and depression (Fisfalen et al., 2005). In the FACE-BD (FondaMental Advanced Centers of Expertise for Bipolar Disorder) cohort including 984 individuals with BD, a density around 0.6 episodes/year was observed during the 2 years follow-up (Henry et al., 2017). A systematic review of 10 naturalistic studies (3904 patients, followed up to 2.1 years) further identified that the pooled recurrence rate was 55.2% (26.3%/year) (Vazquez et al., 2015). Finally, a recent meta-analysis of 12 studies comprising 5.837 patients estimated that the median time to a subsequent mood episode in adults after an index episode was 1.44 years, with a risk of a subsequent mood episode of 44% during the first year (Radua et al., 2017). All these findings consistently highlighted that BD is a highly recurrent disorder with individuals experiencing a probability of recurrence around 25-50% in the first year of follow-up.

Various characteristics have been suggested as potential predictors of mood recurrences in BD, among which: gender (Degenhardt et al., 2012; Tundo et al., 2018), number of previous mood episodes (de Dios et al., 2012b; Judd et al., 2008; Takaesu et al., 2018; Tohen et al., 2012; Tundo et al., 2018), mixed episodes (Gonzalez-Pinto et al., 2011), depressive symptoms at baseline (Degenhardt et al., 2012), persisting residual symptoms (De Dios et al., 2012a; Judd et al., 2008), smoking status (Tohen et al., 2012), rapid cycling (Degenhardt et

al., 2012), comorbidities with anxiety, substance misuse disorders or ADHD (Yen et al., 2016), continued cannabis use (Zorrilla et al., 2015), presence of thyroid diseases (especially hypothyroidism) (Amann et al., 2017), high BMI or obesity (Fagiolini et al., 2003; Hu et al., 2017), sleep disturbances or abnormalities of circadian rhythms (Cretu et al., 2016; Gershon et al., 2017; Saunders et al., 2015; Sylvia et al., 2012; Takaesu et al., 2018), life events or psychosocial stressors (De Dios et al., 2012a; Simhandl et al., 2015), poor adherence to medication and low serum levels of mood stabilizers (Scott and Pope, 2002). However, most predictors have been studied individually, and rarely as combinations of predictors in order to maximize the estimation of the risk of recurrence. Moreover, studies of predictors of mood recurrences have not always taken into account the influence of mood symptoms at inclusion that might confound the genuine effects of some given predictors when they potentially correlated or associated with mood symptoms (sleep disturbances represent one example among others).

Interestingly, in a recent meta-analysis, the risk of mood recurrences was found to be higher in BD-II than in BD-I (Radua et al., 2017), with a median time to subsequent mood episode after an index episode being 0.8 years in BD-II versus 1.7 years in BD-I. In this context, there is an absence of studies exploring the specificity of potential predictors with regards to BD subtype. Indeed, most studies have included only patients with BD-I (for example (Degenhardt et al., 2012; Tohen et al., 2012)), and findings about potential predictors of recurrences might not generalize to patients with BD-II. In a systematic review of naturalistic follow-up studies of patients with BD, around 85% of individuals suffered from BD-I (Vazquez et al., 2015). Most studies have used mixed samples of BD-I and BD-II, therefore the number of included patients with BD-II was too small to allow any stratification on BD subtype. To date, no study has included a large enough sample of individuals with both subtypes to explore any specificity of potential predictors of recurrences in BD-I and BD-II.

The purpose of this study is therefore to compare the time to first mood recurrence in a large sample of patients with BD-I or BD-II and to explore whether predictors of mood recurrences are shared or specific according to BD subtype.

## **Material and methods**

### **Study sample**

The study sample consisted in patients evaluated in the French network of FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD). This network is supported by the French Ministry of Health and has been developed under the aegis of the FondaMental Foundation, to provide support to general practitioners and psychiatrists in the diagnosis and management of patients with BD.

Patients were only outpatients, were referred to the centres mainly by general practitioners and psychiatrists (private or public practice) and were not referred to the centres in emergency or for acute states. There are few exclusion criteria for referral, and all patients who appear to meet the diagnostic criteria for any BD subtype (I, II or not otherwise specified [NOS]) can be assessed. The only exclusion criteria for clinical assessment were dementia or related-disorders (Alzheimer disease, fronto-temporal dementia, dementia with Lewis bodies) or mental retardation. In that case, these individuals followed other paths of assessment and were not including in the follow-up.

All outpatients aged 16 years or older who have been assessed in the expert centers and diagnosed with BD according to DSM-IV criteria (all bipolar subtypes [I, II, and not otherwise specified]) were enrolled in the FACE-BD cohort. Patients were followed up at 6 months, one year, two years and 3 years in each center.

There were 12 expert Centers in France and they all used the same package of thorough and standardized assessment, already described elsewhere (Henry et al. 2017). The assessment protocol was approved by the institutional review board (Comité de Protection des Personnes Ile de France IX; January 18, 2010), in accordance with the French laws for non-interventional studies and requires only an informational letter.

### **Data Collected at baseline**

At baseline, the participants were assessed by a specialized team (nurse, psychiatrist, psychologist and neuropsychologist) that collected and recorded the following variables. A web-based application, e-bipolar© was developed to collate data for clinical monitoring and research purposes. Access to the system is carefully regulated and approval was obtained from the body overseeing the safety of computerized databases (CNIL) (DR-2011-069).

### ***Socio-demographic characteristics***

Age, gender and education level were recorded. Education level was classified as below or above the high school level.

### ***Clinical characteristics***

The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) Axis I Disorders (SCID) (First et al., 1995) was used to confirm the diagnosis of BD, as well as to assess the course of the disease. The SCID was also used to diagnose comorbid psychiatric disorders (anxiety and substance use disorders).

