



Original article

Clinical and biochemical correlates of rapid cycling in bipolar disorder: A 20-year inpatient study

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ARTICLE INFO

Keywords:

Bipolar disorder (BD)

Rapid cycling (RC)

Clinical variables

Biochemical parameters

ABSTRACT

Background and objectives: Rapid cycling (RC) is a severe course specifier of bipolar disorder (BD), associated with worse clinical outcomes and increased treatment complexity. The objective of this study is to identify differences in clinical and biochemical parameters between bipolar patients with or without rapid cycling (RC).

Methods: A total of 468 inpatients were included in the present study. Demographic, clinical and biochemical data, related to the first day of hospitalization, were obtained through a screening of the clinical charts and inpatient hospital applications. The two groups identified by the lifetime presence of RC were compared by t tests for continuous variables and χ^2 tests for qualitative ones; logistic regression models were subsequently performed.

Results: Logistic regressions showed that patients with versus without RC: were more frequently hospitalized for a depressive episode ($p < 0.01$), had more previous psychiatric hospitalizations ($p < 0.01$), presented more often multiple medical comorbidity ($p = 0.05$) and seasonality ($p = 0.02$) as well as lower Global Assessment of Functioning (GAF) scores at the time of hospitalization ($p = 0.02$).

RC patients also exhibited lower creatine phosphokinase (CPK) ($p < 0.01$) and neutrophil levels ($p < 0.01$).

Conclusions: The presence of RC is important in designing a personalized treatment of bipolar patients as it is associated with (1) clinical variables of greater severity, (2) the tendency to a depressive profile and (3) multiple medical comorbidities. Further multi-center studies are needed to confirm the results of the present study in a framework of precision psychiatry.

Introduction

Bipolar Disorder (BD) is a chronic and recurrent psychiatric condition affecting approximately 2.4 % of the adult population worldwide.¹ The onset generally occurs during adolescence or early adulthood,² but delays in diagnosis and treatment are common as a result of late involvement of mental health services.^{3,4} These delays contribute to considerable functional and cognitive impairments,^{5,6} reduced quality of life,^{7,8} and a significantly increased risk of suicide.⁹ Moreover, BD is frequently associated with a high prevalence of psychiatric and medical

comorbidities, including obesity, metabolic syndrome, and cardiovascular conditions, further complicating its management.¹⁰

Among the factors influencing the prognosis of BD, such as an early age at onset,^{11,12} long duration of illness,¹³ long duration of untreated illness (DUI)¹⁴ and lifetime history of psychotic symptoms,^{15–17} the presence of rapid cycling (RC)^{18,19} has obtained significant attention in the last years. Introduced as a course specifier of BD by Dunner and Fieve²⁰ in 1974, RC was formally defined in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) in 1994²¹ and in the International Classification of Diseases 9th Edition-Clinical

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<https://doi.org/10.1016/j.ejpsy.2026.100355>

Received 31 January 2026; Accepted 6 April 2026

Available online 30 April 2026

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Modification (ICD9-CM). It is characterized by the occurrence of at least 4 distinct mood episodes -manic, hypomanic, or depressive- within a 12-month period.²²

RC was associated with a range of demographic and clinical variables, including female gender,^{23,24} early age of onset,²⁵ long duration of illness²⁶ and of untreated illness,²⁵ comorbid hypothyroidism^{26,27} and obesity,²⁸ increased suicidal behaviour,^{29,30} alcohol and other drug misuse,^{24,25} and treatment with antidepressants (in particular tricyclic antidepressants).³¹ Indeed, the role of antidepressants in precipitating the onset of RC remains a topic of debate.^{32,33} Emerging evidence suggests a potential biological underpinning for RC-BD, with some studies indicating DNA damage, endocrine dysfunctions and mild immune activation with elevation of interleukin 6 (IL-6) and IL-8 plasma levels.^{34,35}

Patients with RC-BD often exhibit a poorer treatment response³⁶ and face challenges in achieving long-term stabilization compared to their non-rapid cycling (NRC) counterparts.³⁷ This necessitates the consideration of combination therapies involving mood stabilizers and antipsychotics³⁸ or adjunctive psychological and biological interventions to obtain recovery.³⁹

In conclusion, given the limited and sometimes conflicting literature on the predictors of RC-BD, this study aims to compare a large set of clinical features and biochemical parameters in bipolar patients with versus without RC. Identifying variables associated with RC may provide insights that facilitate earlier diagnosis and more effective treatment strategies for this subgroup of BD patients, going in the direction of precision psychiatry.⁴⁰

Methods

This retrospective cross-sectional study included 468 inpatients (154 males and 314 females) diagnosed with bipolar disorder (BD) with an age ≥ 18 years. All cases were identified from Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico electronic database and clinical charts of inpatients between 2003 and 2023. For admissions occurring after 2013, diagnoses recorded in the medical charts were made according to DSM-5 criteria (American Psychiatry Association, 2013). For admissions prior to 2013, we performed a retrospective harmonization; two senior psychiatrists independently reviewed available notes and, when present, standardized rating scales to re-classify diagnoses and define mood episodes according to DSM-5 criteria. The diagnosis of bipolar disorder (type I or II) and differentiation between RC and NRC were made by a senior psychiatrist experienced in inpatient care. RC was defined as experiencing at least four mood episodes a year,⁴¹ in accordance with DSM-5 criteria. In case of multiple hospitalizations, the last one was taken into account. In the presence of psychiatric comorbidity, BD represented the condition associated with more social dysfunction. The criteria for exclusion were the following: (1) age < 18 years; (2) current pharmacotherapy associated with mood alterations (e.g. corticosteroids)⁴²; (3) re-exacerbation of medical conditions associated with mood disturbances (e.g. Cushing's syndrome)⁴³; (4) peripartum as this period is characterized by vulnerability to mood disorders⁴⁴; (5) patients with a diagnosis of dementia or intellectual disability.

