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Bipolar subtypes and their clinical correlates in a sample of 391 bipolar individuals

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ABSTRACT

Differences between BD-I and BD-II patients with regard to specific illness characteristics are poorly understood. This study is mainly aimed to compare socio-demographic and clinical characteristics between BD-I and BD-II patients with the goal of clarifying possible predictors of clinical course. The sample of this cohort study is composed of 391 currently euthymic bipolar patients. Participants were all receiving only maintenance treatment; their psychopharmacological regimens and psychopathological conditions were stable at assessment. After univariate analyses, BD-II patients were more likely to be female, had more frequently a recent depressive episode and substance abuse/dependence relative to BD-I subjects. BD-II patients were also less likely to have a positive history of psychiatric conditions in family, psychotic symptoms at first episode, and first depressive illness episode. Moreover, BD-II were older at their illness onset and first treatment than BD-I patients. Furthermore, BD-I were more likely to have higher depressive, manic, anxiety, and symptoms severity than BD-II patients. After logistic regression analyses, being female (OR = 0.289), having psychiatric conditions in family (OR = 0.273), and higher severity of illness at CGI (OR = 0.604) were all significantly associated with BD-II. Additional studies are required to replicate these results, and facilitate the prediction of BD outcomes according to the specified profile.

1. Introduction

Bipolar disorder (BD) is ranked as the 12th most common cause of disability worldwide and may be considered a chronic condition characterized by recurrent manic/hypomanic and depressive episodes which are associated with relevant psychosocial impairment (Vieta et al., 2018). Depending on the predominant polarity of the illness, depressive symptoms are usually prevalent throughout the longitudinal course of BD and commonly account for most of patients' lifetime disability (Miller et al., 2014), with BD subjects experiencing a progressive illness course and significant reduction of interepisode intervals linked to impaired treatment response (Passos et al., 2016). Based on the 5th Edition of the Diagnostic and Statistical Manual (DSM-5) (American Psychiatric Association, 2013) classification system, conditions along the bipolar spectrum have been usually divided into bipolar disorder type I (BD-I), bipolar disorder type II (BD-II), cyclothymic disorder, and BD not otherwise specified (NOS) subgroups.

BD-I and BD-II, differentiated by the presence of hypomanic but not manic episodes in case of the latter, may be defined as illness subgroups characterized by variable prevalence, differential socio-demographic and clinical characteristics rather than being more and less severe variants of the same illness, as previoulsy suggested by some researchers (Altamura et al., 2018; Wittchen et al., 2003; Ketter, 2010). The severity and psychosocial impairment related to manic/hypomanic symptoms are usually considered the most relevant clinical difference between the BD-I and BD-II subtypes based on the general assumption that BD-II is commonly less severe than BD-I. However, according to Merikangas and colleagues (2011), the clinical significance of both BD-I

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and BD-II is generally comparable concerning the illness burden, role impairment and suicide risk. Not all studies confirmed the mentioned assumption in spite of these distinctions. For instance, Bora (2018) recently suggested that BD is characterized by a large variability in phenomenological and neurobiological features with only a minor part of this variability that seems to be explicably referring to existing BD subtypes.

To date, two large-scale studies (Axelson et al., 2006; Masi et al., 2007) focused on the phenomenological characteristics of BD-I, BD-II, and BD-NOS subtypes in a sample of 438 children/adolescents and 217 adolescent patients with mood and anxiety disorders, respectively. These authors found higher symptom severity, and comparatively higher psychosis rates, hospitalizations, suicide attempts, and psychotropic medication use in BD-I while more anxiety disorders and lifetime depressive episodes were found in BD-II.

Studies on adult samples tried to identify differential features among bipolar subtypes as well. For instance, Iasevoli and colleagues (2013) trying to evaluate whether specific affective temperaments might be related to a specific mood disorder diagnosis and/or different therapeutic choices in a sample of 129 inpatients, found that hyperthymic temperament was more frequent in BD-I and BD NOS patients, whereas depressive temperament in BD-II. While hyperthymic and irritable temperaments were reported more frequently in mixed episodes, patients with depressive and mixed episodes more frequently showed anxious and depressive temperaments. The authors added that affective temperaments were associated with specific symptom and psychopathology clusters. More unfavorable illness characteristics (Dell'Osso et al., 2015) including a higher number of episodes (Goodwin and Jamison, 2007), more depressive recurrences (Endicott et al., 1985; Judd et al., 2003a, 2003b), higher rates of anxiety comorbid disorders (Henry et al., 2003; Rihmer et al., 2001), positive history of affective disorders in family (Benazzi, 2004) together with more frequent suicide attempts (Baek et al., 2011; Rihmer and Pestality, 1999) and rapid cycling course (Baldessarini et al., 2000; Kupka et al., 2003) have been described in BD-II when compared to BD-I. In addition, treatment-emergent mania and duration of untreated depression represent a common phenomenon that may allow a more consistent stratification of both the psychopathological and neurobiological BD phenotypes but it is inconsistently reported across primary studies (Fornaro et al., 2018; Ghio et al., 2015).

