Annals of General Psychiatry

RESEARCH

Open Access

Exploring the predictive role of the first mood episode on the predominant polarity in bipolar disorder: insights from a path analysis

Daniele Cavaleri[1], Cristina Crocamo[1], Ilaria Riboldi[1*], Federica Boniello[1], Bianca Clerici[1], Martina Molendini[1], Giuseppe Carrà[1†] and Francesco Bartoli[1†]

Abstract

Background The predominant polarity in bipolar disorder (BD) is defined by the skewness of mood episodes towards either the manic or depressive pole. However, since the predominant polarity can only be established over the long term, it is crucial to identify predictors of illness trajectory. Among these factors, the polarity at onset has been suggested to hold important implications, even though research in this field is not entirely consistent so far. In this retrospective study, we thus explored whether the polarity of the first episode can predict the predominant polarity in BD.

Methods We included subjects with BD consecutively referred to two acute inpatient units in the Milan metropolitan area from May 2020 to January 2024. Following Barcelona criteria, a manic (mPP) and a depressive (dPP) predominant polarity were defined as having a ratio ≥ 2:1 of past manic/hypomanic or depressive episodes, respectively. The relationship between first episode polarity and either mPP or dPP was examined using multivariable logistic regression models. A path analysis was then performed to jointly test the associations between putative variables and the predominant polarity.

Results This study included 128 participants. Regression models estimated an association between a manic onset and a mPP ($\beta = 3.23$, $p < 0.001$) as well as between a depressive onset and a dPP ($\beta = 3.65$, $p < 0.001$). Participants with a mPP showed a lower age at onset ($\beta = -0.13$, $p = 0.004$), while subjects diagnosed with BD type I were less likely to show a dPP ($\beta = -2.09$, $p = 0.024$). The path analysis highlighted an association between earlier onset and the likelihood of a first episode of manic polarity (coeff. = − 1.39, $p = 0.021$). A manic onset was associated with a higher likelihood of mPP (coeff. = 3.46, $p < 0.001$) and a lower likelihood of dPP (coeff. = − 3.71, $p < 0.001$). Consistently, participants with a manic onset were more likely to experience a lower number of depressive episodes (coeff. = − 1.36, $p < 0.001$). Finally, cannabis use disorder was associated with a lower number of depressive episodes (coeff. = − 0.57, $p = 0.011$).

Conclusions These results provide important insights into the likely predictive value of first episode polarity in relation to the predominant polarity in BD. Though future studies validating these findings are needed, the polarity at onset may serve as an early marker for illness trajectory.

Keywords Bipolar disorder, Onset, First episode polarity, Predominant polarity

†Giuseppe Carrà and Francesco Bartoli Joint last authors.

*Correspondence:
Ilaria Riboldi
ilaria.riboldi@unimib.it

Background

Bipolar disorder (BD) is a severe mental disorder that affects about 1–2% of the general population [1–3]. BD is marked by acute recurrencies, in which depressive states alternate with manic or hypomanic episodes [4], and is associated with high rates of psychiatric comorbidities [5–7] and an increased burden of disease [8].

A key aspect of BD that has attracted increasing attention is the notion of *predominant polarity*, which refers to the tendency of an individual's mood episodes to be skewed towards either the manic or depressive pole [9–12]. The most common definition of predominant polarity, operationalised by Colom and colleagues [13], defines manic (mPP) and depressive predominant polarity (dPP) when manic/hypomanic or depressive episodes represent at least two thirds of lifetime mood episodes, respectively, whereas the absence of a clear preponderance is labelled as nuclear or undetermined predominant polarity (uPP).

The identification of either mPP or dPP has remarkable clinical implications, as it may provide precious insights into the course of illness and inform treatment decisions in BD [12–17]. It may also influence cognitive functions [18] and neurobiological features of BD [19, 20]. However, by definition, the predominant polarity can only be established over the long term, based on the individual mood episode pattern. Hence, there is the need to identify early clinical features that might help predict the illness trajectory in terms of its manic or depressive predominance.

Among these factors, the available literature suggests that the polarity at onset may hold important implications for the course of BD [14, 15]: a recent meta-analysis has indeed found a strong concordance between the polarity of first episode and either mPP or dPP [21], highlighting the potential predictive value of early mood episodes for long-term outcomes in BD. However, studies in this field are heterogeneous and have generated inconsistent findings [21]. In addition, it remains unclear whether other clinical characteristics related to illness trajectory might influence the relationship between the polarity of the first episode and the long-term predominant polarity. As a result, there is a critical need for research that incorporates a broader range of clinical variables to better understand the predictive value of first episode polarity in determining the predominant polarity.

To address these gaps and further explore this relationship, we conducted an observational study aimed at examining the association between the polarity of the first mood episode and the predominant polarity in a sample of individuals diagnosed with BD, taking into account several clinical variables and potential confounding factors.

Methods

This cross-sectional observational study was designed and reported following the "Strengthening the Reporting of Observational studies in Epidemiology (STROBE)" statement [22]. It was carried out in accordance with the Declaration of Helsinki [23]. The study was approved by the local Ethics Committee ("Comitato Etico Territoriale Area 3", Milan) as a part of the broader Northern Milan Area Cohort (NOMIAC) project (registration number: 672–17112020) [24, 25]. Written informed consent was collected for the processing of personal data as part of routine clinical care.

Setting and inclusion criteria

We included adults with BD consecutively admitted from May 2020 to January 2024 to the two acute inpatient units (accounting for a total of 27 beds) of the Department of Mental Health and Addictions of the local Nord Milano Health and Social Care Trust, which delivers mental health services to the 280,000 residents within a highly urbanised catchment area in the north-east part of the Metropolitan City of Milan [24–28].

Eligible diagnoses were BD type I (F31.X), BD type II (F31.81), BD and related disorders with other specification (F31.89), BD and related disorders without specification (F31.9) according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and Fifth Edition, Text Revision (DSM-5-TR) criteria [4, 29]. The diagnosis was confirmed by trained assessors (part of the 'NOMIAC Investigators' staff) using the Structured Clinical Interview for DSM-5 (SCID-5) [30].