The following variables were recorded in the database: BD subtype (type I or type II, according to DSM-IV criteria), age of onset of BD, illness duration (age at inclusion minus age at onset of BD), number of lifetime episodes (including episodes of all polarities: manic, hypomanic, mixed or depressive), lifetime presence of at least one suicide attempt (as assessed by the appropriate section of the SCID), lifetime history of rapid cycling (defined according to DSM-IV criteria), lifetime history of seasonal pattern (defined according to DSM-IV criteria).

Age of onset of BD was defined as the age at which a given participant presented with a first mood episode of any polarity (manic, hypomanic, mixed or depressive) according to DSM-IV criteria as retrospectively assessed using the SCID.

Smoking status at baseline was defined as current smoker *versus* past or never smoker.

DSM-IV criteria for lifetime abuse or dependence to alcohol, cannabis and other illicit drugs were assessed using the corresponding sections of the SCID and pooled into a single category ‘substance use disorders’ that is coded ‘yes’ when the patient has fulfilled the DSM-IV criteria for abuse or dependence for at least one of these substances at any time during the lifespan.

DSM-IV criteria for anxiety disorders (panic disorder, agoraphobia, simple phobia, social phobia, obsessive-compulsive disorder and generalized anxiety disorder) were assessed using the corresponding sections of the SCID and pooled into a single category ‘anxiety disorders’ that is coded ‘yes’ when the patient has fulfilled the DSM-IV criteria for at least one of these disorders at any time across the lifespan.

### ***Observer-rated questionnaires***

Current mood state (residual depressive and hypomanic symptoms) was assessed by clinicians with the Montgomery Asberg Depression Rating Scale (Montgomery and Asberg, 1979) and the Young Mania Rating Scale (Young et al., 1978).

Global functioning was measured using the Functioning Assessment Short Test (FAST) (Rosa et al., 2007). The FAST is scored during a structured interview and has been specifically developed and validated to assess the level of disability in individuals with BD. The FAST includes 24 items within 6 domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time). Here, we used the total score (ranging from 0 to 72) of the FAST as a continuous variable with a higher score being indicative of a worse social functioning. The FAST has high internal consistency (Cronbach's alpha of 0.90), good concurrent validity since correlated with the DSM-IV Global Assessment of Functioning (GAF) ( $\rho = -0.90$ ) and good test-retest reliability (Intra Class Correlation = 0.98). We used the validated French version (Daban et al., 2012).

### ***Patient-rated questionnaires***

Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a 19-item self-completed questionnaire requiring the participant to describe patterns of sleep, such as typical bedtime and waking time, sleep latency, actual sleep time and sleep disturbances. The PSQI total score ranges from 0 to 21 and is used in this study as a continuous variable. A higher PSQI total score is indicative of a worse sleep quality. The PSQI has high internal consistency (Cronbach's alpha of 0.83), and good test-retest reliability (Intra Class Correlation = 0.85). The French version of this questionnaire has been validated by (Blais et al., 1997).

The history of childhood traumatic events and maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The CTQ is a 28-item self-completed questionnaire that generates a total score (ranging from 25 to 125). It also generates scores for five subtypes of trauma that were not used in this study. The CTQ has good internal consistency in sub-scores (Cronbach's alpha between 0,68 and 0,91), and good test-retest reliability in sub-scores (Intra Class Correlation between 0,73 and 0,94). The French version of this questionnaire has been validated by (Paquette et al., 2004). In the analyses, we used only the CTQ total score as a continuous variable.



Behavioral inhibition/activation was measured using the MATHyS (Multidimensional Assessment of Thymic States) (Henry et al., 2008). The MATHyS is a visual analogic self-reported scale consisting of 20 items. These items correspond to five quantitative dimensions ranging from inhibition to activation: emotional reactivity, thought processes, psychomotor function, motivation and sensory perception. This scale allows to determine a general level of inhibition/activation (lower scores indicate global inhibition while higher scores indicate global activation). The total score can range from 0 to 200. As proposed by the authors, patients with a score lower than 91 can be considered as having global inhibition whereas patients with a score higher than 109 can be considered as having global activation. The total score was thus used in this study in three categories corresponding to the inhibition/normal/activation states. The MATHyS has a good internal consistency (Cronbach's alpha coefficient = 0.95). The MathyS scale is moderately correlated with depressive symptoms (depressive score;  $r = -0.45$ ) and manic symptoms (manic score;  $r = 0.56$ ) (Henry et al., 2013).

### ***Metabolic syndrome***

A physical examination was carried out, and a blood sample was collected at inclusion. Body Mass Index (BMI) ( $\text{kg}/\text{m}^2$ ) was recorded. Metabolic syndrome (MetS) was then defined according to the criteria of the International Diabetes Federation (Alberti et al., 2005), which requires that 3 or more of the following 5 criteria be met: high waist circumference ( $> 94$  cm for men and  $> 80$  cm for women), hypertriglyceridemia ( $\geq 1.7$  mmol/L or on lipid-lowering medication), low HDL cholesterol level ( $< 1.03$  mmol/L in men and  $< 1.29$  mmol/L in women), high blood pressure ( $\geq 130/85$  mm Hg or on antihypertensive medication), and high fasting glucose concentration ( $\geq 5.6$  mmol/L or on glucose-lowering medication). The variable MetS was then coded as presence or absence.

### ***Medications and related measures***

Current psychotropic treatments (first-generation neuroleptics, atypical antipsychotics agents (APA), mood stabilizers (including lithium and anticonvulsants), and antidepressants) were recorded at baseline.