Given this general framework and considering the contradictory nature of the available data, it has becoming increasingly evident that BD-II should not be simply considered a less severe form of BD; in addition, differences between BD-I and BD-II patients with regard to specific illness characteristics (e.g., positive history of psychiatric conditions in family, substance abuse/dependence, first depressive illness episode, psychotic symptoms at first episode, age of illness onset and first treatment) need to be more clearly elucidated. Thus, the present study is mainly aimed to compare socio-demographic and clinical features between BD-I and BD-II subtypes in a large Italian sample. Our goal is to clarify whether BD-I and BD-II may significantly differ concerning their main presentations and clinical course. In order to address this important issue, we mainly hypothesized that BD-II patients significantly differ according to specific socio-demographic and clinical characteristics (e.g., gender, psychiatric conditions in family, more recent depressive episode, and illness severity) from BD-I patients and that certain differential features may, at least partially, explain the differential burden of disease related to these specific bipolar subtypes.

2. Method

2.1. Participants

The sample of this cohort study is composed of 391 currently euthymic bipolar patients. Clinically euthymia is defined using the specific psychometric criteria of Young Mania Rating Scale (YMRS) (Young et al., 1978) score $\leq$12. Among participants, 177 had BD-I (45.3%) and 214 BD-II (54.7%) with age ranging from 18 to 85 years (mean = 51.9 $\pm$ 15.1). The present sample includes predominantly bipolar outpatients (73.6%) with a smaller portion of participants who were bipolar inpatients (26.4%). Participants were all consecutive euthymic BD patients receiving only maintenance treatment. In particular, their psychopharmacological regimens (both for outpatients and inpatients) together with psychopathological conditions were stable for at least 2 weeks. Bipolar outpatients have been followed and treated by our university outpatient service for at least 12 months while bipolar inpatients belong to our catchment area and are regularly followed by our local psychiatric services.

2.2. Procedure

All participants were admitted to the Department of Neuroscience (DINOGMI), University of Genoa, outpatient and inpatient services, between July 2014 and March 2019. The inclusion criteria were as follows: (1) diagnosis of remitted BD (type I o type II); (2) current age of > 18 years. Affective symptoms (at the time of evaluation) were rated and classified based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, 2013). Exclusion criteria were: (1) any conditions affecting the ability to fill out the assessment including disabling conditions such as delirium or Alzheimer's disease, (2) any severe neurological disorders including mental retardation, (3) denial of the informed consent, (4) history of active substances abuse/dependence during the past 6 months. Lifetime substance use which was retraced by clinicians performing the mental examination was not considered an exclusion criterion. The history of active substances abuse/dependence during the past 6 months has been carefully evaluated through clinical interview and not using objective testing. Mental retardation has been assessed initially with a comprehensive physical examination and a complete medical, family, social, and educational history which is carried out from existing medical and school records as well as interviews with parents. If mental retardation is suspected, the Wechsler Adult Intelligence Scale was administered (Wechsler, (2003). Socio-demographic, medical, and psychiatric data were carefully collected using existing hospital records as well as active interviews with parents.

2.3. Data collection and measurements

Subjective histories and assessment of clinical variables were initially extracted from clinical records (FS, AA, AA), systematically collected and verified independently by senior authors (GS, MA) using the Mini International Neuropsychiatric Interview (MINI) updated to map to DSM-5 (Sheehan et al., 1998). The examination of previous medical records and direct interviews with both the patient and family members allowed the comprehensive collection of clinical information and affective episodes prior the patients' recruitment in our Institute.