We excluded people: (i) aged < 18 years at the time of data collection; (ii) diagnosed with cyclothymic disorder; (iii) with BD and related disorders induced by substances/medications; (iv) with BD and related disorders due to another medical condition; (v) having experienced only one mood episode, preventing the determination of the predominant polarity; (vi) lacking sufficient information regarding predominant polarity, history of mood episodes, and past hospitalizations.

For participants with multiple admissions, we used data from the last admission during the study period.

Data collection

We collected data on socio-demographic characteristics—including age, gender, education, employment, marital status, and housing—as well as on clinical features such as age at onset (defined as the age at which the subject first had a mood episode, obtained from structured interviews with them and their relatives as well as from their medical records) and duration of illness, polarity of first episode, BD subtype, number of manic/hypomanic, depressive, and total episodes, hospitalizations,

family history of mood disorders, lifetime diagnosis of alcohol use disorder (AUD) (F10.X) and/or substance use disorder (SUD) with substance specifiers (F11–F19), comorbid Cluster B personality disorders, history of suicide attempts, and psychopharmacological treatment at discharge.

Data were retrieved from clinical interviews, clinical records, and chart review from the electronic hospital data management platform. When necessary, they were supplemented with additional information from outpatient paper records.

The collected data were entered into a custom-designed database. Information was managed in compliance with privacy regulations and anonymized to minimise the potential risk of identification.

Definition of the predominant polarity

To define the predominant polarity, the Barcelona proposal formulated by Colom et al. [11] was applied. Accordingly, mPP was defined as having a ratio ≥ 2:1 of past episodes fulfilling DSM-5 criteria [4] for a manic or hypomanic episode, while dPP was defined as having a ratio ≥ 2:1 of past episodes fulfilling DSM-5 criteria [4] for a major depressive episode. If there was no clear predominance, it was defined as uPP. Such restrictive definition, splitting study participants in three groups (mPP, dPP, and uPP), is deemed more stable and conservative over time than other definitions [e.g., [31]], making subjects less likely to be switched between groups across different episodes.

Statistical analyses

Standard descriptive statistics—including count (N,n) and percentage (%) for categorical variables as well as mean with standard deviation (SD) (if the data were normally distributed) or median with interquartile range (IQR) (if the data were not normally distributed) for continuous variables—were used to summarise sample characteristics.

The normality of data distribution was assessed using the Shapiro–Wilk test.

Univariate comparisons were performed to explore correlates of mPP and dPP. For categorical variables, Chi-squared test or Fisher's exact test (according to expected frequencies) were used. For continuous variables, Student's T-test and Mann–Whitney U test were performed for normally and non-normally distributed variables, respectively.

The relationship between the polarity of the first episode and the predominant polarity was examined using multivariable logistic regression models, with mPP and dPP as the dependent variables' labels. Analyses were adjusted for age and gender as a priori variables, as well as for clinical variables associated with each predominant polarity label (p-value < 0.05 at the univariate level). The number of manic and depressive episodes as well as treatment-related variables were excluded from regression models since they may represent "endogenous variables" (i.e., variables that are inherently related to the dependent variable and/or some independent variables) that could introduce bias or somewhat distort the true relationships between predictive variables and the dependent variable (predominant polarity) in the models. Logistic regression assumptions were verified, and multicollinearity tests were performed where appropriate.

Then, a path analysis was performed to jointly test multivariate associations between putative variables and the predominant polarity. Considering this model on a theoretical basis, we hypothesized the role of an earlier onset as a precursor of a first manic episode [16, 32], while cannabis use disorder as a potential contributing factor of mood relapses [6, 33, 34]. Relevant coefficients and p-values were reported.

Data analyses were performed using Stata statistical software, release 18 (StataCorp LLC, 2023, College Station, TX, USA).

Results

Sample characteristics

Of the 412 people admitted to our two acute inpatient units for a mood episode at least once during the study period, 169 had a diagnosis of BD. For 36 of them, it was not possible to determine the predominant polarity, while an additional five had experienced only a single mood episode. Ultimately, 128 subjects with sufficient data to establish the predominant polarity were included in the analysis.

The mean age of study participants, including 66 (51.6%) males and 62 (48.4%) females, was 48.7 ± 15.9 years. The median age at onset of BD was 28 years (IQR: 15 years). The polarity of the first episode was manic in 62.6% of observations (n = 67) and depressive in the remaining (n = 40, 37.4%). Participants experienced a median of 6 mood episodes (IQR: 8) and 4 hospitalizations (IQR: 6) since their illness onset. Most participants (n = 100, 78.1%) had a diagnosis of BD type I.

A mPP could be determined in 63 (49.2%) participants and a dPP in 37 (28.9%) of them. The remaining 28 subjects (21.9%) had an uPP.

The characteristics of the study population are presented in Table 1.

Correlates of predominant polarity in bipolar disorder: univariate analyses

Univariate analyses revealed that participants with a mPP showed a younger age at onset (p = 0.004), were

Table 1 Socio-demographic and clinical characteristics of the whole sample and differences between subjects with manic and depressive predominant polarity