Adherence to medication was assessed using the Medication Adherence Rating Scale (MARS) (Thompson et al., 2000). MARS is a 10-yes/no item self-report. The total score ranges from 0

to 10. A low score is representative of a low likelihood of medication adherence while a total score  $\geq 8$  is associated with a higher likelihood of medication adherence. The MARS has good internal consistency (Cronbach's alpha of 0.75), and reasonable test-retest reliability (Intra Class Correlation = 0.72). The French version of the MARS has been validated by (Misdrahi et al., 2004). In this study we used the total score of the MARS as a continuous variable.

### **Definition of the outcome**

A mood recurrence was defined as any newly occurring mood episode of any polarity (manic, hypomanic, mixed or depressive) defined according to DSM-IV criteria and assessed using the SCID during the follow-up. If a given patient has been included in remission, the first mood recurrence was allowed to occur at any time. If a given patient has been included with current depressive or manic symptoms (MADRS or YMRS scores above 8), the first mood recurrence was allowed to occur only after 8 consecutive weeks without clinically significant depressive or (hypo)manic symptoms. In this study, we used the guidelines of the International Society for Bipolar Disorders that recommend that relapse and recurrence are defined as a new episode occurring within 8 weeks and  $> 8$  weeks, respectively, after having achieved symptomatic remission from the index episode (Tohen et al., 2009). The FAST or the GAF (or any significant changes on these scales during the follow-up) were not considered in the definition of recurrence used in this study.

### **Statistical analysis**

Categorical variables were expressed as numbers and percentages, and continuous variables as median and interquartile range (IQR). As the time interval during which the first mood recurrence occurred is known but not the exact starting date, interval-censored survival analysis was used to examine the association between risk factors and time to a first recurrence during follow-up. Turbull's extension of the Kaplan-Meier analysis for interval-censored data was used to estimate the cumulative probability of recurrence over time. Time to first recurrence was compared across the BD type I and type II. To determine socio-demographics factors, clinical characteristics, co-morbidities, and treatment factors that might predict recurrence over the 3 years of follow-up, interval-censored proportional

hazards models were fitted and separate models were performed in individuals with BDI and then BDII subtype. Age, gender and educational level were forced into the models to adjust for these three variables and then all parameters for which univariable analyses shown p-values lower than 0.15 were entered in the multivariable analysis for BDI and then for BDII (two separate models) with a stepwise option. Outliers were excluded and multivariate analyses were performed in the samples without missing data. Multicollinearity was tested using the correlation matrix and the variance inflation factor (VIF). All VIF were  $< 2$  and were given in the result tables. Receiver Operating Characteristic (ROC) curves and Area Under the Curve (AUC) were generated.

Then, sensitivity analyses in patients without rapid cycling and with MADRS  $< 8$  and YMRS  $< 8$  were also performed. These characteristics were defined as at enrollment time. Therefore, four separate models were performed: in BDI without rapid cycling, in BDII without rapid cycling, in BDI without rapid cycling and with low current mood symptoms (MADRS  $< 8$  and YMRS  $< 8$ ), and in BDII without rapid cycling and with low current mood symptoms (MADRS  $< 8$  and YMRS  $< 8$ ). Receiver Operating Characteristic (ROC) curves and Area Under the Curve (AUC) were generated.

In total, we performed two separate multivariate models to identify factors being associated to the time to a first mood recurrence in BD type I and in BD type II and 4 additional multivariate models (for the sensitivity analyses).

Statistical analyses were performed with SAS (release 9.4; SAS Statistical Institute, Cary, NC). All statistical tests were two-tailed. A Bonferroni correction for multiple testing was applied for univariate analyses only (25 tests in each BD subtype leading to a corrected p value of  $0,05/100$ , i.e.  $0,0005$ ). No correction was applied to the multivariate models

## **Results**

### ***Sample description***

A flow chart of the inclusion and exclusion criteria for the study is provided in figure S1. The samples consisted in 1135 patients (630 with BD-I and 505 with BD-II). In this sample, 13% of participants were referred by their general practitioners, 40.7% by their private psychiatrists and 39.6% by their psychiatrists (public or hospital-based practice). Some participants (6.7%) were referred from other sources (by themselves or by associations of patients). The

comparison between the two groups is described in supplementary table 1 (see Table S1). The most significant differences between groups are as followed. Patients with BD-II were older at inclusion, presented with more residual manic symptoms, a global activation, and were more likely to receive antidepressants at baseline. Patients with BD-I were more frequently current smokers, had a higher level of sleep disturbances and were more likely to receive atypical antipsychotics agents (APA) at baseline.

#### ***Follow-up data: time to first mood recurrence***

The mean duration of follow-up was 14.6 (9.5) months (IQR:12-24). The mean duration of follow-up was similar in BD-I and BD-II patients (14.7 (9.6) *versus* 14.6 (9.4)  $p=0.88$ ).

During the follow-up period, 693 patients (54.1%) have experienced at least one mood recurrence whatever the polarity. When stratifying on BD subtype, 325 individuals with BD-I (51.6%) have experienced a mood recurrence *versus* 296 (58.6%) of individuals with BD-II ( $p=0.018$ ). Figures 1.1, 1.2 and 1.3 describe the results of the survival analysis. Patients with BD-II have a higher risk of recurrence during the follow-up as compared to patients with BD-I (HR=1.2 95CI(1.0-1.4),  $p=0.03$ ) (see figure 1.1). Different patterns of recurrences were observed according to the polarity of the first mood recurrence during the follow-up. The first depressive recurrence occurred earlier in patients with BD-II (HR=1.6 95CI(1.3-1.9),  $p<0.0001$ ) (see Figure 1.2), whereas the first (hypo)manic recurrence occurred earlier in patients with BD-I (HR=2.0 95CI(1.3-3.4),  $p=0.0003$ ) (see Figure 1.3).