Specifically, a detailed data collection was performed for the following clinical variables: (1) socio-demographic data; (2) personal information (e.g., personal autonomy, significant distressing life-events in the last 6 months, lifetime substance abuse, use of psychiatric medications and psychotherapy in the past, and adherence to treatment); (3) positive history of specific conditions in family (e.g., psychiatric disorders and suicidal behavior); (4) comorbid conditions (such as medical and psychiatric disorders); (5) illness characteristics (e.g., recent melancholic, atypical depressive features, seasonality, rapid cycling, psychotic symptoms at first episode, first polarity of illness episode, most recent mood episode, presence of residual interepisodic symptoms, duration of illness, untreated illness, and current episode, number of illness episodes, age of illness onset, first treatment, and first hospitalization); (6) suicide risk (e.g., lifetime suicide attempts, and suicidal ideation). Socio-economic level was categorized into the following three categories: below average, average, and above average; working

status and living status were categorized as follows: employed, unemployed, retired, and student status; alone, with family, with friends, and with others status, respectively.

In addition, specific rating scales/comprehensive structured interviews (Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), Clinical Global Impression (CGI) (Guy, 1976), Young Mania Rating Scale (YMRS) (Young et al., 1978), Hamilton Anxiety Rating Scale (HARS) (Maier et al., 1988), Intent Score Scale (ISS) (Pierce, 1981), and Scale for Suicidal Ideation (SSI) (Beck et al., 1988)) were administered by clinicians (FS, AA, AA), who were adequately trained to improve the interrater reliability, and used to collect clinical information.

The illness histories and clinical information were retraced using the clinical files and lifetime computerized medical records. All participants (both inpatients and outpatients) accepted voluntarily to participate in the study and provided their informed consent. The study design was approved by the local Ethical Review Board.

2.4. Statistical method

Subjects were categorized according to the diagnosis of BD-I and BD-II and divided into two groups (remitted BD-I vs. BD-II), similarly to existing published studies (Faurholt-Jepsen et al., 2019; Vaskinn et al., 2017; Dell'Osso et al., 2016). Data for categorical variables were analyzed with Student's *t*-tests and Pearson chi-square/Fisher's exact test in contingency tables (χ^2). The Kolmogorov–Smirnov test was performed to confirm whether all the investigated variables in the sample followed the normal distribution. Significance was set at $P \leq 0.05$ (two-tailed).

A binary logistic regression analysis considering specific socio-demographic characteristics (gender) as well as other variables such as psychiatric conditions in family (presence/absence), more recent depressive vs. other episodes, CGI item 1 (severity of symptoms), HARS, and MADRS total scores, age at illness onset and first treatment (clinical variables that resulted significant at the univariate analyses) was also performed to investigate the contribution of these characteristics in predicting BD-I or BD-II. We excluded multicollinearity and extreme cases, and carefully checked normality of residuals (histograms and P–P plots). All the analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows 21.0.

3. Results

3.1. Socio-demographic and clinical variables in BD-I compared to BD-II patients

Overall, 397 subjects were screened but 6 patients were excluded due to incomplete data. The final sample consisted of 391 currently euthymic patients who were consecutively recruited at the Department of Neuroscience (DINOGMI), University of Genoa. Among participants, 177 (45.7%) had BD-I and 214 (54.3%) BD-II. Specifically, 133 were males (34.4%) and 258 females (65.6%). All the recruited subjects come directly from our catchment area and were voluntary admitted to our university hospital service. In this sample, 17% had lifetime substance abuse/dependence and the most frequently reported lifetime substance abuse types were: alcohol (12.4%), cannabis/marijuana (5%), stimulants/cocaine (2.9%), heroin (1.6%), and major sedatives (1.3%)). The most relevant socio-demographic and clinical characteristics of the total sample are summarized in Table 1.

Characteristics differed regarding the most recent mood episode with BD-II patients who had more frequently a recent depressive episode (61.7% vs. 39.7%) ($\chi^2_{(3)} = 88.933$, $p \leq .001$) relative to BD-I. When compared with BD-I, BD-II were more likely to be female (72.0% vs. 58.8%) ($\chi^2_{(1)} = 7.527$, $p \leq .005$), and have substance abuse/dependence (20.1% vs. 13.2%) ($\chi^2_{(1)} = 3.187$, $p \leq .05$). BD-II patients were also less likely to have a positive history of psychiatric conditions in family (34.9% vs. 48.9%) ($\chi^2_{(1)} = 7.594$, $p \leq .005$), psychotic symptoms at first episode (12.2% vs. 27.5%) ($\chi^2_{(1)} = 4.948$, $p \leq .05$) and first depressive illness episode (63.8% vs. 49.1%) ($\chi^2_{(1)} = 5.112$, $p \leq .05$).