Variables	N	Overall sample (N = 128, 100%)	Manic predominant polarity (n = 63, 49.2%)	Undetermined predominant polarity (n = 28, 21.9%)	Depressive predominant polarity (n = 37, 28.9%)	Manic predominant polarity †	Depressive predominant polarity ‡
Age (years)	128	N = 128	n = 63	n = 28	n = 37	z = 1.67 p = 0.096	**z = –3.17 p = 0.002**
Mean ± SD		48.7 ± 15.9	46.1 ± 14.4	45.0 ± 15.5	55.8 ± 16.8		
Median (IQR)		50.5 (23.7)	48.7 (18.8)	42.9 (25.9)	54.65 (24.8)		
Males, *n (%)*	128	66/128 (51.6%)	34/63 (54.0%)	17/28 (60.7%)	15/37 (40.5%)	$\chi^2 = 0.29$ p = 0.592	$\chi^2 = 2.53$ p = 0.112
University/master's degree, *n (%)*	121	20/121 (16.5%)	12/57 (21.1%)	4/28 (14.3%)	4/36 (11.1%)	$\chi^2 = 1.60$ p = 0.206	$\chi^2 = 1.09$ p = 0.296
Unemployed, *n (%)*	127	59/127 (46.5%)	33/62 (53.2%)	12/28 (42.9%)	14/37 (37.8%)	$\chi^2 = 2.23$ p = 0.135	$\chi^2 = 1.56$ p = 0.212
Married/with partner, *n (%)*	126	42/126 (33.3%)	18/62 (29.0%)	10/28 (35.7%)	15/36 (41.7%)	$\chi^2 = 1.02$ p = 0.313	$\chi^2 = 1.58$ p = 0.209
Living alone, *n (%)*	127	41/127 (32.3%)	21/62 (33.9%)	8/28 (28.6%)	12/37 (32.4%)	$\chi^2 = 0.14$ p = 0.709	$\chi^2 = 0.0005$ p = 0.982
Age at onset (years)	117	N = 117	n = 56	n = 27	n = 34	**z = 2.89 p = 0.004**	**z = –2.44 p = 0.015**
Mean ± SD		29.6 ± 10.8	26.5 ± 8.7	30.2 ± 9.3	34.2 ± 13.4		
Median (IQR)		28 (15)	24.5 (12)	30 (12)	31.5 (19)		
Duration of illness (years)	117	N = 117	n = 56	n = 27	n = 34	z = –0.45 p = 0.655	z = –1.67 p = 0.095
Mean ± SD		10.8 ± 12.8	19.0 ± 12.5	13.8 ± 12.8	21.6 ± 12.5		
Median (IQR)		17.4 (20.0)	18.3 (20.0)	10.1 (18.5)	20.4 (19.5)		
Bipolar disorder type I, *n (%)*	128	100/128 (78.1%)	57/63 (90.5%)	25/28 (89.3%)	18/37 (48.6%)	**$\chi^2 = 11.1$ p = 0.001**	**$\chi^2 = 26.46$ p = < 0.001**
Polarity of first episode	107					**p = < 0.001 §**	**p = < 0.001 §**
Manic polarity, *n (%)*		67/107 (62.6%)	50/53 (94.3%)	15/24 (62.5%)	2/30 (6.7%)		
Depressive polarity, *n (%)*		40/107 (37.4%)	3/53 (5.7%)	9/24 (37.5%)	28/30 (93.3%)		
Total number of manic/hypomanic episodes	118	N = 118	n = 56	n = 28	n = 34	**z = –4.16 p = < 0.001**	**z = 4.52 p = < 0.001**
Mean ± SD		4.92 ± 4.91	6.20 ± 5.17	5.14 ± 5.43	2.65 ± 2.95		
Median (IQR)		3 (4)	4 (6)	3 (5)	1 (2)		
Total number of depressive episodes	118	N = 118	n = 56	n = 28	n = 34	**z = 7.78 p = < 0.001**	**z = –6.52 p = < 0.001**
Mean ± SD		4.14 ± 5.83	1.13 ± 1.55	4.96 ± 6.05	8.41 ± 7.18		
Median (IQR)		2 (5)	1 (1)	3 (4.5)	6.5 (7)		
Total mood episodes	118	N = 118	n = 56	n = 28	n = 34	**z = 2.25 p = 0.024**	**z = –2.26 p = 0.024**
Mean ± SD		9.1 ± 8.9	7.3 ± 6.4	10.1 ± 11.3	11.1 ± 9.9		
Median (IQR)		6 (8)	5 (6.5)	6.5 (9)	8.5 (8)		
Hospitalizations	118	N = 118	n = 56	n = 28	n = 34	z = –1.54 p = 0.123	z = 0.50 p = 0.619
Mean ± SD		5.86 ± 5.78	6.38 ± 6.32	5.43 ± 6.17	5.38 (4.45)		
Median (IQR)		4 (6)	4 (4.5)	3.5 (3.5)	3.5 (6)		
Family history of mood disorders, *n (%)*	128	28/128 (21.9%)	16/63 (25.4%)	2/28 (7.1%)	10/37 (27.0%)	$\chi^2 = 0.90$ p = 0.343	$\chi^2 = 0.81$ p = 0.369
Alcohol use disorder, *n (%)*	128	29/128 (22.7%)	15/63 (23.8%)	7/28 (25.0%)	7/37 (18.9%)	$\chi^2 = 0.09$ p = 0.759	$\chi^2 = 0.41$ p = 0.520
Cannabis use disorder, *n (%)*	127	42/128 (32.8%)	26/62 (41.9%)	10/28 (35.7%)	6/37 (16.2%)	**$\chi^2 = 4.30$ p = 0.038**	**$\chi^2 = 6.70$ p = 0.010**
Cocaine use disorder, *n (%)*	127	20/127 (15.7%)	11/62 (17.7%)	5/28 (17.9%)	4/37 (10.8%)	$\chi^2 = 0.36$ p = 0.547	$\chi^2 = 0.96$ p = 0.327
Other substances, *n (%)*	127	9/127 (7.1%)	7/62 (11.3%)	2/28 (7.1%)	0/37 (0%)	p = 0.091 §	p = 0.058 §
Comorbid Cluster B personality disorder, *n (%)*	128	25/128 (19.5%)	9/63 (14.3%)	7/28 (25.0%)	9/37 (24.3%)	$\chi^2 = 2.17$ p = 0.141	$\chi^2 = 0.76$ p = 0.383

Table 1 (continued)