#### ***Baseline variables associated to time to first recurrence according to BD subtype***

The univariable analyses identified a large number of baseline characteristics as being associated with the time to a first mood recurrence. Results are detailed in supplementary table 2 and summarized in figure 2. When focusing only on results that remained significant after the correction for multiple testing, higher depressive symptoms and worse functioning at baseline were associated with the time to first mood recurrence both in BDI and BD-II patients. Higher manic symptoms, lower sleep quality, and lifetime history of rapid cycling were associated with the time to first recurrence in patients with BD-I only. After correction for multiple testing, no other predictor (except higher depressive symptoms and worse functioning at baseline) was associated to the time to first mood recurrence was identified specifically in BD-II.

We then performed multivariable analyses to predict the time to a first mood recurrence in BD-I and in BD-II patients (including all variables previously identified with a  $p < 0.15$ ). For BD type I, the following variables were thus included: age, gender, educational level (forced entry to adjust for these three variables), baseline depressive and manic symptoms, baseline functioning, lifetime rapid cycling, lifetime seasonal pattern, baseline global activation, childhood trauma, baseline smoking status, lifetime substance use and anxiety disorders, baseline sleep disorders, baseline metabolic syndrome, baseline adherence to medication, baseline antidepressant treatment and number of psychotropic medication at baseline (with a stepwise option). For BD type II, the following variables were included: age, gender, educational level (forced entry to adjust for these three variables), age of onset, illness duration, baseline depressive and manic symptoms, baseline functioning, lifetime rapid cycling, baseline global activation, childhood trauma, number of lifetime mood episode, lifetime substance use and anxiety disorders, baseline sleep disorders, baseline adherence to medication, atypical antipsychotics treatment at baseline and number of psychotropic medication at baseline (with a stepwise option).

Regarding clinical variables, in patients with BD-I, the time to a first mood recurrence was independently associated with higher depressive symptoms ( $HR=1.04$  95CI(1.02-1.06),  $p=0.0005$ ), a lifetime history of rapid cycling ( $HR=2.23$  95CI(1.43-3.48),  $p=0.0004$ ), a global activation ( $HR=1.82$  95CI(1.22-2.73),  $p=0.014$ ) and the number of psychotropic medications at inclusion ( $HR=1.16$  95CI(1.01-1.32),  $p=0.031$ ). The AUC for the model including these four variables was 0.71. Regarding clinical variables, in patients with BD-II, the time to a first mood recurrence was independently associated with a younger age at onset of BD-II ( $HR=0.98$  95CI(0.96-0.99),  $p=0.033$ ) and the number of lifetime mood episodes ( $HR=1.03$  95CI(1.01-1.05),  $p=0.004$ ). The AUC for the model including these three variables was 0.67.

We performed sensitivity analyses in the subgroups of individuals without rapid cycling during lifetime and then with further exclusion of those who were not euthymic at baseline (MADRS and YMRS scores above 8), these two factors being known to be highly associated with the risk of recurrences. In individuals without lifetime history of rapid cycling, the time to first recurrence was associated with depressive symptoms ( $HR=1.06$  95CI(1.05-1.09)

$p < 0.001$ ) and a global activation ( $HR = 2.12$  95CI(1.35–3.33)  $p = 0.005$ ) in BD-I (AUC=0.66), whereas it was associated with depressive symptoms ( $HR = 1.02$  95CI(1.01–1.04);  $p = 0.024$ ) and the number of lifetime mood episodes ( $HR = 1.03$  95CI(1.01–1.05);  $p = 0.008$ ) in BD-II (AUC=0.67).

When further excluding those individuals with a MADRS or a YMRS score above 8, the time to a first mood recurrence was predicted only by depressive symptoms ( $HR = 1.18$  95CI(1.05–1.33);  $p = 0.006$ ) in BD-I (AUC=0.64) and by the number of lifetime mood episodes ( $HR = 1.05$  (1.02–1.09);  $p = 0.005$ ), and to a lesser extent by anxiety disorders and substance use disorders (respectively  $HR = 2.04$  (1.0–4.1);  $p = 0.048$  and  $HR = 2.28$  (1.02–5.09);  $p = 0.045$ ) in BD-II (AUC=0.63).

Since some of these variables did not fit a normal distribution (depressive symptoms assessed using the MADRS, number of lifetime mood episodes, age at onset, and number of psychotropic medications at inclusion), the two main multivariate models were performed again, but with log-transformed variables. Results remains mostly unchanged, except for the association between the time to a first mood recurrence and the number of psychotropic medications at inclusion that was no longer significant in BD type I (data available on request upon the authors).

## **Discussion**

This study confirmed that more than a half of individuals with BD will experience a mood recurrence during the follow-up period. It also confirmed that patient with BD-II were relapsing faster as compared to BD-I, this being significant only when considering a first depressive recurrence. Many baseline clinical variables were predictive of the time to a first mood recurrence in the univariable analyses, with a few specificities related to BD subtype. However, when all these variables were included in a multivariable model, only very few remained predictors of the time to a first mood recurrence in BD-I and in BD-II. Furthermore, these multivariable models had a moderate ability to predict the time to a first recurrence given the values of AUC.