In addition, BD-II were older at their illness onset (36.3 ± 18.1 vs. 32.5 ± 14.7, $t_{357} = -2.199$, $p \leq .05$), and first treatment (39.9 ± 17.7 vs. 35.5 ± 13.8, $t_{354} = -2.585$, $p \leq .05$) than BD-I patients. Moreover, BD-I were more likely to have higher MADRS total score (17.6 ± 12.9 vs. 13.4 ± 13.1, $t_{232} = 2.468$, $p \leq .05$), CGI item 1 score (3.6 ± 1.5 vs. 2.9 ± 1.6, $t_{189} = 3.197$, $p \leq .005$), YMRS (9.9 ± 10.2 vs. 6.5 ± 9.1, $t_{208} = 2.574$, $p \leq .05$) and HARS total score (11.0 ± 7.7 vs. 8.4 ± 8.3, $t_{234} = 2.491$, $p \leq .05$) when compared to BD-II patients (for more details, see Table 1).

Table 2 reported the most relevant medical comorbidities in the total sample.

3.2. Multivariate regression analyses including BD type I/II as dependent variable in the total sample

All clinical factors that resulted significant at the univariate analyses were entered into a binary logistic regression analysis with illness type (BD-I/BD-II) as the dependent variable. Specific socio-demographic characteristics such as gender, psychiatric conditions in family (presence/absence) and clinical variables (e.g., more recent depressive vs. other episodes, CGI item 1 (severity of symptoms) score, HARS, YMRS, and MADRS total scores, and age at first treatment) were introduced into the regression model. The amount of variation in the first outcome variable (BD-I/BD-II) that was accounted for all predictors (R^2-value) was 33.1% ($p \leq .005$) (see Table 3).

Being female with an OR of 0.289 ($p \leq .05$), having a positive history of psychiatric conditions in family with an OR of 0.273 ($p \leq .05$), and having a higher severity of illness at CGI with an OR of 0.604 ($p \leq .05$) were all significantly associated with BD-II.

4. Discussion

In our sample of 391 euthymic affective disorder patients, we found that the majority of participants were BD-II (54.3%). This finding is in contrast with previous estimations and in line with the current increasing assumption that BD-II subtype is at least as prevalent as BD-I (Merikangas et al., 2011). However, in spite of its high and often underestimated prevalence coupled with significant morbidity (Datto et al., 2016) together with the association with sufferings and functional impairment, clinical differential characteristics of BD-II have not been explored as extensively as those of BD-I subtype. Our findings shed light on distinct socio-demographic and clinical characteristics between BD-I and BD-II with potential clinical relevance.

4.1. Socio-demographic and clinical characteristics of BD-I vs. BD-II patients

To date, despite the advances of current neurobiological knowledge into the pathophysiology of major psychiatric disorders, there is only modest evidence that clinical symptoms and illness severity related to BD-I and BD-II subtypes consistently differ (Datto et al., 2016) even considering that the major classification systems (e.g., DSM-5, ICD-10, and ICD-11) still do not differentiate between distinct illness subtypes. Although a more complex approach to bipolar disorders goes even beyond DSM-5 differentiating between clinical variants based on the clinical presentation and course, associated factors, and pharmacological characteristics (Stahl, 2013), BD has been typically reported for decades as a manic-depressive illness clearly overfocusing on BD-I. However, recently BD-II has been increasingly conceptualized and observed to be associated with multiple unfavorable illness characteristics, similarly to BD-I (Dell'Osso et al., 2015).

In the present study, univariate analyses pointed towards several significant and relevant differences between BD-I and BD-II patients

Table 1
Socio-demographic and clinical variables (categorical and quantitative) in patients with bipolar disorder type I ($N = 177$) compared with those with bipolar disorder type II ($N = 214$).