Data on clinical and biochemical parameters were gathered from patient clinical charts, the Lombardy electronic database, intranet hospital applications and, where necessary, interviews with patients and their relatives.

The collected data included:

- Clinical variables: age, gender, age at illness onset, duration of hospitalization (days), duration of untreated illness DUI (years), duration of illness DI (years), number of psychiatric hospitalizations, number of acute episodes (manic, hypomanic, depressive), mood episodes in the previous year by type, mixed features in current episode, lifetime mixed features, lifetime psychotic symptoms, type of current mood episode, lifetime seasonality, number of previous

suicide attempts, bipolar subtype, family history of psychiatric disorders, multiple family history of psychiatric disorders, lifetime substance use disorders, lifetime multiple substance use disorders, previous substance-induced episodes, current tobacco smoking, number of smoked cigarettes, comorbid personality disorder, psychiatric comorbidity, previous suicide attempts, medical comorbidity, medical poli-comorbidity, obstetrical complications, comorbid thyroid diseases, comorbid diabetes, hypercholesterolemia and obesity, current treatment with statins, current treatment with levothyroxine, type of the last mood episode, administration of polytherapy during the last mood episode, achievement of treatment response in the current episode, achievement of treatment remission in the current episode.

- Scores on rating scales administered the first day of hospitalization: Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Brief Psychiatric Rating Scale (BPRS), Hamilton Anxiety Rating Scale (HAM-A) and Global Assessment of Functioning (GAF) Scale.
- Biochemical parameters (assessed the first day of hospitalization): white blood cells ($10^9/L$), red blood cells ($10^6/mm^3$), haemoglobin (g/dL), mean corpuscular volume (MCV) (fL), platelets ($10^9/L$), mean platelet volume MPV (fL), neutrophils ($10^9/L$), lymphocyte ($10^9/L$), blood glucose (mg/dL), uraemia (mg/dL), creatininemia (mg/dL), sodium (mmol/L), potassium (mmol/L), uric acid (mg/dL), aspartate transaminase (AST) (mU/mL), alanine transaminase (ALT) (mU/mL), gamma-glutamyl-transferase (GGT) (U/L), bilirubin (mg/dL), plasmatic protein (g/dL), albumin (g/dL), lactate dehydrogenase (LDH) (mU/mL), creatine phosphokinase (CPK) (U/L), pseudocholinesterase (PCHE) (U/L), total cholesterol (mg/dL), blood iron ($\mu g/dL$), thyroid-stimulating hormone (TSH) (mU/L), C-reactive protein (PCR) (mg/L), Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), AST/ALT, sodium/potassium ratio.

The study protocol was approved by the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Ethical Committee (study identification number: 1789) in line with the principles of Helsinki Declaration. DUI was defined as the time between illness onset and the prescription of a proper treatment for BD (mood stabilizers or atypical antipsychotics).⁴ Treatment response was considered the reduction of at least 50 % of baseline rating scale scores with the exception of the GAF.⁴⁵ Remission in the current episode was defined as an endpoint HAM-D score < 8 and a YMRS score < 10 .⁴⁵

Data analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Windows (version 28.0). Descriptive analyses were performed for the total sample, and RC and NRC groups were compared using independent sample Student's *t* tests for continuous variables and Chi-Square (χ^2) tests for qualitative variables (with odds ratio-OR and 95 % confidence-CI interval calculation where appropriate). Statistical significance was set at $p \leq 0.05$. Benjamini-Hochberg procedure was applied for multiple comparisons. Statistically significant variables from these preliminary analyses were entered into two distinct binary logistic regression models (one for quantitative and one for qualitative variables), with RC status as dependent variable. Variables at high risk of collinearity were excluded despite statistical significance. Finally, significant variables from these two intermediate models were inserted in a final binary logistic regression model with the presence of RC as dependent variable. The goodness of the mentioned binary logistic regression models was verified by the Omnibus and Hosmer-Lemeshow tests.

Imputation of missing data (both series mean and linear interpolator methods) were performed for HAM-D and MADRS scores.

Results

A total of 468 individuals were recruited in the study. Among them, 64 (13.7 %) were classified as having RC-BD (RC), while 404 (86.3 %) were NRC subjects.

Information about the mail pharmacological treatment at the beginning of hospitalization was available for 231 patients: 4 were without pharmacotherapy, 54 were treated with valproic acid, 59 with lithium, 2 with risperidone, 14 with haloperidol, 3 with paliperidone, 21 with olanzapine, 21 with quetiapine, 10 with aripiprazole, 3 with lamotrigine, 1 with asenapine, 8 with Selective Serotonin Reuptake Inhibitors (SSRIs), 9 with Selective Serotonin Noradrenalin Reuptake Inhibitors (SNRIs), 4 with zuclopenthixol, 3 with gabapentin, 3 with carbamazepine, 3 with clozapine, 2 with mirtazapine, 2 with trazodone, 1 with tricyclic antidepressants, 1 with lurasidone, 1 with olanzapine pamoate, 1 with paliperidone palmitate, 1 with aripiprazole depot. No differences between groups were detected in relation to treatment at the time of hospitalization ($\chi^2 = 28.16$, $p = 0.27$), even when the single compounds are grouped in pharmacological classes ($\chi^2 = 1.62$, $p = 0.46$).

Descriptive statistics as well as the results of comparisons between groups are summarized in Table 1 (qualitative variables) and Table 2 (continuous variables).