First, this study confirmed that BD is characterized by a high risk of mood recurrences, even when patients were currently treated with mood stabilizers which is the case in this sample. Consistently with the results obtained by Radua et al. (Radua et al., 2017), more than a half of the patients will present a subsequent mood episode during the 2 years follow-up period. Interestingly, this recurrence rate is (i) higher in BD-II as compared to BD-I and (ii) mainly involved depressive recurrences. This highlights the fact that, even though sometimes considered as an “attenuated” form of BD, BD-II is characterized by a higher risk of depressive recurrences as compared to BD-I. As such, individuals with BD-II should be the subject of a reinforced scrutiny. More globally, the risk of a depressive recurrence also exceeded the risk of a manic recurrence in patients with BD whatever the subtype (I or II), meaning that the scrutiny in daily practice should mainly examine the depressive polarity. This is consistent with the literature that has described and/or explored the concept of predominant polarity that is depressive in a majority of individuals with BD (Henry and Etain, 2010; Pallaskorpi et al., 2019) and with studies showing that the burden of BD is mainly linked to the depressive polarity (Miller et al., 2014). In longitudinal studies, this depressive burden has been related to other prognosis factors such as alcohol or drug abuse or adherence to medication. As examples, BD patients with good adherence to lithium had fewer episodes with depressive features than poor adherers (Gonzalez-Pinto et al., 2018), and predominantly depressive group had a worse prognosis and maintained alcohol and other substance abuse during the follow-up (Gonzalez-Pinto et al., 2010).

Based on the results of the univariable analyses, our results were highly consistent with those obtained in previous studies, suggesting that the time to a first recurrence in BD is multidetermined by a large set of socio-demographic, clinical and dimensional variables. Most clinical factors were predictors of recurrence both in BD-I and BD-II with little specificities being identified according to BD subtype. However, anxiety disorders, metabolic syndrome, global activation and adherence to medication were predictive of the risk of recurrence in BD-I only, whereas age at onset was predictive of the risk of recurrence in BD-II only. We cannot exclude here a lack of power in the BD-II sample (even numerically well balanced with the BD-I sample) that prevented us to identify (more specific) signals in this particular subgroup. Interestingly, regarding current medication use, atypical antipsychotics

were predictive of the risk of recurrence in BD-II only, whereas antidepressants were predictive of the risk of recurrence in BD-I only.

While univariable analyses identified many variables that individually predicted mood recurrence, only a few remained significant when combined in the multivariable analyses with AUC values around 0.65-0.70. The final model retained depressive symptoms, rapid cycling, global activation and the number of psychotropic medications at inclusion for the prediction of recurrences in BD-I while age at onset and number of lifetime mood episodes were predictor of the time to a first mood recurrence in BD-II. This leads to suggest that even an exhaustive clinical assessment may be not sufficient enough to fairly predict the risk of recurrences, hence with a relevance in daily clinical practice that may remain questionable. Furthermore, when excluding rapid cycling and then clinically relevant mood symptoms for sensitivity analyses, the models retained very few potential predictors (mainly depressive symptoms in BD-I and the number of lifetime mood episodes in BD-II) with a relatively low predictive value (AUC around 0.65). Here again, the exclusion of individuals who had rapid cycling and/or were not euthymic at baseline have decreased the sample size and might therefore alter the power to identify predictors. Nevertheless, the relevance of the use of such clinical predictors in the daily practice is therefore questionable.

This study has several limitations including the moderate sample size (although of reasonable size as compared to the available literature), the potential lack of representativeness of a sample that has been assessed in tertiary academic affiliated services, a lack of covariation by the different previous sequences of psychotropic drugs, the lack of adjustment for potential modifications of psychotropic drugs having occurred during the follow-up. We also not used the serum level of mood stabilizers that can be measured in blood to estimate the current exposure to medications and be used as predictors of recurrence (Scott and Pope, 2002). No information was recorded in the database related to potential triggering factors of a given mood recurrence. This would be important to explore whether some factors, such as stressful life events and medical disorders that occurred during the follow-up might be associated with an increased risk of recurrences as suggested in previous studies (Amann et al., 2017; de Dios et al., 2012b; Simhandl et al., 2015). Some potential predictors were not included in the analyses because no information was recorded



in the database. This was the case for Post-Traumatic Stress Disorder, learning disorders or other cognitive difficulties and personality disorders that were not assessed in this study. Such potential predictors would deserve consideration in future studies. Furthermore, family history of mood disorders was assessed in this study only by the self-reported information collected from the patients about their first-degree relatives. We did not include such a potential predictor in the analyses since we consider that this type of assessment is not reliable as compared to the use of a structured interview such as the FIGS (Family Interview for Genetic Studies) (NIMH Genetics Initiative, 1992). We also did not provide any objective measures of cognitive functioning nor IQ. This would be however interesting for future studies since a recent study suggested that global cognitive deficits were independent predictors of both hypo/manic episode density and time spent with hypo/manic symptoms during follow-up in a sample of 76 outpatients with BD (follow-up period of at least 48 months) (Valerio et al., 2020). Finally, no information was recorded in our database related to social isolation or connection and the level of engagement of caregivers, relatives and friends in the participants' self-management (and the strategies for preventing recurrences). This should be studied in future studies.

Nevertheless, some strengths should be highlighted. This study is the first to compare the potential specificities of predictors to recurrence in BD-I and BD-II and the stratification on BD subtype is a novel question. The duration of the follow-up was long enough to reliably capture the occurrence of a new mood episode given previous data from the literature (Radua et al., 2017). The clinical assessment was exhaustive, including not only structured interviews but also some self-reports. Multivariable analyses and sensitivity analyses added to the robustness of findings even if they decrease the sample size.