Variables	BD type I ($N = 177$)		BD type II ($N = 214$)			
	N	%	*N*	%	Statistic (χ^2)	*p*
Gender (female)	104	58.8	154	72.0	$\chi^2_{(1)} = 7.527$	**.004***
Marital status						
Single	54	30.7	64	30.0	$\chi^2_{(3)} = 0.083$	.994
Married	73	41.5	91	42.7		
Divorced	34	19.3	41	19.2		
Widowed	15	8.5	17	8.0		
Educational level						
Elementary schools	7	4.1	8	3.8	$\chi^2_{(4)} = 1.034$	.905
Junior high schools	57	33.5	67	32.4		
Secondary high schools	80	47.1	96	46.4		
Academy	26	15.3	36	17.4		
Living status						
Alone	40	23.1	49	23.6	$\chi^2_{(3)} = 1.300$	.729
With family	121	69.9	150	72.1		
With friends	6	3.5	4	1.9		
With others	6	3.5	5	2.4		
Working status						
Employed	81	45.8	92	43.8	$\chi^2_{(3)} = 3.955$	.266
Unemployed	60	33.9	58	27.6		
Retired	32	18.1	53	25.3		
Student	4	2.2	7	3.3		
Socio-economic level						
Below average	63	36.4	75	35.4	$\chi^2_{(2)} = 0.731$	.694
Average	95	54.9	123	58.0		
Above average	15	8.7	14	6.6		
Personal autonomy						
Bad	8	13.1	8	8.9	$\chi^2_{(1)} = 0.685$	.286*
Good	53	86.9	82	91.1		
Significant distressing life-events in the last 6 months	54	30.5	67	31.6	$\chi^2_{(1)} = 0.054$	.452*
Positive history of psychiatric conditions in family	85	48.9	73	34.9	$\chi^2_{(1)} = 7.594$	**.004***
Family history of suicidal behavior	7	12.5	7	8.2	$\chi^2_{(1)} = 0.687$	.291*
Comorbid psychiatric conditions	24	19.7	48	28.6	$\chi^2_{(1)} = 2.999$	.055*
Psychiatric medications in the past	158	89.3	187	87.8	$\chi^2_{(1)} = 0.205$	.386*
Lifetime substance abuse/ dependence	23	13.2	42	20.1	$\chi^2_{(1)} = 3.187$	**.048***
Psychotherapy in the past	30	17.1	47	22.2	$\chi^2_{(1)} = 1.520$	.134*
Psychopharmacological medications in the past						
None	38	22.0	49	23.8	$\chi^2_{(5)} = 2.432$	.266*
Anxiolytics	55	31.8	73	35.4		
Antidepressants	34	19.7	46	22.3		
Mood stabilizers	24	13.9	26	12.6		
Antipsychotics	22	12.1	12	5.8		
First depressive illness episode	52	49.1	81	63.8	$\chi^2_{(1)} = 5.112$	**.017***
Psychotic symptoms at first episode	14	27.5	10	12.2	$\chi^2_{(1)} = 4.948$	**.024***
Most recent mood episode						
Depressive	48	39.7	103	61.7	$\chi^2_{(3)} = 88.933$	< **.001***
Manic	23	19.0	1	0.6		
Hypomanic	6	5.0	51	30.5		
Mixed	44	36.3	12	7.2		
Recent atypical depressive characteristics§	6	9.7	11	12.5	$\chi^2_{(1)} = 0.288$	.396*
Recent melancholic characteristics§	1	1.7	4	4.3	$\chi^2_{(1)} = 0.821$	.343*
Seasonality	2	3.4	7	8.0	$\chi^2_{(1)} = 1.280$	.221*
BMI						
< 18	7	4.0	9	4.2	$\chi^2_{(3)} = 3.441$	.328*

(*continued on next page*)

Table 1 (*continued*)

Variables	BD type I (N = 177)		BD type II (N = 214)			
	N	%	*N*	%	Statistic (χ^2)	*p*
18–25	104	58.8	136	63.8		
25–30	45	25.3	54	25.4		
> 30	21	11.9	14	6.6		
Rapid cycling	4	7.5	5	5.9	$\chi^2_{(1)} = 0.148$	.478*
Residual interepisodic symptoms	99	59.6	103	52.3	$\chi^2_{(2)} = 3.383$	.184*
Lifetime suicide attempts						
None	139	78.5	161	75.9	$\chi^2_{(4)} = 3.603$	.462
0–3	32	18.1	41	19.3		
> 3	6	3.4	6	2.9		
Missing cases	0	0.0	4	1.9		
Lifetime suicidal ideation	14	14.3	18	14.5	$\chi^2_{(1)} = 0.002$	.559*
Adherence to treatment						
Bad	41	36.0	48	36.4	$\chi^2_{(1)} = 0.004$	.528*
Good	73	64.0	84	63.6		