With regard to qualitative variables, RC versus NRC subjects resulted: to be more frequently hospitalized for a current depressive episode ($\chi^2 = 58.8$, $OR = 7.44$, $p < 0.01$), to present more often lifetime mixed features ($\chi^2 = 11.59$, $OR = 3.11$, $p < 0.001$) and seasonality ($\chi^2 = 11.23$, $OR = 4.22$, $p < 0.01$), to be more frequently current tobacco smokers ($\chi^2 = 5.02$, $OR = 2.33$, $p = 0.03$), to have received more often a polytherapy during the last mood episode ($\chi^2 = 4.57$, $OR = 1.95$, $p = 0.03$), to have more frequently a history of suicide attempts ($\chi^2 = 7.56$, $OR = 2.20$, $p < 0.01$) and medical polymorbidity ($\chi^2 = 5.10$, $OR = 2.18$, $p = 0.02$), to be more often in treatment with statins ($\chi^2 = 5.97$, $OR = 3.23$, $p = 0.02$). Type of current mood episode, lifetime presence of mixed features and seasonality kept statistical significance after Benjamini-Hochberg correction ($p \leq 0.05$).

With regard to clinical continuous variables, RC versus NRC subjects resulted: to have a longer duration of hospitalization ($t = 2.06$, $p = 0.04$) and duration of illness ($t = 2.25$, $p = 0.03$); to experience more previous psychiatric hospitalizations ($t = 3.92$, $p < 0.001$), lifetime mood acute episodes ($t = 4.51$, $p < 0.01$), manic episodes ($t = 3.27$, $p = 0.002$) as well as hypomanic ($t = 2.85$, $p = 0.01$) and depressive episodes ($t = 4.00$, $p < 0.01$); to present a history of more suicide attempts ($t = 2.18$, $p = 0.03$) and to have experienced more mood episodes in the last year ($t = 5.08$, $p < 0.01$) as well as hypomanic ($t = 3.19$, $p < 0.01$) and depressive episodes ($t = 3.85$, $p < 0.01$). In addition, at the time of hospitalization RC versus NRC patients had higher MADRS scores ($t = 2.12$, $p = 0.04$: confirmed by imputation of missing data), but lower GAF ($t = 2.75$, $p = 0.01$), YMRS ($t = 6.40$, $p < 0.01$) and BPRS ($t = 2.18$, $p = 0.03$) scores. Previous psychiatric hospitalizations, lifetime mood acute episodes (as well as manic, hypomanic, depressive ones), mood episodes in the last year (as well as hypomanic and depressive ones), GAF and YMRS scores maintained statistical significance after Benjamini-Hochberg correction ($p \leq 0.05$). Finally, with regard to biochemical parameters, RC versus NRC patients had less neutrophils ($t = 3.05$, $p < 0.01$) and CPK levels ($t = 4.97$, $p < 0.01$), but higher total cholesterol levels at borderline statistical significance ($t = 1.91$, $p = 0.06$). The first two results maintained statistical significance after Benjamini-Hochberg correction ($p \leq 0.05$).

The first intermediate binary logistic regression model with continuous variables as predictors (Table 3) resulted to be reliable (Omnibus test: $\chi^2 = 28.60$, $p < 0.01$; Hosmer and Lemeshow test: $\chi^2 = 8.11$, $p = 0.42$) allowing for a correct classification of 91.5 % of cases. The model confirmed that RC patients (compared to NRC ones) had more previous hospitalizations ($p = 0.03$), but less BPRS ($p = 0.01$) and GAF scores ($p = 0.02$).

The second intermediate binary logistic regression model with qualitative variables as predictors (Table 4) resulted to be reliable (Omnibus test: $\chi^2 = 30.04$, $p < 0.01$; Hosmer and Lemeshow test: $\chi^2 = 6.71$, $p = 0.46$) allowing for a correct classification of 91.5 % of cases. The model confirmed that RC patients (compared to NRC ones) were more frequently hospitalized for a current major depressive episode ($p < 0.01$), presented more frequently lifetime seasonality ($p = 0.02$) and multiple medical comorbidity ($p = 0.05$).

The final binary logistic regression model (Table 5) was reliable (Omnibus test: $\chi^2 = 56.93$, $p < 0.01$; Hosmer and Lemeshow test: $\chi^2 = 5.33$, $p = 0.72$) allowing for a correct classification of 90.4 % of cases. RC versus NRC patients presented more previous psychiatric hospitalizations ($p < 0.01$) and were more frequently hospitalized for a current major depressive episode ($p < 0.01$).

Discussion

Summary of main findings

The present study identified several clinical characteristics that characterize RC bipolar patients. Compared with NRC patients, individuals with RC showed a greater history of depressive morbidity, more previous psychiatric hospitalizations, higher rates of suicide attempts, and a greater burden of medical multi-comorbidity. At the biological level, RC patients displayed significantly lower CPK and neutrophil levels. In addition to these core findings, we also observed a significance or a trend toward significance for other variables, such as seasonality and total cholesterol, which may suggest further clinical and metabolic vulnerability associated with RC.