The prediction of mood recurrences in individuals with BD is part of a mandatory step towards a more personalized medicine but remains a challenge. Since many individual predictors of mood recurrences were identified by the univariate analyses, these results may serve as some material for psychoeducational purpose. Indeed, patients should be aware that a wide range of clinical variables might increase their vulnerability to recurrences, some of them being potential future targets to be included as part of their care plan. However, this assertion is toned down by the multivariable analyses that suggested that the ability of

the model to predict the time to a first recurrence remained moderate. Since we have suggested that combining data from the clinical assessment and from self-questionnaires might be of moderate relevance for a transfer in the clinical daily practice, further researches are required. First, we have not included any measure from the routine blood samples that were drawn from all patients being assessed within the network. For example, it has been suggested that higher neutrophil-lymphocyte and platelet-lymphocyte ratios might be associated with more episodes and hospitalizations after 18 months of follow-up in individuals with BD (Melo et al., 2019). Even though not used in clinical practice, some cytokines or adipokines may also be predictive of depressive recurrence in a 12 months follow-up period (Bond et al., 2016, 2017). The prediction of mood recurrences may also benefit from the integration of neurocognitive data in the risk estimation. As an example, recurrence of mania has been suggested to be predicted by verbal free recall at the Auditive Verbal Learning Test (Bauer et al., 2017). However, more potential predictors might be expected to come from the bench (so called “omics” approaches) or from neuroimaging techniques, even if the literature in this domain is still scarce. In the case of inclusion of sets of data coming from multiple type of assessment, machine learning techniques may offer the appropriate tools for an optimized prediction of recurrences in BD (Salvini et al., 2015). However, for an integration in the clinical practice, we have to bear in mind that predictors of recurrence should be reliable, reproducible, easy to ease (or to measure) but also cost-effective.

Despite the progresses made in its clinical and therapeutically management, BD is a disorder that is still characterized by a high risk of recurrence. The prediction of mood recurrence remains a challenge and even if some clinical predictors were identified in this study, they may lack a predictive value good enough to be applicable in the daily practice. The integration of predictors coming from different fields of research (clinical, neurocognitive, neuroimaging, molecular research) is probably the mandatory next step to move to a more predictive medicine in BD.

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FACE-BD Clinical Coordinating Center (Fondation FondaMental): B. Etain, E. Olié, M. Leboyer, PM Llorca, C. Henry;

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Département d’Urgence et Post Urgence Psychiatrique, CHRU Montpellier, Montpellier, France : C. Abettan, L. Bardin, A. Cazals, P. Courtet, B. Deffinis, D. Ducasse, M. Gachet, A. Henrion, E. Martinerie, F. Molière, B. Noisette, E. Olié and G. Tarquini;

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#### **Authors Contributions:**

Godin and Etain: Conceptualization; Data curation; Formal analysis; Writing - original draft

Leboyer: Funding acquisition; Writing - review & editing.

Bellivier, Olié, Aouizerate, Aubin, Belzeaux, Courtet, Dubertret, Schwan, Roux and Polosan: Validation ; Writing - review & editing.

All other authors contributed to data collection, proposed critical review of the manuscript and approved the final version of the article final.

#### **Data availability statement**

The data that support the findings of this study are available from Fondation Fondamental. Restrictions apply to the availability of these data, which were used under license for this study.

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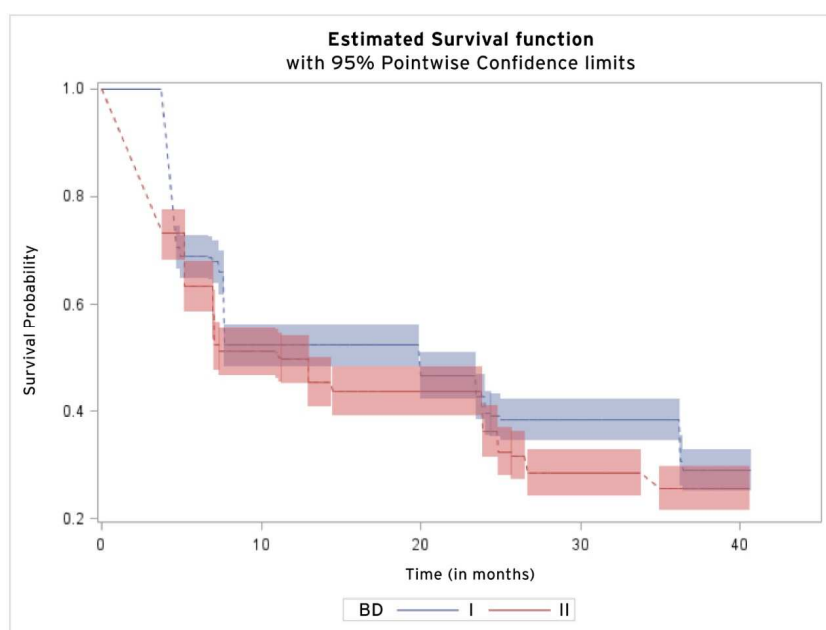
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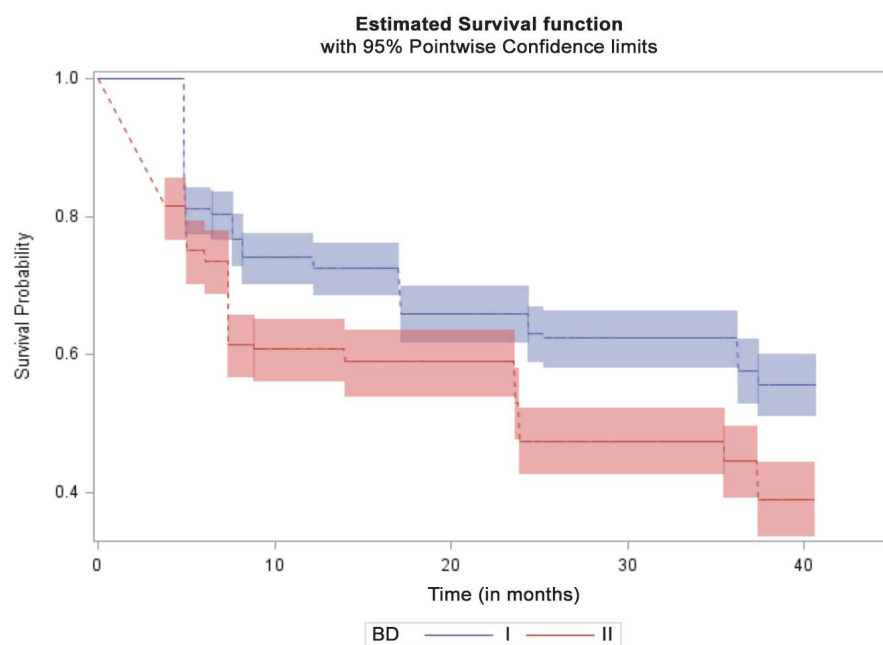