Variables	N	Overall sample (N = 128, 100%)	Manic predominant polarity (n = 63, 49.2%)	Undetermined predominant polarity (n = 28, 21.9%)	Depressive predominant polarity (n = 37, 28.9%)	Manic predominant polarity †	Depressive predominant polarity ‡
History of suicide attempts, *n (%)*	128	28/128 (21.9%)	9/63 (14.3%)	4/28 (14.3%)	15/37 (40.5%)	**$\chi^2 = 4.18$ p = 0.041**	**$\chi^2 = 10.61$ p = 0.001**
Mood stabilizers, *n (%)*	126	91/126 (72.2%)	41/62 (66.1%)	24/27 (88.9%)	26/37 (70.3%)	$\chi^2 = 2.26$ p = 0.133	$\chi^2 = 0.10$ p = 0.752
Lithium, *n (%)*	126	57/126 (45.2%)	25/62 (40.3%)	19/27 (70.4%)	13/37 (35.1%)	$\chi^2 = 1.19$ p = 0.275	$\chi^2 = 2.16$ p = 0.142
Anticonvulsants, *n (%)*	126	45/126 (35.7%)	21/62 (33.9%)	9/27 (33.3%)	15/37 (40.5%)	$\chi^2 = 0.18$ p = 0.671	$\chi^2 = 0.53$ p = 0.466
Antipsychotics, *n (%)*	126	105/126 (83.3%)	53/62 (85.5%)	22/27 (81.5%)	30/37 (81.1%)	$\chi^2 = 0.41$ p = 0.524	$\chi^2 = 0.19$ p = 0.662
Second-generation antipsychotics, *n (%)*	125	95/125 (76.0%)	48/62 (77.4%)	18/27 (66.7%)	29/36 (80.6%)	$\chi^2 = 0.14$ p = 0.712	$\chi^2 = 0.58$ p = 0.448
First-generation antipsychotics, *n (%)*	126	28/126 (22.2%)	19/62 (30.6%)	6/27 (22.2%)	3/37 (8.1%)	**$\chi^2 = 5.01$ p = 0.025**	**p = 0.017** §
Antidepressants, *n (%)*	126	28/126 (22.2%)	2/62 (3.2%)	4/27 (14.8%)	22/37 (59.5%)	**$\chi^2 = 25.48$ p = < 0.001**	**$\chi^2 = 42.02$ p = < 0.001**
Benzodiazepines, *n (%)*	126	105/126 (83.3%)	51/62 (82.3%)	23/27 (85.2%)	31/37 (83.8%)	$\chi^2 = 0.10$ p = 0.750	$\chi^2 = 0.008$ p = 0.930

† vs. Undetermined + Depressive predominant polarity

‡ vs. Undetermined + Manic predominant polarity

§ Fisher's exact test's p-value

z values were obtained from Mann–Whitney U tests. χ^2 values were obtained from Chi-squared tests

IQR, interquartile range; N/n, number of subjects with data available for each variable; SD, standard deviation

more likely to have experienced a first episode of manic polarity ($p < 0.001$), were more frequently diagnosed with BD type I ($p = 0.001$), had fewer total mood episodes along their illness ($p = 0.024$), were more frequently diagnosed with lifetime cannabis use disorder ($p = 0.038$), and were less likely to have attempted suicide during their life ($p = 0.041$). As regards pharmacotherapy, they were more likely to be prescribed with first-generation antipsychotics ($p = 0.025$) and less with antidepressants ($p < 0.001$).

On the other hand, participants with a dPP were older at admission ($p = 0.002$), had an older age at onset ($p = 0.015$), were more likely to have experienced a first episode of depressive polarity ($p < 0.001$), were less frequently diagnosed with BD type I ($p < 0.001$), had a higher number of total mood episodes ($p = 0.024$), were less frequently diagnosed with lifetime cannabis use disorder ($p = 0.010$), and were more likely to have attempted suicide during their life ($p = 0.001$). Concerning psychopharmacological treatment, they were less likely to be prescribed with first-generation antipsychotics ($p = 0.017$) and more with antidepressants ($p < 0.001$).

The characteristics of each subgroup according to its predominant polarity and the results of univariate comparisons are reported in Table 1.

Correlates of predominant polarity in bipolar disorder: multivariable logistic regression models

An association between a first episode of manic polarity and a mPP emerged after controlling for age and gender (regression coefficient $\beta = 3.59$, 95% CI 2.27 to 4.93, $p < 0.001$) and for all variables associated with a mPP at the univariate level ($\beta = 3.23$, 95% CI 1.57 to 4.89, $p < 0.001$). In addition, people with mPP showed a lower age at onset as compared to subjects with either a dPP or uPP ($\beta = -0.13$, 95% CI −0.21 to −0.04, $p = 0.004$). No association between cannabis use disorder and mPP was found ($\beta = 1.46$, 95% CI −0.02 to 2.95, $p = 0.53$). The results are reported in Table 2.

Similarly, a relationship between a first episode of depressive polarity and a dPP was observed. The association was confirmed after adjusting for age and gender ($\beta = 4.26$, 95% CI 2.65 to 5.87, $p < 0.001$) and for variables associated with a dPP according to univariate analyses ($\beta = 3.65$, 95% CI 1.77 to 5.53, $p < 0.001$). Moreover, participants diagnosed with BD type I were less likely to show a dPP ($\beta = -2.09$, 95% CI −3.90 to −0.28, $p = 0.024$).

The results are summarised in Table 3.

Table 2 Correlates of manic predominant polarity in people with bipolar disorder: multivariable logistic regression model

Variables	β [95% CI]	SE	Wald χ^2	p-value
Manic polarity of first episode (vs. depressive)	3.23 [1.57 to 4.89]	0.85	14.52	**p < 0.001**
Age at onset	−0.13 [−0.21 to −0.04]	0.04	8.23	**p = 0.004**
Bipolar disorder type I	1.63 [−0.18 to 3.45]	0.93	3.11	p = 0.078
Total mood episodes	−0.11 [−0.24 to 0.01]	0.06	3.40	p = 0.065
History of suicide attempts	−0.28 [−1.94 to 1.37]	0.85	0.11	p = 0.738
Cannabis use disorder	1.46 [−0.02 to 2.95]	0.76	3.74	p = 0.053

Manic predominant polarity vs. Undetermined + Depressive predominant polarity. The analysis is adjusted for age and gender

B, regression coefficient; 95% CI, 95% confidence interval; SE, standard error

Table 3 Correlates of depressive predominant polarity in people with bipolar disorder: multivariable logistic regression model

Variables	β [95% CI]	SE	Wald χ^2	p-value
Depressive polarity of first episode (vs. manic)	3.65 [1.77 to 5.53]	0.96	14.46	**p < 0.001**
Age at onset	0.01 [−0.07 to 0.09]	0.04	0.07	p = 0.796
Bipolar disorder type I	−2.09 [−3.90 to −0.28]	0.92	5.12	**p = 0.024**
Total mood episodes	−0.01 [−0.08 to 0.06]	0.03	0.10	p = 0.753
History of suicide attempts	0.78 [−0.91 to 2.46]	0.86	0.82	p = 0.366
Cannabis use disorder	−0.55 [−2.60 to 1.50]	1.04	0.28	p = 0.599

Depressive predominant polarity vs. Undetermined + Manic predominant polarity. The analysis is adjusted for age and gender

B, regression coefficient; 95% CI, 95% confidence interval; SE, standard error

Correlates of predominant polarity in bipolar disorder: a path analysis

Jointly testing the multivariate associations between putative variables and the predominant polarity, an association between younger age at onset and the likelihood of manic polarity of the first episode was estimated (β = −1.39, p = 0.021).