Comparison with existing literature

Our results confirm previous evidence highlighting that depressive polarity represents the central driver of mood instability in RC-BD.^{22,46} The rating scale scores at the time of inpatient clinic admission confirm that depressive episodes have a great impact on RC bipolar subjects and are the main reason for hospitalization of these patients. This consideration is corroborated by the fact that, in line with our results, RC patients would experience more depressive episodes with mixed feature compared to NRC subjects.⁴⁷

The increased number of previous hospitalizations (confirmed by final logistic regression model) and the higher rate of suicidal behaviour are also consistent with studies indicating poorer prognosis and greater service utilization among RC patients.^{23,48}

The association between seasonality and RC has been less explored until now, although seasonal light variations and temperature can play a role in triggering mood episodes⁴⁹ and consequently the development of RC.⁵⁰ In agreement with our findings, previous research identified seasonal pattern as a predictor of RC.⁵¹

The existing literature agrees in indicating the difficulty in managing these patients¹⁸ who are more frequently smokers,⁵² experience longer hospitalizations and are often treated with multiple psychopharmacological therapies.⁵³ On the other hand, the therapeutic choice for RC patients is complicated by their greater tendency towards chronicity (longer duration of illness) and by the frequent co-presence of multiple medical illnesses that require specific treatments such as statins.⁵⁴

Regarding biochemical findings, reduced CPK levels and lower neutrophil counts have been less frequently reported. Preliminary studies found that CPK serum levels⁵⁵ or activity of this enzyme⁵⁶ change according to symptom severity in BD. Our results converge with studies suggesting alterations in stress-response systems, bioenergetic metabolism and low-grade immune dysregulation in RC disorder.^{35,57,58}

The last interesting result is that RC patients show higher total cholesterol plasma levels than the counterpart (at borderline statistical significance), although the former are in treatment with statins. This result is similar to that found in another study by our group on a smaller

Table 1

Qualitative clinical variables of the total sample and of the two groups divided according to the presence of rapid cycling.

Variables		Total sample N = 468	Non-Rapid Cycling N = 404 (86.3 %)	Rapid Cycling N = 64 (13.7 %)	χ^2	OR (95 % CI)	p	Adjusted FDR p
Gender	<i>Male</i>	154 (32.9 %)	128 (31.7 %)	26 (40.6 %)	2.00	0.68 (0.40–1.16)	0.16	0.32
	<i>Female</i>	314 (67.1 %)	276 (68.3 %)	38 (59.4 %)				
Type of current mood episode	<i>Manic</i>	359 (76.7 %)	334 (82.7 %)	25 (39.1 %)	58.8	7.44 (4.23–13.09)	<0.01	0.01
	<i>Depressive</i>	109 (23.3 %)	70 (17.3 %)	39 (60.9 %)				
Mixed features in current episode Missing n = 1	<i>Yes</i>	154 (33 %)	129 (32.0 %)	25 (39.1 %)	1.24	1.36 (0.79–2.35)	0.27	0.40
	<i>No</i>	313 (67 %)	274 (68.0 %)	39 (60.9 %)				
Lifetime presence of mixed features Missing n = 70	<i>Yes</i>	219 (55 %)	179 (51.7 %)	40 (76.9 %)	11.59	3.11 (1.58–6.13)	<0.01	0.01
	<i>No</i>	179 (45 %)	167 (48.3 %)	12 (23.1 %)				
Lifetime presence of psychotic symptoms Missing n = 3	<i>Yes</i>	296 (63.7 %)	256 (63.7 %)	40 (63.5 %)	<0.01	0.99 (0.57–1.72)	0.98	0.98
	<i>No</i>	169 (36.3 %)	146 (36.3 %)	23 (36.5 %)				
Type of Bipolar Disorder Missing n = 1	<i>1</i>	457 (97.9 %)	397 (98.5 %)	60 (93.8 %)	5.98	4.41 (1.21–16.09)	0.02	0.08
	<i>2</i>	10 (2.1 %)	6 (1.5 %)	4 (6.2 %)				
Lifetime presence of seasonality Missing n = 75	<i>Yes</i>	26 (6.6 %)	18 (5.1 %)	8 (18.6 %)	11.23	4.22 (1.71–10.40)	<0.01	0.04
	<i>No</i>	367 (93.4 %)	332 (94.9 %)	35 (81.4 %)				
Family history of psychiatric disorders Missing n = 85	<i>Yes</i>	189 (49.3 %)	163 (48.2 %)	26 (57.8 %)	1.45	1.47 (0.78–2.76)	0.23	0.37
	<i>No</i>	194 (50.7 %)	175 (51.8 %)	19 (42.2 %)				
Multiple family history of psychiatric disorders* Missing n = 94	<i>Yes</i>	117 (31.3 %)	98 (29.6 %)	19 (44.2 %)	3.76	1.88 (0.99–3.59)	0.05	0.13
	<i>No</i>	257 (68.7 %)	233 (70.4 %)	24 (55.8 %)				
Presence of lifetime substance use disorders Missing n = 29	<i>Yes</i>	165 (37.6 %)	139 (36.9 %)	26 (41.9 %)	0.58	1.24 (0.72–2.14)	0.45	0.53
	<i>No</i>	274 (62.4 %)	238 (63.1 %)	36 (58.1 %)				
Presence of lifetime multiple substance use disorders Missing n = 36	<i>Yes</i>	65 (15.0 %)	54 (14.5 %)	11 (18.3 %)	0.59	1.32 (0.65–2.70)	0.44	0.53
	<i>No</i>	367 (85.0 %)	318 (85.5 %)	49 (81.7 %)				
Current tobacco smoking* Missing n = 157	<i>Yes</i>	154 (49.5 %)	131 (47.3 %)	23 (67.7 %)	5.02	2.33 (1.10–4.96)	0.03	0.09
	<i>No</i>	157 (50.5 %)	146 (52.7 %)	11 (32.3 %)				
Type of the last mood episode* Missing n = 139	<i>Current first episode</i>	3 (0.9 %)	3 (1.1 %)	0 (0.0 %)	1.69	NA	0.64	0.69
	<i>Depressive</i>	140 (42.6 %)	116 (41.3 %)	24 (50.0 %)				
	<i>Manic</i>	137 (41.6 %)	119 (42.3 %)	18 (37.5 %)				
	<i>Hypomanic</i>	49 (14.9 %)	43 (15.3 %)	6 (12.5 %)				
Administration of poly-therapy during the last mood episode* Missing n = 96	<i>Yes</i>	160 (43.0 %)	133 (40.9 %)	27 (57.5 %)	4.57	1.95 (1.05–3.62)	0.03	0.09
	<i>No</i>	212 (57.0 %)	192 (59.1 %)	20 (42.5 %)				
Comorbid personality disorder Missing n = 29	<i>Yes</i>	59 (13.4 %)	48 (12.6 %)	11 (19.0 %)	1.75	1.62 (0.79–3.35)	0.19	0.33
	<i>No</i>	380 (86.6 %)	333 (87.4 %)	47 (81.0 %)				
Psychiatric comorbidity* Missing n = 292	<i>Yes</i>	75 (42.6 %)	61 (41.2 %)	14 (50.0 %)	0.74	1.43 (0.64–3.21)	0.39	0.52
	<i>No</i>	101 (57.4 %)	87 (58.8 %)	14 (50.0 %)				
Previous suicide attempts Missing n = 31	<i>Yes</i>	104 (23.8 %)	81 (21.5 %)	23 (37.7 %)	7.56	2.20 (1.24–3.91)	<0.01	0.06
	<i>No</i>							