**Figure 1.1: Survival plots in patients with BD-I and with BD-II (time to first mood recurrence)**



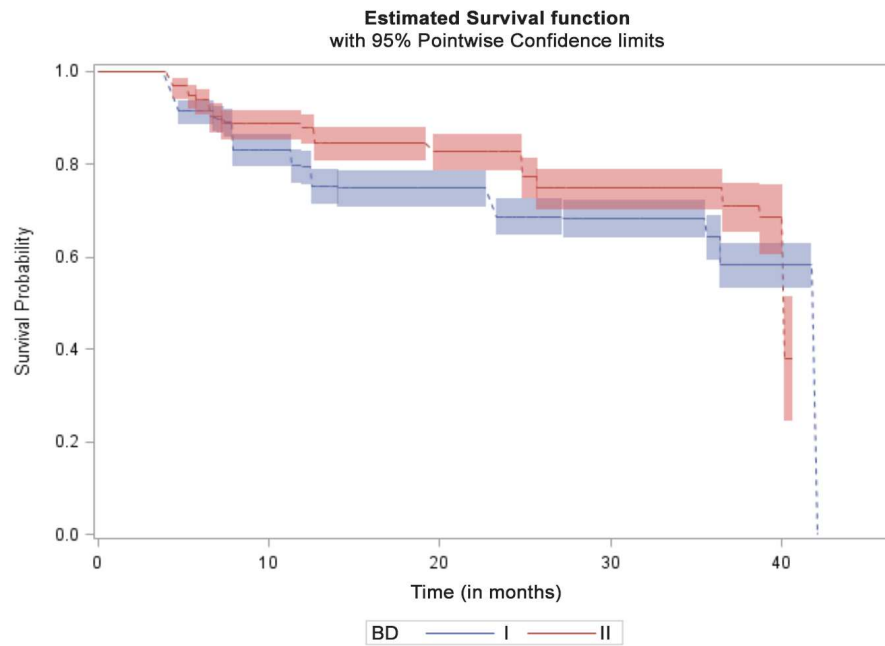
Comparison between BD-II and BD-I (reference): HR=1.2 95CI(1.0-1.4), p=0.03)

**Figure 1.2: Survival plots in patients with BD-I and with BD-II (time to first depressive recurrence)**



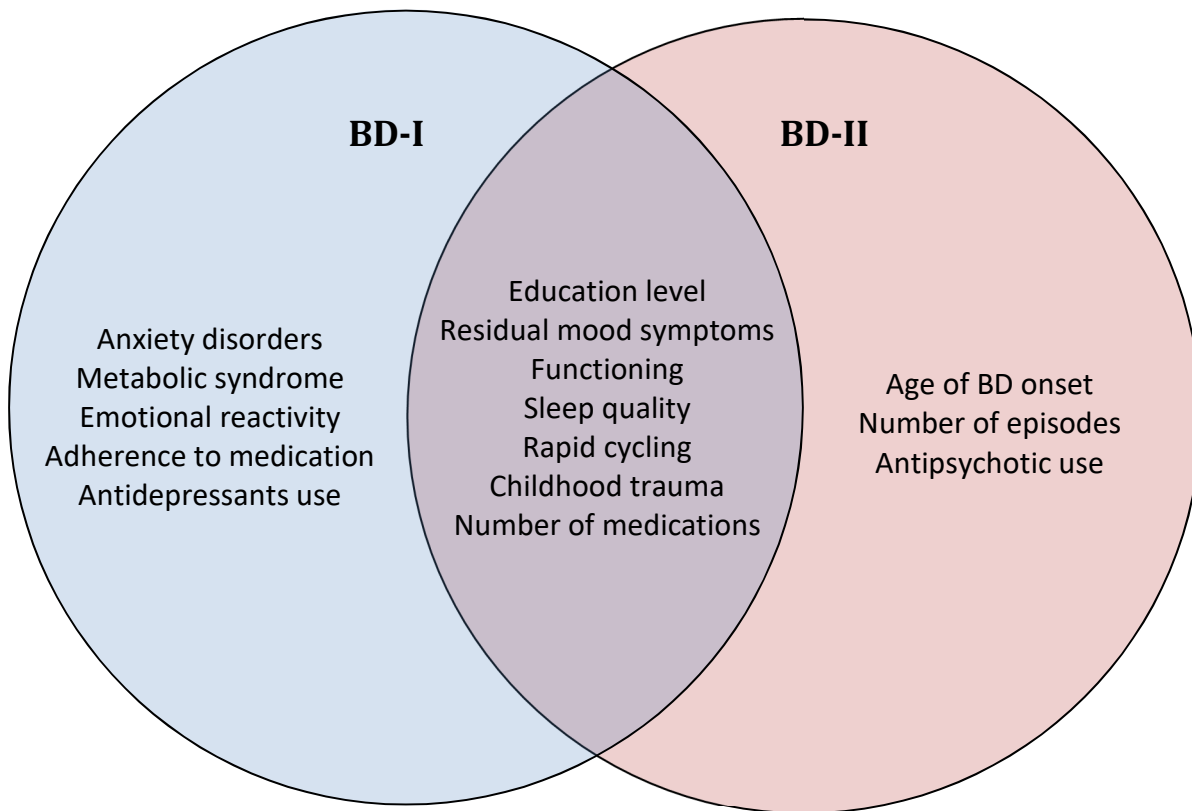
Comparison between BD-II and BD-I (reference): (HR=1.6 95CI(1.3-1.9), p<0.0001)