In addition, considering the number of mood episodes, a first episode of manic polarity was associated with a lower number of depressive episodes (β = −1.36, p < 0.001), while no association was found for the number of manic episodes (p = 0.084).

Moreover, a first episode of manic polarity was associated with a higher likelihood of mPP (β = 3.46, p < 0.001) regardless of the total number of manic episodes, and a lower likelihood of dPP (β = −3.71, p < 0.001) regardless of the total number of depressive episodes.

Finally, cannabis use disorder was associated with a lower number of depressive episodes (coeff. = −0.57, p = 0.011).

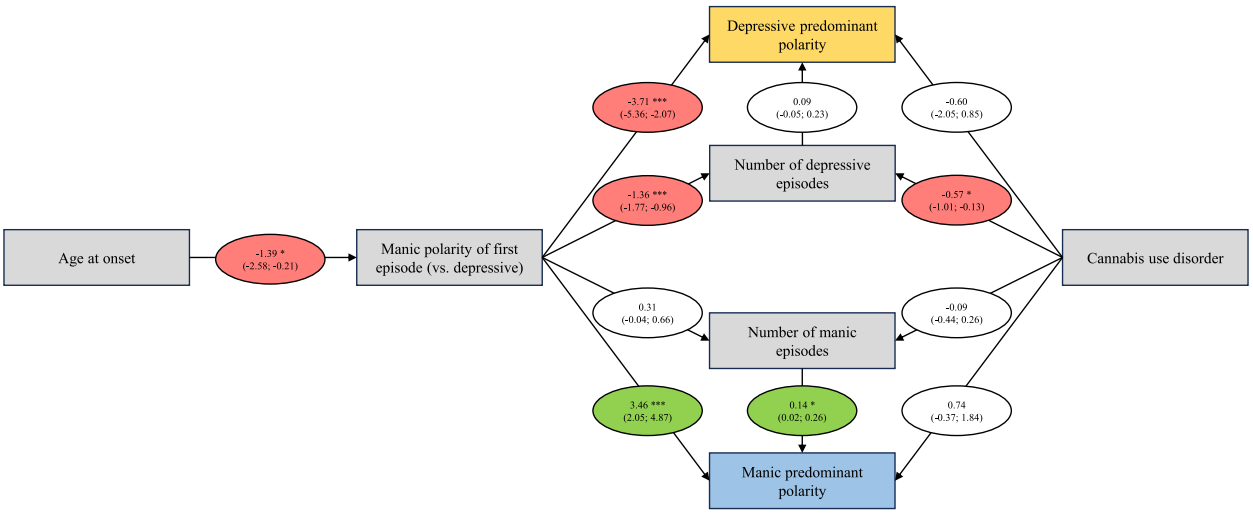
Relevant paths are displayed in Fig. 1.

Discussion

In this study, we investigated the relationship between the polarity of the first episode and the predominant polarity in 128 subjects with BD. To determine the predominant polarity, we conducted a thorough and integrated data collection and applied the Barcelona criteria as posited by Colom and colleagues [11]. This study offers additional insights and new perspectives into the mixed results generated by scientific literature so far [21]. Accounting for several variables and confounders, our regression models found that a manic and depressive polarity of the first mood episode were associated with an illness course characterised by a mPP and a dPP, respectively, even when controlling for age, gender, and other significant covariates. Moreover, benefitting from a simultaneous analysis of multiple interrelations, we were able to provide a comprehensive overview of the contributing effect of putative clinical variables on the number of mood episodes and related predominant polarity. Indeed, the path analysis showed that a manic polarity at illness onset was associated with a higher likelihood of mPP and a lower likelihood of dPP, regardless of the number of manic and depressive episodes, respectively.

The findings of our study are consistent with previous research that emphasised the importance of early illness characteristics in predicting future polarity patterns [35, 36]. In particular, these are in line with a recent meta-analysis [21] which found evidence of moderate quality indicating that the polarity of the first episode is strongly correlated with the predominant polarity shown by the individual over time.

Consistently with the available literature [17, 32], our analyses also showed the relationship between a lower age at onset and the likelihood of developing a mPP. Therefore, as previously suggested [37], our findings may imply that individuals who experience an early onset of manic polarity may be more prone to develop a mPP over the course of their illness. On the other hand, a diagnosis of BD type I was less likely to be observed in participants with a dPP. This finding is consistent with the nosographic entity and the intrinsic characteristics of BD type I, which is primarily defined by the occurrence of manic episodes, underscoring the clinical distinction between BD subtypes [38].



* p<0.05; ** p <0.01; *** p <0.001

Fig. 1 Path analysis jointly testing the multivariate associations between putative variables and the predominant polarity

Furthermore, in our sample cannabis use disorder was more prevalent in people with mPP than in those with dPP, and this was associated with a lower number of depressive episodes. This finding is counterintuitive as the literature identified cannabis use as a potential contributor to mood relapses in individuals with BD [39, 40]. It can be hypothesized that cannabis use may identify a distinctive subgroup of patients with manic episodes, but few, subthreshold, or even no depressive episodes [41]. Moreover, some subjects in our sample may benefit from self-medication with cannabis in terms of depressive symptoms, while the limited power of our analysis prevented us from demonstrating its detrimental effect on manic relapses [42].