(continued on next page)

Table 1 (continued)

Variables		Total sample N = 468	Non-Rapid Cycling N = 404 (86.3 %)	Rapid Cycling N = 64 (13.7 %)	χ^2	OR (95 % CI)	p	Adjusted FDR p
Medical comorbidity Missing n = 84	No	333 (76.2 %)	295 (78.5 %)	38 (62.3 %)	2.27	1.67 (0.85–3.28)	0.13	0.28
	Yes	168 (43.7 %)	147 (42.5 %)	21 (55.3 %)				
Medical policomorbidity Missing n = 89	No	216 (56.3 %)	199 (57.5 %)	17 (44.7 %)	5.10	2.18 (1.09–4.34)	0.02	0.08
	Yes	113 (29.8 %)	96 (28.1 %)	17 (45.9 %)				
Obstetrical complications Missing n = 29	No	266 (70.2 %)	246 (71.9 %)	20 (54.1 %)	0.65	1.91 (0.39–9.42)	0.42	0.52
	Yes	9 (2.1 %)	7 (1.8 %)	2 (3.5 %)				
Comorbidity with thyroid diseases Missing n = 17	No	430 (97.9 %)	374 (98.2 %)	56 (96.5 %)	1.23	NA	0.27	0.40
	Yes	75 (16.6 %)	68 (17.4 %)	7 (11.7 %)				
Comorbidity with diabetes Missing n = 20	No	376 (83.4 %)	323 (82.6 %)	53 (88.3 %)	1.87	1.77 (0.77–4.06)	0.17	0.32
	Yes	39 (8.7 %)	31 (8.00 %)	8 (13.3 %)				
Comorbidity with hyper-cholesterolemia Missing n = 81	No	409 (91.3 %)	357 (92.0 %)	52 (86.7 %)	0.95	1.42 (0.70–2.87)	0.33	0.46
	Yes	101 (26.1 %)	88 (25.4 %)	13 (32.5 %)				
Comorbidity with obesity* Missing n = 104	No	286 (73.9 %)	259 (74.6 %)	27 (67.5 %)	3.54	2.47 (0.94–6.51)	0.06	0.14
	Yes	29 (8.0 %)	23 (7.1 %)	6 (15.8 %)				
Achievement of treatment response in the current episode Missing n = 9	No	335 (92.0 %)	303 (92.9 %)	32 (84.2 %)	0.08	1.17 (0.40–3.44)	0.78	0.80
	Yes	426 (92.8 %)	367 (92.7 %)	59 (93.6 %)				
Achievement of treatment remission in the current episode Missing n = 9	No	33 (7.2 %)	29 (7.3 %)	4 (6.4 %)	3.72	0.59 (0.34–1.01)	0.05	0.13
	Yes	304 (66.2 %)	269 (67.9 %)	35 (55.6 %)				
Current treatment with statins Missing n = 62	No	155 (33.8 %)	127 (32.1 %)	28 (44.4 %)	5.97	3.23 (1.20–8.69)	0.02	0.08
	Yes	23 (5.7 %)	17 (4.7 %)	6 (13.6 %)				
Current treatment with levothyroxine* Missing n = 132	No	383 (94.3 %)	348 (95.3 %)	38 (86.4 %)	0.38	0.53 (0.07 – 4.12)	0.54	0.60
	Yes	31 (9.2 %)	30 (9.5 %)	1 (5.3 %)				
	No	305 (90.8 %)	287 (90.5 %)	18 (94.7 %)				

Legend: CI: confidence interval.

FDR: false discovery rate.

χ^2 : chi square.

NA: not applicable.

OR: odds ratio.

p: p value.

Frequencies with percentages are reported into brackets. In bold statistically significant p (≤ 0.05). OR refers to rapid cycling versus non-rapid cycling.

* :% missing data >20 %.

sample of bipolar outpatients⁵⁹ and deserves further investigation.

Possible biological interpretation

Our biochemical profile reflect a shared vulnerability at the interface between cellular energy metabolism and stress physiology. In this scenario, CPK levels could represent a biochemical parameter worthy of further study and a potential biomarker for RC-BD, although causal relationships cannot be inferred due to the cross-sectional design. Furthermore, lower neutrophil levels may be related to a more prominent hypothalamus-pituitary-adrenal axis dysfunction, as previously suggested for RC-BD,⁶⁰ while reduced CPK levels could indicate altered metabolic resilience during mood episodes, given the role of this enzyme

in energy homeostasis. Therefore, low CPK levels may reflect bio-energetic exhaustion in patients with RC, which would explain their greater clinical severity.

Limitations of the study

While this study provides important insights, certain limitations must be acknowledged.