**Figure 1.3: Survival plots in patients with BD-I and with BD-II (time to first (hypo)manic recurrence)**



Comparison between BD-I and BD-II (reference): (HR=2.0 95CI(1.3-3.4), p=0.0003)

**Figure 2: Baseline variables associated with time to first mood recurrence in patients with Bipolar Disorder (BD) type I and BD type II (univariate analyses)**



**Table 1: Multivariable analyses of factors associated with the time to a first mood recurrence in individuals with BD**

|   | In all individuals<br>(n=1135) |             |      |      | Individuals without rapid cycling<br>(n=988) |             |      | Individuals without rapid cycling<br>AND with MADRS and YMRS<br><8 (n=494) |             |      |
|---|--------------------------------|-------------|------|------|--|-------------|------|--|-------------|------|
|   | HR (95% CI)                    | P<br>value* | VIF  | AUC  | HR (95% CI)                                  | P<br>value* | AUC  | HR (95% CI)  | P<br>value* | AUC  |
| Gender (female) **                              | 0.73 (0.52-1.06)               | 0.072       | 1.21 | 0.71 | 0.91 (0.64-1.30)                             | 0.613       | 0.66 | 0.71 (0.42-1.20)   | 0.202       | 0.64 |
| Age **  | 0.98 (0.97-1.00)               | 0.056       | 1.25 |      | 0.99 (0.97-1.00)                             | 0.218       |      | 0.98 (0.96-1.00)   | 0.115       |      |
| High education level **                         | 0.69 (0.45-1.05)               | 0.083       | 1.11 |      | 0.75 (0.47-1.21)                             | 0.240       |      | 0.80 (0.37-1.71)   | 0.568       |      |
| Depressive symptoms                             | 1.04 (1.02-1.06)               | 0.0005      | 1.98 |      | 1.06 (1.05-1.09)                             | <0.001      |      | 1.18 (1.05-1.33)   | 0.006       |      |
| Lifetime rapid cycling                          | 2.23 (1.43-3.48)               | 0.0004      | 1.14 |      | -  | -           |      | -  | -           |      |
| Global activation                               | 1.82 (1.22-2.73)               | 0.014       | 1.34 |      | 2.12 (1.35-3.33)                             | 0.005       |      | -  | -           |      |
| Number of psychotropic medication (at baseline) | 1.16 (1.01-1.32)               | 0.031       | 1.47 |      | -  | -           |      | -  | -           |      |
|   | HR (95% CI)                    | P<br>value* | VIF  | AUC  | HR (95% CI)                                  | P<br>value* | AUC  | HR (95% CI)  | P<br>value* | AUC  |
| Gender (female) **                              | 0.94 (0.66-1.31)               | 0.667       | 1.10 | 0.67 | 1.14 (0.79-1.64)                             | 0.462       | 0.67 | 1.32 (0.68-2.55)   | 0.413       | 0.63 |
| Age **  | 1.01 (0.99-1.02)               | 0.556       | 1.55 |      | 0.99 (0.98-1.01)                             | 0.455       |      | 1.02 (0.98-1.05)   | 0.133       |      |
| High education level **                         | 0.60 (0.41-0.87)               | 0.007       | 1.05 |      | 0.60 (0.40-0.88)                             | 0.011       |      | 0.64 (0.31-1.32)   | 0.223       |      |
| Age at onset                                    | 0.98 (0.96-0.99)               | 0.033       | 1.46 |      | -  | -           |      | -  | -           |      |
| Depressive symptoms                             | -                              | -           | 1.87 |      | 1.02 (1.01-1.04)                             | 0.024       |      | -  | -           |      |
| Number of lifetime mood episodes                | 1.03 (1.01-1.05)               | 0.004       | 1.23 |      | 1.03 (1.01-1.05)                             | 0.008       |      | 1.05 (1.02-1.09)   | 0.005       |      |
| Lifetime anxiety disorders                      | -                              | -           | 1.27 |      | -  | -           |      | 2.04 (1.01-4.13)   | 0.048       |      |
| Lifetime substance misuse                       | -                              | -           | 1.27 |      | -  | -           |      | 2.28 (1.02-5.09)   | 0.045       |      |

\* Multivariable interval-censored proportional hazards models (variables with p value < 0.15 in univariable analysis were entered in the models; age, gender and educational level being forced in the models) \*\* variables that were forced into the models

- indicates no association

BD: Bipolar Disorder, HR: Hazard Risk, CI: Confidence Interval, VIF: Variable Inflation Factor, AUC: Area Under the Curve