Building upon the groundwork laid by previous reports [43], our study contributes novel insights by accounting for a wide range of socio-demographic and clinical features that provide a clearer, clinically relevant picture of how first-episode polarity and early illness characteristics—such as age at onset and BD subtype—can inform the long-term course of BD. In particular, we demonstrate that the polarity of the first episode retains its predictive value even when these variables are taken into account altogether, offering a more refined and meaningful perspective on this relationship. Indeed, establishing that the polarity of the first episode has a central role in shaping long-term clinical outcomes in BD may have significant implications for clinical practice. An early recognition of future relapse patterns may not only help predicting illness progression but also inform treatment strategies and guide personalised care approaches for people with BD [44]. In particular, the polarity at onset may be useful as a supporting element in setting up follow-up care and psychopharmacological therapy during the later maintenance phase [45]. Indeed, it is well known that, among drugs with mood stabilising properties, some are more effective in preventing manic relapses while some others have a greater effect in protecting from depressive recurrences [12, 32]. Given this difference [46–48], an early identification of the predominant polarity can help clinicians selecting the most appropriate pharmacological options [49–51].

Interestingly, our findings might also speculatively challenge the conventional view of BD as a condition characterised by extreme variability in relapse patterns and disease progression. Instead, our study hints that the polarity at onset might serve as an early marker for the stratification of people suffering from BD into distinct subtypes, each characterised by a separate trajectory. This might support the idea that the clinical course of BD may not be as inherently heterogeneous and unpredictable as traditionally perceived.

Some limitations should be acknowledged. First, our study relies on a relatively small sample of inpatients, which may not fully represent the entire population of individuals with BD. This may limit the generalizability of the results to less severe populations who do not require hospitalisation. Second, the retrospective nature of data collection prevented us from clearly classifying mixed features. Given their importance in determining the course of BD [52], future research should clarify whether they might also influence the predominant polarity. Third, the observation period of younger participants and/or those with a shorter illness history may have acted as a confounding factor regarding the number of mood episodes and hospitalizations

observed. In addition, the collection of data concerning some clinical variables may have been influenced by recall bias during clinical interviews and by the incompleteness of medical records. Moreover, it was not possible to assess whether use of alcohol and substance occurred before or after BD onset, thus preventing to explore their possible contribution to first episode characteristics.

Conclusions

The findings of our work provide significant insights into the likely predictive value of the polarity of the first episode in relation to the predominant polarity in BD, reinforcing the existing evidence while offering new perspectives. The identification of onset polarity as a predictor of the subsequent predominant polarity can have significant clinical implications, as it may influence early treatment strategies, prognosis, and long-term management of BD, potentially reducing the frequency of relapses and ultimately improving clinical outcomes. Future research should privilege longitudinal assessments to shed light on the link between the first episode and the predominant polarity in people suffering from BD.

Abbreviations

AUD	Alcohol use disorder
BD	Bipolar disorder
dPP	Depressive predominant polarity
DSM-5	Diagnostic and statistical manual of mental disorders, Fifth edition
DSM-5-TR	Diagnostic and statistical manual of mental disorders, Fifth Edition, Text Revision
mPP	Manic/hypomanic predominant polarity
NOMIAC	Northern Milan Area Cohort
SCID-5	Structured clinical interview for DSM-5
STROBE	Strengthening the reporting of observational studies in epidemiology
SUD	Substance use disorder
uPP	Undetermined predominant polarity

Acknowledgements

The Authors thank all NOMIAC Investigators for their valuable contributions to data collection.

Author contributions

D.C. contributed to the conception and design of the work, to the acquisition, analysis, and interpretation of data, and drafted the manuscript. C.C. contributed to the analysis and interpretation of data, and substantively revised the manuscript. I.R., F.Bo., B.C., and M.M. contributed to the acquisition and interpretation of data, and substantively revised the manuscript. G.C. contributed to the conception of the work, to the interpretation of data, and substantively revised the manuscript. F.Ba. contributed to the conception and design of the work, to the analysis, and interpretation of data, and substantively revised the manuscript. All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The study was carried out in accordance with the Declaration of Helsinki. It was approved by the local Ethics Committee ("Comitato Etico Territoriale Area 3", Milan) as part of the broader Northern Milan Area Cohort (NOMIAC) project (Registration Number: 672-17112020). Written informed consent was collected for the processing of personal data as part of routine clinical care.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]School of Medicine and Surgery, University of Milano-Bicocca, Via Cadore 48, 20900 Monza, Italy.

Received: 20 December 2024 Accepted: 11 March 2025
Published online: 31 March 2025

References

1. McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, et al. Bipolar disorders. Lancet. 2020;396:1841–56. https://doi.org/10.1016/s0140-6736(20)31544-0.
2. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. Nat Rev Dis Primers. 2018;4:18008. https://doi.org/10.1038/nrdp.2018.8.
3. Goes FS. Diagnosis and management of bipolar disorders. BMJ. 2023;381:e073591. https://doi.org/10.1136/bmj-2022-073591.
4. American Psychiatric Association. Diagnostic and Statistical manual of mental disorders, fifth edition, text revision. Washington, DC: American Psychiatric Association Publishing; 2022.
5. Bartoli F, Callovini T, Cavaleri D, Cioni RM, Bachi B, Calabrese A, et al. Clinical correlates of comorbid attention deficit hyperactivity disorder in adults suffering from bipolar disorder: a meta-analysis. Aust N Z J Psychiatry. 2023;57:34–48. https://doi.org/10.1177/00048674221106669.
6. Bartoli F, Crocamo C, Carrà G. Cannabis use disorder and suicide attempts in bipolar disorder: a meta-analysis. Neurosci Biobehav Rev. 2019;103:14–20. https://doi.org/10.1016/j.neubiorev.2019.05.017.
7. Léda-Rêgo G, Studart-Bottó P, Abbade P, Rabelo-Da-Ponte FD, Casqueiro JS, Sarmento S, et al. Lifetime prevalence of psychiatric comorbidities in patients with bipolar disorder: a systematic review and meta-analysis. Psychiatry Res. 2024;337: 115953. https://doi.org/10.1016/j.psychres.2024.115953.
8. Lai J, Li S, Wei C, Chen J, Fang Y, Song P, Hu S. Mapping the global, regional and national burden of bipolar disorder from 1990 to 2019: trend analysis on the Global Burden of Disease Study 2019. Br J Psychiatry. 2024;224:36–46. https://doi.org/10.1192/bjp.2023.127.
9. Angst J. The course of affective disorders. II. Typology of bipolar manic-depressive illness. Archiv fur Psychiatrie und Nervenkrankheiten. 1978;226:65–73. https://doi.org/10.1007/bf00344125.
10. Carvalho AF, McIntyre RS, Dimelis D, Gonda X, Berk M, Nunes-Neto PR, et al. Predominant polarity as a course specifier for bipolar disorder: a systematic review. J Affect Disord. 2014;163:56–64. https://doi.org/10.1016/j.jad.2014.03.035.
11. Bartoli F, Malhi GS, Carrà G. Combining predominant polarity and affective spectrum concepts in bipolar disorder: towards a novel theoretical and clinical perspective. Int J Bipolar Disord. 2024;12:14. https://doi.org/10.1186/s40345-024-00336-9.
12. Colom F, Vieta E, Daban C, Pacchiarotti I, Sánchez-Moreno J. Clinical and therapeutic implications of predominant polarity in bipolar disorder. J Affect Disord. 2006;93:13–7. https://doi.org/10.1016/j.jad.2006.01.032.
13. Colom F, Vieta E, Suppes T. Predominant polarity in bipolar disorders: refining or redefining diagnosis? Acta Psychiatr Scand. 2015;132:324–6. https://doi.org/10.1111/acps.12503.