	BD type I (N = 177)		BD type II (N = 214)			
	Mean	SD	Mean	SD	Statistic (Student's *t*-test)	*p*
Current age	50.7	13.8	52.9	15.9	$T_{388} = -1.442$	.150
Age at illness onset	32.5	14.7	36.3	18.1	$T_{357} = -2.199$	**.029**
Number of illness episodes	4.6	5.4	4.1	4.5	$T_{305} = 0.984$	.326
Age at first treatment	35.5	13.8	39.9	17.7	$T_{354} = -2.585$	**.010**
Age at first hospitalization	18.1	20.3	18.9	23.7	$T_{376} = -0.348$	.728
Duration of illness (years)	17.9	15.2	16.7	15.7	$T_{345} = -0.731$	.465
Duration of untreated illness (years)	3.0	6.9	3.4	6.0	$T_{279} = -.544$	.587
Duration of current episode (days)	199.7	550.9	138.1	165.1	$T_{292} = 1.356$	.176
Duration of substance abuse (years)	2.6	7.3	2.1	5.5	$T_{335} = 0.747$	.456
MADRS total score	17.6	12.9	13.4	13.1	$T_{232} = 2.468$	**.014**
CGI (severity of symptoms)	3.6	1.5	2.9	1.6	$T_{189} = 3.197$	**.002**
YMRS total score	9.9	10.2	6.5	9.1	$T_{208} = 2.574$	**.011**
HARS total score	11.0	7.7	8.4	8.3	$T_{234} = 2.491$	**.013**
ISS total score	6.6	4.9	6.5	5.6	$T_{27} = 0.052$	.959
SSI total score	3.4	6.1	4.1	5.8	$T_{54} = 0.914$	.700

* Fisher's exact test (significance two-tailed); percentages were calculated per column.
§ During the last symptomatic episode.

Table 2
Medical comorbidity in patients with bipolar disorder type I (N = 177) compared with those with bipolar disorder type II (N = 214).

	BD type I (N = 177)		BD type II (N = 214)			
	N	%	*N*	%	Statistic (χ^2)	*p*
Medical comorbidities	91	51.7	115	54.0	$\chi^2_{(1)} = 0.202$	.364*
Neurological comorbid disorders	6	4.1	6	3.2	$\chi^2_{(1)} = 0.217$	.428*
Cardiological comorbid disorders	12	8.2	19	10.0	$\chi^2_{(1)} = 0.313$	.359
Endocrinological comorbid disorders	11	7.5	11	5.8	$\chi^2_{(1)} = 0.411$	.336*
Inflammatory/immunological comorbid disorders	12	8.2	12	6.3	$\chi^2_{(1)} = 0.451$	.322*
Metabolic disorders	10	6.8	17	8.9	$\chi^2_{(1)} = 0.492$	.311*
Mild cognitive impairment (amnesic)	1	0.7	1	0.5	$\chi^2_{(1)} = 0.035$	.681*
Comorbid polmonary diseases	0	0.0	1	0.5	$\chi^2_{(1)} = 0.771$	.565*
Comorbid cancer	1	0.7	2	1.1	$\chi^2_{(1)} = 0.126$	.598*
Comorbid chronic renal failure	1	0.7	1	0.5	$\chi^2_{(1)} = 0.035$	.681*
Comorbid HIV	1	0.7	1	0.5	$\chi^2_{(1)} = 0.035$	.681*

* Fisher's exact test (significance two-tailed); percentages were calculated per column; HIV = human immunodeficiency virus.

including gender distribution, substance abuse/dependence, first illness polarity, and most recent illness episode with BD-II patients who were more likely to be female, suffer from substance abuse, have a first depressed illness episode, and a more frequent recent episode with depressive polarity. Conversely, BD-I patients were more likely to have psychiatric conditions in family, psychotic symptoms at first episode, earlier age at illness onset and first treatment, and higher severity of illness as evaluated using CGI item 1, higher manic symptoms based on YMRS total score, higher anxiety and depressive symptoms as assessed by MADRS and HARS, respectively.

These results seem to suggest the existence of a markedly different profile between BD-I and BD-II subjects based on specific socio-demographic and clinical features and are generally in line with the most replicated findings reporting that BD-II patients are usually more likely to be female, with less severe but more frequent and chronic depressive episodes (Goodwin and Jamison, 2007). Our findings regarding the higher frequency of the first depressive illness onset in BD-II subtype are also in line with those of Koukopoulos and colleagues (2013), who

Table 3
Multiple regression model of BD I/II adjusted for current gender in the total sample (N = 391).