First, the inclusion of records spanning 2003–2023, with diagnostic criteria evolving over time, and the necessity to apply a retrospective harmonization to ensure DSM-5 consistency, could lead to potential misclassification and challenges.

Second, given the retrospective nature of the study, some data could

Table 2

Continuous variables of the total sample and of the two groups divided according to the presence of rapid cycling.

Variables	Total sample N = 468	Non-Rapid Cycling N = 404 (86.3 %)	Rapid Cycling N = 64 (13.7 %)	t	p	Adjusted FDR p
Duration of hospitalization (days) Missing n = 1	12.98 ± 8.41	12.66 ± 8.29	14.98 ± 8.96	2.06	0.04	0.12
Age at admission (years)	48.06 ± 14.99	47.75 ± 15.22	50.06 ± 13.42	1.15	0.25	0.52
Age at illness onset (years) Missing n = 12	29.53 ± 11.58	29.67 ± 11.77	28.64 ± 10.37	0.66	0.51	0.74
Duration of Untreated Illness (years) Missing n = 59	3.14 ± 5.46	3.25 ± 5.59	2.44 ± 4.55	1.00	0.32	0.61
Duration of illness (years) Missing n = 12	18.41 ± 13.13	17.92 ± 13.36	21.42 ± 11.25	2.25	0.03	0.11
Number of previous psychiatric hospitalizations* Missing n = 95	3.85 ± 3.10	2.65 ± 3.33	5.52 ± 5.38	3.92	<0.01	0.01
Number of previous mood episodes Missing n = 44	6.25 ± 5.61	5.57 ± 4.72	10.73 ± 8.38	4.51	<0.01	0.01
Number of previous manic episodes Missing n = 43	2.57 ± 3.56	2.21 ± 2.83	4.93 ± 6.11	3.27	<0.01	0.01
Number of previous hypomanic episodes Missing n = 44	1.38 ± 1.95	1.23 ± 1.72	2.36 ± 2.89	2.85	<0.01	0.03
Number of previous depressive episodes Missing n = 45	2.28 ± 2.08	2.10 ± 1.97	3.45 ± 2.40	4.00	<0.01	0.01
Number of previous suicide attempts Missing n = 38	0.39 ± 0.88	0.34 ± 0.82	0.68 ± 1.14	2.18	0.03	0.11
Number of manic episodes in the last year Missing n = 69	1.02 ± 0.65	1.00 ± 0.58	1.17 ± 1.10	0.95	0.35	0.61
Number of hypomanic episodes in the last year Missing n = 68	0.22 ± 0.59	0.16 ± 0.46	0.71 ± 1.11	3.19	<0.01	0.02
Number of depressive episodes in the last year Missing n = 70	0.33 ± 0.67	0.27 ± 0.57	0.93 ± 1.08	3.85	<0.01	0.01
Cumulative number of mood episodes in the last year Missing n = 68	1.54 ± 1.02	1.41 ± 0.85	2.64 ± 1.54	5.08	<0.01	0.01
Number of previous substance-induced episodes Missing n = 102	0.14 ± 0.47	0.11 ± 0.33	0.42 ± 1.11	1.68	0.10	0.25
Current YMRS score Missing n = 8	20.47 ± 10.78	21.80 ± 10.06	12.05 ± 11.42	6.40	<0.01	0.01
Current HAM-D score* Missing n = 311	14.70 ± 6.58	14.84 ± 7.12	14.34 ± 5.01	0.50	0.62	0.84
Current MADRS score* Missing n = 351	22.53 ± 8.65	21.32 ± 9.03	24.85 ± 7.42	2.12	0.04	0.12
Current BPRS score Missing n = 11	40.86 ± 8.51	41.21 ± 8.44	38.72 ± 8.70	2.18	0.03	0.11
Current HAM-A score* Missing n = 368	8.92 ± 4.39	9.34 ± 4.42	8.24 ± 4.31	1.22	0.23	0.50
Current GAF score (Global Assessment of Functioning) Missing n = 91	57.06 ± 14.40	57.91 ± 14.23	52.26 ± 14.53	2.75	0.01	0.04
Cigarettes/day* Missing n = 167	8.53 ± 11.49	8.13 ± 11.38	11.94 ± 12.04	1.78	0.08	0.22
Sodium (mmol/L)* Missing n = 143	141.73 ± 2.72	141.70 ± 2.73	141.96 ± 2.64	0.54	0.59	0.83
Potassium (mmol/L)* Missing n = 146	4.29 ± 2.53	4.30 ± 2.68	4.14 ± 0.38	0.36	0.72	0.88
White Blood Cells (10⁹/L)* Missing n = 147	7.57 ± 2.74	7.59 ± 2.84	7.48 ± 2.17	0.25	0.80	0.88
Red Blood Cells (10⁶/mm³)* Missing n = 137	4.50 ± 0.55	4.51 ± 0.54	4.49 ± 0.58	0.22	0.82	0.88
Haemoglobin (g/dL)* Missing n = 136	13.32 ± 1.63	13.33 ± 1.61	13.26 ± 1.76	0.32	0.75	0.88
MCV (fL)* Missing n = 142	86.59 ± 8.94	86.66 ± 8.98	86.20 ± 8.76	0.35	0.73	0.88
Platelets (10⁹/L) Missing n = 146	246.32 ± 66.60	248.84 ± 67.09	233.21 ± 63.01	1.55	0.12	0.28
MPV (fL) Missing n = 146	11.05 ± 4.71	11.08 ± 5.11	10.89 ± 1.14	0.25	0.80	0.88
Neutrophils (10⁹/L)* Missing n = 157	3.94 ± 2.57	4.13 ± 2.61	2.96 ± 2.11	3.05	<0.01	0.01
Lymphocyte (10⁹/L)* Missing n = 156	2.16 ± 0.75	2.15 ± 0.73	2.19 ± 0.87	0.25	0.80	0.88
Blood Glucose (mg/dL)* Missing n = 157	92.18 ± 27.70	93.42 ± 28.83	85.90 ± 20.10	1.78	0.08	0.22
Uraemia (mg/dL)* Missing n = 236	29.94 ± 18.01	29.95 ± 18.07	29.76 ± 17.68	0.04	0.97	0.98
Creatininemia (mg/dL)* Missing n = 147	0.84 ± 0.40	0.84 ± 0.42	0.85 ± 0.27	0.23	0.82	0.89
Uric acid (mg/dL)* Missing n = 174	5.14 ± 1.94	5.10 ± 2.01	5.32 ± 1.54	0.72	0.47	0.74