14. Rosa AR, Andreazza AC, Kunz M, Gomes F, Santin A, Sanchez-Moreno J, et al. Predominant polarity in bipolar disorder: diagnostic implications. J Affect Disord. 2008;107:45–51. https://doi.org/10.1016/j.jad.2007.07.021.
15. Belizario GO, Junior RGB, Salvini R, Lafer B, Dias RDS. Predominant polarity classification and associated clinical variables in bipolar disorder: a machine learning approach. J Affect Disord. 2019;245:279–82. https://doi.org/10.1016/j.jad.2018.11.051.
16. Vieta E, Berk M, Wang W, Colom F, Tohen M, Baldessarini RJ. Predominant previous polarity as an outcome predictor in a controlled treatment trial for depression in bipolar I disorder patients. J Affect Disord. 2009;119:22–7. https://doi.org/10.1016/j.jad.2009.02.028.
17. Grover S, Avasthi A, Chakravarty R, Dan A, Chakraborty K, Neogi R, et al. Predominant polarity in bipolar disorder: findings from the bipolar disorder course and outcome study from India (BiD-CoIN study). Compr Psychiatry. 2021;109: 152249. https://doi.org/10.1016/j.comppsych.2021.152249.
18. Atay E, Ermiş Ç, Gökbayrak Atay İN, Aydemir Ö, Özmen E. The role of predominant polarity on cognitive dysfunctions in patients with bipolar disorder. Int J Bipolar Disord. 2024;12:41. https://doi.org/10.1186/s40345-024-00363-6.
19. Argyropoulos GD, Christidi F, Karavasilis E, Bede P, Antoniou A, Velonakis G, et al. Predominant polarity as a neurobiological specifier in bipolar disorder: evidence from a multimodal neuroimaging study. Prog Neuropsychopharmacol Biol Psychiatry. 2023;123: 110718. https://doi.org/10.1016/j.pnpbp.2023.110718.
20. Janiri D, Simonetti A, Piras F, Ciullo V, Spalletta G, Sani G. Predominant polarity and hippocampal subfield volumes in Bipolar disorders. Bipolar Disord. 2020;22:490–7. https://doi.org/10.1111/bdi.12857.
21. Bartoli F, Bassetti C, Gazzola M, Gianfelice L, Cavaleri D, Crocamo C, et al. Prevalence and correlates of manic/hypomanic and depressive predominant polarity in bipolar disorder: systematic review and meta-analysis. Br J Psychiatry Open. 2024;10: e100. https://doi.org/10.1192/bjo.2024.51.
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (strobe) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;2008(61):344–9. https://doi.org/10.1016/j.jclinepi.2007.11.008.
23. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Med Assoc. 2013;310:2191–4. https://doi.org/10.1001/jama.2013.281053.
24. Bartoli F, Bachi B, Callovini T, Palpella D, Piacenti S, Morreale M, et al. Anxious distress in people with major depressive episodes: a cross-sectional analysis of clinical correlates. CNS Spectr. 2024;29:49–53. https://doi.org/10.1017/s1092852923002377.
25. Bartoli F, Bachi B, Calabrese A, Cioni RM, Guzzi P, Nasti C, et al. Effect of long-acting injectable antipsychotics on emergency department visits and hospital admissions in people with bipolar disorder: a retrospective mirror-image analysis from the Northern Milan Area Cohort (NOMIAC) study. J Affect Disord. 2022;318:88–93. https://doi.org/10.1016/j.jad.2022.08.096.
26. Bartoli F, Cavaleri D, Callovini T, Palpella D, Piacenti S, Crocamo C, et al. Clinical and metabolic correlates of DSM-5 mixed features in subjects with bipolar depression and mania: a cross-sectional study. J Psychosom Res. 2024;188: 111990. https://doi.org/10.1016/j.jpsychores.2024.111990.
27. Bartoli F, Calabrese A, Moretti F, Castiglioni M, Prestifilippo L, De Pietra A, et al. Exploring depression in people with schizophrenia spectrum disorders: a cross-sectional analysis of the clinical relationship with positive and negative syndrome scale dimensions. Braz J Psychiatry. 2024;46: e20233418. https://doi.org/10.47626/1516-4446-2023-3418.
28. Cavaleri D, De Pietra A, Gazzola M, Crocamo C, Bartoli F, Carrà G. Complete blood count-based inflammation indexes and symptom severity in people with schizophrenia spectrum disorders: an analysis based on structural equation modelling. Psychoneuroendocrinology. 2024;168: 107134. https://doi.org/10.1016/j.psyneuen.2024.107134.
29. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association Publishing; 2013.
30. First MB, Williams JBW, Karg RS, Spitzer RL. User's guide for the SCID-5-CV Structured clinical interview for DSM-5 disorders: clinical version. Washington, DC: American Psychiatric Association Publishing; 2016.
31. Baldessarini RJ, Undurraga J, Vázquez GH, Tondo L, Salvatore P, Ha K, et al. Predominant recurrence polarity among 928 adult international bipolar I disorder patients. Acta Psychiatr Scand. 2012;125:293–302. https://doi.org/10.1111/j.1600-0447.2011.01818.x.
32. Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. Eur Neuropsychopharmacol. 2012;22:339–46. https://doi.org/10.1016/j.euroneuro.2011.09.008.
33. Agrawal A, Nurnberger JI Jr, Lynskey MT, Bipolar Genome Study. cannabis involvement in individuals with bipolar disorder. Psychiatry Res. 2011;85(3):459–61. https://doi.org/10.1016/j.psychres.2010.07.007.