Variable	*P*	Exp (*B*)	95% CI	
Gender	**.015**	0.289	0.107	0.785
Psychiatric conditions in family	**.012**	0.273	0.100	0.749
More recent depressive episode *vs.* other episodes	.833	1.114	0.408	3.044
Age at first treatment	.730	0.995	0.964	1.026
CGI item 1	**.014**	0.604	0.404	0.901
YMRS total score	.222	0.954	0.884	1.029
HARS total score	.445	0.953	0.842	1.079
MADRS total score	.967	1.002	0.925	1.084
Constant	≤**.001**	177.772		

Note. Dependent variable: BD type I/type II. All predictors were entered in one block (hierarchical method). Model summary: $R = 0.246$, $R^2 = 0.331$; significance: $P \leq .005$. Bold values denote statistical significance.

reported that bipolar patients with a depression-mania-interval (DMI) illness course were more likely to be BD-II, while patients with a mania-depression-interval (MDI) illness course were more represented in BD-I patients. Importantly, the frequency and duration of depressive episodes together with the chronicity of illness are typically greater in BD-II than BD-I (Weinstock et al., 2010); this is reflected in our finding suggesting that in case of BD-II patients, both initial and most current affective episode were more likely to be depressive. Of interest is even, in our study, the finding regarding the older age at illness onset and first treatment observed for BD-II patients. Unfortunately, based on these results it is not currently possible to determine whether this refers to a later disease manifestation, or simply reflects a delayed diagnosis due to the more frequent recognition of disorders such as unipolar depression or other psychiatric conditions.

The fact that a higher frequency of comorbid substance abuse disorder was found in BD-II patients may reflect the overlap underlying neurobiological processes in the background of depression and substance abuse, but is more likely to suggest substance abuse as a consequence of increased frequency and/or severity of depression associated with this subtype in the form of a self-medication attempt. Indeed, besides the frequent comorbidity between affective and substance use disorders (Arias et al., 2017), BD-II subtype is, in some cases, even masked by substance use disorders that usually delay its appropriate diagnosis (Masodkar et al., 2016).

Several other findings deserve further comments. We also found that BD-II patients were less likely to present psychotic symptoms at first episode, which is in line with findings that psychotic symptoms at illness onset are a more frequent clinical characteristic of BD-I subtype. In addition, our result concerning the higher frequency of psychiatric conditions in family in BD-I at the univariate analyses partially contradicts reports of other studies (Parker et al., 2018) and needs further additional investigations.

In disagreement with existing studies that documented an increased risk of medical comorbidities, such as autoimmune disorders, obesity, diabetes, and cardiovascular disease in patients with BD (SayuriYamagata et al., 2017), higher adversities, morbidity, and early mortality of both BD-I and BD-II (Post et al., 2014), and the negative long-term impact of specific physical comorbidities such as thyroid diseases, and especially hypothyroidism on BD with more manic episodes (Amann et al., 2017), we found no difference between the two subtype groups concerning medical comorbidities. Lastly, although the differentiation of BD-I from BD-II patients concerning the presence/absence of mixed symptoms is of particular interest based on the well-known debate over “mixed specifiers” for these conditions in DSM-5 (Frankland et al., 2015), we found no specific differences to this specific regard.

4.2. Predictors of BD type I/II

Although historically, as already mentioned, BD-II has been perceived as a less severe and invalidating condition compared to BD-I, in disagreement with this assumption we found, after logistic regression analysis, that BD-II patients were more likely to be female (OR = 0.289), have positive history of psychiatric conditions in family (OR = 0.273), and higher severity of illness at CGI-1 (OR = 0.604) when compared to BD-II patients. These results, at least partially, contradict the initial findings at the univariate analyses based on which BD-II patients were less likely to have psychiatric conditions in family, and lower severity of illness as evaluated using CGI-1 relative to BD-I patients.

As the functional impairment is more associated with depression in case of bipolar disorders, our results question that from the aspect of subjective well-being, suffering, quality of life and functioning, BD-II is a less severe and invalidating form of bipolar illness over the long-term period. This is of particular relevance given that diagnoses such as BD-II were not as commonly accepted prior to the publication of the Diagnostic and Statistical Manual, 4th edition (DSM-IV) in 1994 (Goodwin and Jamison, 2007). Our results strengthen the relevant impact and disability associated with BD-II although the persistent general under-recognition of this bipolar subtype and its related psychosocial impairment.