(continued on next page)

Table 2 (continued)

Variables	Total sample N = 468	Non-Rapid Cycling N = 404 (86.3 %)	Rapid Cycling N = 64 (13.7 %)	t	p	Adjusted FDR p
AST (mU/mL)* Missing n = 301	22.87 ± 13.11	23.09 ± 13.35	18.50 ± 5.01	0.97	0.34	0.61
ALT (mU/mL)* Missing n = 237	21.42 ± 13.83	21.75 ± 14.10	17.50 ± 9.64	1.25	0.21	0.47
GGT (U/L)* Missing n = 247	22.06 ± 29.29	22.44 ± 30.24	16.82 ± 7.45	0.72	0.47	0.74
Bilirubin (mg/dL)* Missing n = 164	0.51 ± 0.35	0.52 ± 0.36	0.48 ± 0.29	0.70	0.49	0.74
Plasmatic protein (g/dL)* Missing n = 183	6.55 ± 0.55	6.55 ± 0.55	6.55 ± 0.52	0.02	0.98	0.98
Albumin (g/dL)* Missing n = 177	4.23 ± 0.43	4.24 ± 0.44	4.19 ± 0.38	0.70	0.49	0.74
LDH (mU/mL)* Missing n = 249	202.94 ± 75.35	204.44 ± 77.19	183.88 ± 43.27	1.05	0.30	0.6
CPK (U/L)* Missing n = 160	194.71 ± 282.85	212.07 ± 304.52	105.18 ± 71.52	4.97	<0.01	0.01
PCHE (U/L)* Missing n = 258	7248.92 ± 1740.68	7246.85 ± 1753.43	7274.06 ± 1630.28	0.06	0.95	0.98
Total cholesterol (mg/dL)* Missing n = 174	175.02 ± 42.05	173.04 ± 40.08	185.98 ± 50.76	1.91	0.06	0.18
Blood Iron (µg/dL)* Missing n = 276	82.61 ± 39.17	82.94 ± 38.70	78.43 ± 46.16	0.41	0.68	0.88
TSH (mU/L)* Missing n = 193	2.28 ± 2.53	2.17 ± 2.50	2.82 ± 2.62	1.55	0.12	0.28
PCR (mg/L)* Missing n = 356	0.90 ± 2.53	0.93 ± 2.71	0.69 ± 0.90	0.35	0.73	0.88
NLR* Missing n = 157	2.14 ± 1.90	2.18 ± 1.81	1.91 ± 2.33	0.93	0.35	0.61
PLR* Missing n = 156	126.29 ± 54.42	126.55 ± 51.71	125.00 ± 66.90	0.19	0.85	0.90
AST/ALT* Missing n = 303	1.30 ± 0.97	1.28 ± 0.99	1.60 ± 0.50	0.89	0.37	0.62
Sodium/Potassium Ratio* Missing n = 147	34.43 ± 3.88	34.39 ± 4.00	34.75 ± 2.78	0.53	0.60	0.83

Legend: ALT: alanine transaminase.

AST: aspartate transaminase.

BMI: Body Mass Index.

BPRS: Brief Psychiatric Rating Scale.

CPK: creatine phosphokinase.

FDR: false discovery rate.

GAF: Global Assessment of Functioning.

GGT: gamma-glutamyl-transferase.

HAM-A: Hamilton Anxiety Rating Scale.

HAM-D: Hamilton Depression Rating Scale.

HDL: high-density lipoproteins.

LDH: lactate dehydrogenase.

LDL: low-density lipoproteins.

MADRS: Montgomery and Asberg Depression Rating Scale

MCV: mean corpuscular volume.

MPV: mean platelet volume.

NLR: Neutrophil to Lymphocyte Ratio.

p: p value.

PCHE: pseudocholinesterase.

PCR: C-reactive protein.

PLR: Platelet to Lymphocyte Ratio.

t: Student's t.

TSH: thyroid-stimulating hormone.

YMRS: Young Mania Rating Scale.

In bold statistically significant p (≤0.05). Means ± standard deviations are reported.

* :% missing data >20 %.

be not always accurate, despite the use of electronic databases. Furthermore, the cross-sectional design precludes causal inferences.

Third, several clinical and biochemical variables showed missing data exceeding 20 %: some rating scales (HAM-D, MADRS, HAM-A), biochemical parameters (e.g., ALT, AST; PCR, LDH, PCHE, CPK, blood iron, sodium/potassium ration), smoking-related measures, and selected historical or clinical features (e.g., medical comorbidity, type of last episode, levothyroxine treatment). Although we decided to report them descriptively to maintain transparency and provide a complete clinical

overview, the extent of missing data limits the interpretability of these measures and reduces the robustness of conclusions related to them. Of note, imputation of missing data (both series mean and linear interpolator methods) were performed for HAM-D and MADRS scores with no changes in the results.