34. Zorrilla I, Aguado J, Haro JM, et al. Cannabis and bipolar disorder: does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes? Acta Psychiatr Scand. 2015;131(2):100–10. https://doi.org/10.1111/acps.12366e.
35. Forty L, Jones L, Jones I, Smith DJ, Caesar S, Fraser C, et al. Polarity at illness onset in bipolar I disorder and clinical course of illness. Bipolar Disord. 2009;11:82–8. https://doi.org/10.1111/j.1399-5618.2008.00654.x.
36. Perlis RH, Delbello MP, Miyahara S, Wisniewski SR, Sachs GS, Nierenberg AA, STEP-BD investigators. Revisiting depressive-prone bipolar disorder: polarity of initial mood episode and disease course among bipolar I systematic treatment enhancement program for bipolar disorder participants. Biol Psychiatry. 2005;2005(58):549–53. https://doi.org/10.1016/j.biopsych.2005.07.029.
37. Etain B, Lajnef M, Bellivier F, Mathieu F, Raust A, Cochet B, et al. Clinical expression of bipolar disorder type I as a function of age and polarity at onset: convergent findings in samples from France and the United States. J Clin Psychiatry. 2012;73:e561–6. https://doi.org/10.4088/jcp.10m06504.
38. Aguglia A, Giacomini G, De Michiel CF, Garbarino N, Lechiara A, Magni C, et al. Characterization of bipolar disorder I and II: clinical features, comorbidities, and pharmacological pattern. Alpha Psychiatry. 2024;25:472–9. https://doi.org/10.5152/alphapsychiatry.2024.241474.
39. Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: a systematic review and meta-analysis. J Affect Disord. 2015;171:39–47. https://doi.org/10.1016/j.jad.2014.09.016.
40. Sorkhou M, Dent EL, George TP. Cannabis use and mood disorders: a systematic review. Front Public Health. 2024;12:1346207. https://doi.org/10.3389/fpubh.2024.1346207.
41. Bartoli F, Nasti C, Palpella D, Piacenti S, Di Lella ME, Mauro S, Prestifilippo L, Crocamo C, Carrà G. Characterizing the clinical profile of mania without major depressive episodes: a systematic review and meta-analysis of factors associated with unipolar mania. Psychol Med. 2023;53(15):7277–86. https://doi.org/10.1017/S0033291723000831.
42. Kvitland LR, Melle I, Aminoff SR, Demmo C, Lagerberg TV, Andreassen OA, Ringen PA. Continued cannabis use at one year follow up is associated with elevated mood and lower global functioning in bipolar I disorder. BMC Psychiatry. 2015;15:11. https://doi.org/10.1186/s12888-015-0389-x.
43. García-Jiménez J, Gutiérrez-Rojas L, Jiménez-Fernández S, González-Domenech PJ, Carretero MD, Gurpegui M. Features associated with depressive predominant polarity and early illness onset in patients with bipolar disorder. Front Psychiatry. 2020;11: 584501. https://doi.org/10.3389/fpsyt.2020.584501.
44. Kamali M, Pegg S, Janos JA, Bobo WV, Brody B, Gao K, et al. Illness stage and predominant polarity in bipolar disorder: correlation with burden of illness and moderation of treatment outcome. J Psychiatr Res. 2021;140:205–13. https://doi.org/10.1016/j.jpsychires.2021.05.082.
45. Daban C, Colom F, Sanchez-Moreno J, García-Amador M, Vieta E. Clinical correlates of first-episode polarity in bipolar disorder. Compr Psychiatry. 2006;47:433–7. https://doi.org/10.1016/j.comppsych.2006.03.009.
46. Albert U, Manchia M, Burato S, Carpiniello B, Di Salvo G, Pinna F, et al. Predominant polarity and polarity index of maintenance treatments for bipolar disorder: a validation study in a large naturalistic sample in Italy. Medicina (Kaunas). 2021;57:598. https://doi.org/10.3390/medicina57060598.
47. Carvalho AF, Quevedo J, McIntyre RS, Soeiro-de-Souza MG, Fountoulakis KN, Berk M. Treatment implications of pre-dominant polarity and the polarity index: a comprehensive review. Int J Neuropsychopharmacol. 2015;18:079. https://doi.org/10.1093/ijnp/pyu079.
48. Popovic D, Torrent C, Goikolea JM, Cruz N, Sánchez-Moreno J, González-Pinto A, et al. Clinical implications of predominant polarity and the

polarity index in bipolar disorder: a naturalistic study. Acta Psychiatr Scand. 2014;129:366–74. https://doi.org/10.1111/acps.12179.
49. Ghosal S, Mallik N, Acharya R, Dasgupta G, Mondal DK, Pal A. Medication adherence in bipolar disorder: exploring the role of predominant polarity. Int J Psychiatry Med. 2021. https://doi.org/10.1177/00912174211030163.
50. Pallaskorpi S, Suominen K, Rosenström T, Mantere O, Arvilommi P, Valtonen H, et al. Predominant polarity in bipolar I and II disorders: a five-year follow-up study. J Affect Disord. 2019;246:806–13. https://doi.org/10.1016/j.jad.2018.12.093.
51. Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN. The international society for bipolar disorders (ISBD) task force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord. 2009;11:453–73. https://doi.org/10.1111/j.1399-5618.2009.00726.x.
52. Bartoli F, Crocamo C, Carrà G. Clinical correlates of DSM-5 mixed features in bipolar disorder: a meta-analysis. J Affect Disord. 2020;276:234–40. https://doi.org/10.1016/j.jad.2020.07.035.

Publisher's Note