While in the clinical practice, the two subtypes have been usually distinguished according to the careful recognition of manic/hypomanic episodes for BD-I and BD-II, respectively, we propose that a specific clinical profile might immediately guide clinicians towards the diagnosis of BD-II (rather than BD-I) within the spectrum of major affective disorders. These results are of potential clinical importance as once the patient manifested the mentioned characteristics at their illness presentation, clinicians may immediately predict the likely predominant and disabling illness subtype (e.g., BD-II), according to the knowledge of the specified clinical features. This may also have important therapeutic implications given that patients with BD-II typically respond more slowly to treatments (including lithium) with a consequent greater delay in symptom improvement than BD-I patients (Datto et al., 2016).

While in some respects BD-II was considered an intermediate form between BD-I and unipolar disorders (Akiskal and Pinto, 1999; Angst and Marneros, 2001; Marneros, 2001; Ghaemi et al., 2002), there are even data supporting the notion that they are two distinct illness subgroups. Here, according to these results we support the general assumption that, conversely to BD-I patients, BD-II suffer from a specific disease subtype which is associated with a relevant disabling illness trajectory.

Finally, although BD-II patients showed a greater severity of illness according to CGI-1, they had not an earlier age of hospitalization or longer more recent illness episode, nor higher suicide rates as supported elsewhere. This may be mainly related to the mixed nature (both inpatients and outpatients) of the recruited sample. However, these data, being preliminary and mainly exploratory in nature, need to be replicated in larger samples.

4.3. Limitations and strengths

One of the most relevant strengths of this study was including the effects of a comprehensive set of potential clinical variables on the main outcome. An additional strength was the recruitment of a sample of bipolar patients who were clearly euthymic at baseline.

However, this study needs to be interpreted in the light of the following limitations/caveats. First, the present patient sample is not based on a large multicentric population of subjects with BD but simply derived by a single psychiatric sample admitted and treated in a specialized University setting. In addition, the sample size is relatively small and heterogeneous; thus, the main findings are difficult to be

generalized to other existing patient populations, as they could not represent patients with BD in general with particular regard to the explored socio-demographic and clinical features. Moreover, the cross-sectional nature of the study design does not allow the correct distinction between cause and effect and further limits the generalization of our findings. In addition, the two analyzed subgroups of subjects that were compared (BD-I and BD-II) in this study are composed by both outpatients and inpatients potentially biasing the present results. Therefore, these findings should be considered exploratory in their main nature. Moreover, although the present study tried to consider, at least partially, the most relevant socio-demographic and clinical characteristics of the recruited subjects, this might not have allowed the correct identification of the main predictors of BD-II based on the illness presentation of the analyzed BD population. Another study design aimed to investigate only the illness characteristics at first episode would permit to better address the BD-II prediction. Finally, it was not possible to investigate the potential confounding effect directly related to psychoactive medications (e.g., antidepressants, mood-stabilizers, antipsychotics, and benzodiazepines) which were taken by participants. In particular, in our sample 130 patients (33.6%) were receiving antidepressants, 214 (55.3%) benzodiazepines, 254 (65.6%) mood stabilizers, and 191 (49.4%) antipsychotics at the time of study assessment.

Despite the mentioned shortcomings, our study, considering an extended set of possible predictors related to BD-II and significantly accounting for the illness course in a representative sample of BD euthymic outpatients, extends prior knowledge providing novel information and advances in the field and facilitate the better understanding of BD-II episodes emergence as well as its clinical management.

In conclusion, given that bipolar groups are heterogeneous conditions and according to the general need for identifying valid and reliable BD subtypes according to the phenotypic BD characteristics, in this study we reported that BD-II patients were more likely to be female, have a more frequent history of psychiatric conditions in family, and higher severity of illness at CGI-1 when compared to BD-I patients. These findings shed light on the assumption that BD-II cannot be considered a less severe and disabling bipolar subtype, in disagreement to previous perspectives.

Longitudinal follow-up studies using larger samples are required to replicate these preliminary results, enhance the prediction of BD outcomes based on the socio-demographic and clinical profile, and provide the most appropriate treatments accordingly.

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CRediT authorship contribution statement

Gianluca Serafini: Writing - original draft, Writing - review & editing. **Xenia Gonda:** Investigation, Formal analysis, Writing - review & editing. **Andrea Aguglia:** Writing - original draft, Writing - review & editing. **Andrea Amerio:** Writing - original draft, Writing - review & editing. **Francesca Santi:** Writing - original draft, Writing - review & editing. **Maurizio Pompili:** Supervision, Investigation, Writing - review & editing. **Mario Amore:** Writing - review & editing.

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