A further limitation involves the large number of comparisons performed and for this reason Benjamini–Hochberg procedure was applied. Future prospective studies are warranted to minimize multiplicity and employ more robust frameworks to confirm and refine the present

Table 3

Summary of the statistics of the binary regression model for continuous variables.

Variables	B	S.E.	Wald	P	EXP (B)	95 % CI for EXP (B)
Duration of hospitalization (days)	0.02	0.03	0.37	0.54	1.02	0.96 – 1.08
Current GAF score	−0.04	0.02	5.60	0.02	0.96	0.93 – 0.99
Duration of illness (years)	−0.01	0.02	0.44	0.51	0.99	0.95 – 1.03
Number of previous psychiatric hospitalizations	0.09	0.04	4.51	0.03	1.10	1.01 – 1.20
Current BPRS score	−0.08	0.03	6.18	0.01	0.93	0.87 – 0.98
Neutrophils (10 ⁹ /L)	−0.19	0.13	2.22	0.14	0.83	0.65 – 1.06
CPK (U/L)	−0.002	0.002	1.39	0.24	1.00	0.99 – 1.00

Legend: In this analysis the dependent variable was Non-Rapid Cycling versus Rapid Cycling. In bold statistically significant p.

B = regression coefficient; BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; EXP(B)=B exponential; GAF = Global Assessment of Functioning;

P = p value; S.E. = standard error of B; Wld = Wald statistics.

Table 4

Summary of the statistics of binary regression model for qualitative variables.

Variables	B	S.E.	Wald	P	EXP (B)	95 % CI for EXP(B)
Type of current mood episode (manic versus depressive)	2.50	0.82	9.32	<0.01	12.19	2.45 – 60.75
Lifetime presence of mixed features (No versus yes)	0.50	0.68	0.54	0.46	1.65	0.44 – 6.19
Lifetime presence of seasonality (No versus yes)	1.76	0.76	5.42	0.02	2.36	0.29 – 19.14
Current tobacco smoking (No versus yes)	0.65	0.66	0.98	0.32	1.92	0.53 – 6.95
Administration of polytherapy during the last mood episode (No versus yes)	1.05	0.66	2.48	0.12	2.85	0.78 – 10.44
Previous suicide attempts (No versus yes)	−0.68	0.80	0.73	0.39	0.51	0.11 – 2.42
Medical policomorbidity (No versus yes)	1.28	0.65	3.86	0.05	3.59	1.00 – 12.88
Current treatment with statins (No versus yes)	0.86	1.07	0.64	0.42	2.36	0.29 – 19.14

Legend: In this analysis the dependent variable was Non-Rapid Cycling versus Rapid Cycling. In bold statistically significant p.

B = regression coefficient; CI=confidence interval; EXP(B)=B exponential; P = p value; S.E. = standard error of B; Wald = Wald statistics.

findings.

Other considerations include the possible alteration of biochemical parameters caused by medical comorbidity or pharmacological treatments and the fact that the sample derives from a single centre and can be affected by cultural aspects and type of organization of mental health services so that it is not possible a total generalizability of our findings.

Table 5

Final binary logistic regression model.

Variables	B	S.E.	Wald	P	EXP (B)	95 % CI for OR
Type of current mood episode (manic versus depressive)	2.78	0.63	19.23	<0.01	16.08	4.65 – 55.64
Lifetime presence of seasonality (No versus yes)	1.98	0.80	6.19	0.01	7.24	1.52 – 34.44
Medical policomorbidity (No versus yes)	0.45	0.52	0.75	0.39	16.08	4.65 – 55.64
Number of previous psychiatric hospitalizations	0.20	0.05	13.04	<0.01	1.22	1.09 – 1.35
Current GAF score (Global Assessment of Functioning)	−0.004	0.02	0.03	0.86	1.00	0.96 – 1.04
Current BPRS score	−0.004	0.04	0.01	0.91	1.00	0.93 – 1.07

In this analysis the dependent variable was Non-Rapid Cycling versus Rapid Cycling. In bold statistically significant p.

B = regression coefficient; BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; EXP(B)=B exponential; GAF = Global Assessment of Functioning; P = p value; S.E. = standard error of B; Wald=Wald statistics.

Clinical implications

The presence of RC is important in designing a personalized treatment for bipolar patients as it is associated with (1) clinical variables of greater severity such as suicide vulnerability or mixed features, (2) the tendency to a depressive profile and (3) medical comorbidities such as metabolic complications as also confirmed by biochemical parameters (CPK and total cholesterol levels), although causal relationships cannot be implied.

Regarding the first point, it will be necessary to evaluate the possible use of combined pharmacological therapies⁶¹ or compounds that have greater specificity on suicidal ideation (e.g. lithium) or on mixed aspects (e.g. quetiapine).⁶² Furthermore, it would be advised to carry out psychoeducation interventions to increase insight into the disorder, adherence to treatments and reduce the risk of suicide and multiple hospitalizations.⁶³ Similarly, in light of the greater impact of depressive episodes in subjects with RC, it will be important to set up a treatment that is effective in preventing depressive episodes without the risk of a switch towards a counterpolar episode.⁶⁴ Finally, patients with RC are more subject to metabolic alterations and multiple medical comorbidities which must be carefully monitored and taken into consideration when setting up the treatment.⁶⁵

Conclusions

The presence of rapid cycling implies the presence of specific clinical and biochemical characteristics that require personalized treatment. Future studies will be needed to implement knowledge on this bipolar subtype from a precision psychiatry perspective.

Ethical considerations

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico (protocol code: 1789).

Funding

The Department of Pathophysiology and Transplantation, University of Milan, is funded by the Italian Ministry of Education and Research

(MUR): Dipartimenti di Eccellenza Program 2023 to 2027.

No funding sources were received for the present manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

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