Scientific Research Publishing

Open Journal of Psychiatry, 2025, 15(2), 73-95
https://www.scirp.org/journal/ojpsych
ISSN Online: 2161-7333
ISSN Print: 2161-7325

Developing a Screening Chart for Distinguishing Unipolar from Bipolar Depression during the Index Depressive Episode

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How to cite this paper: Simov, V. (2025) Developing a Screening Chart for Distinguishing Unipolar from Bipolar Depression during the Index Depressive Episode. *Open Journal of Psychiatry*, **15**, 73-95.
https://doi.org/10.4236/ojpsych.2025.152007

Received: January 1, 2025
Accepted: March 2, 2025
Published: March 5, 2025

Abstract

Background: The study focused on the search for differences between depression within bipolar disorder (BD) and unipolar depression (UPD), based on the cited findings in the scientific literature and the results from the studied clinical samples. The ultimate goal of the study was to develop a screening tool for bipolar depression (BPD) during the index depressive episode. **Methods:** 140 consecutively hospitalized patients, 23 men and 37 women with UPD (n = 60) and 23 men and 57 women (n = 80) with BPD diagnosed with M.I.N.I. PWC 5.0.0 Bulgarian Version (DSM–IV) and Hamilton Depression Rating Scale (HDRS-17) were examined with a specially designed screening chart for bipolar depression (SCBPD). The chart encompasses more than 69 parameters covering demographic parameters, somatic and psychiatric comorbidities, individual development, onset, course, clinical markers, cognitive deficits and disease outcome all aimed at detecting differences between UPD and BPD. **Results:** 15 significant parameters such as clinical symptoms, comorbidities (migraine and thyroid pathology), alcohol abuse, behavioural and temperamental characteristics were isolated on the basis of the applied screening chart. These grouped factors were called the abbreviated screening chart for bipolar depression (ASCBPD). The receiver-operating characteristic (ROC) curve showed that ASCBPD correctly classified 76 of 80 cases (95.00%) as BPD (sensitivity) and correctly classified 58 out of 60 cases (96.67%) as UPD (specificity). The ASCBPD has shown high reliability, validity, and accuracy in discriminating BPD from UPD during index depressive episode. **Discussion:** Clinical symptoms such as mood reactivity and affective swings, impulsivity, irritability, mood alternation, increased motor drive and logorrhoea along with comorbidities for alcohol abuse and migraine, behavioural and temperamental traits can serve reliably for differentiating BPD from UPD.

Keywords

Bipolar Disorder, Bipolar Depression, Unipolar Depression, Screening Chart, Index Depressive Episode

1. Introduction

The classification of depressive disorders has been a subject of ongoing debate and controversy within the field of psychiatry. While some researchers view depression as a single phenomenon with varying degrees of severity, others argue for the existence of distinct subtypes, such as unipolar and bipolar depression, each with its own clinical characteristics, course and prognosis. The distinction between unipolar and bipolar depression is important, as it has significant implications for treatment and prognosis as individuals with bipolar depression may require different pharmacological and psychotherapeutic interventions compared to those with UPD, and the long-term course of the illness may also differ. Misdiagnosing BPD as UPD depression has another two potentially deleterious consequences such as an increased suicidal rate and greater health care costs. Last but not least the problem of misdiagnosing these two different types of depression has an enormous impact on the individual's personal history and the coping strategies of their families.

Along with depressed mood UPD is characterized by anhedonia, significant unintentional weight loss or weight gain, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to concentrate, insomnia or hypersomnia and psychomotor agitation or retardation. The current understanding of BD is a lifelong condition with periods of partial or full recovery in between recurrent episodes of manic, hypomanic, mixed, and depressive episodes, and significant subsyndromal symptoms that are often present. This symptomatic variety leads to a reduced quality of life, functional, and cognitive impairment, and ultimately to a premature death [1] [2]. The complexity of BD is complicated by the presence of medical (e.g., hypertension, diabetes, obesity) and psychiatric comorbidities such as anxiety and personality disorders, attention-deficit/hyperactivity disorder, and alcohol and elicit substance abuse [3]. The 2013 Global Burden of Disease Study indicated that 48.8 million people worldwide suffered from BD, with the disease being more prevalent in women and patients aged 25 - 29 years [4]. In addition, among mental disorders, BD ranks fifth in terms of years of healthy life loss [5]. Patients with BD have up to 20 - 30 times greater suicide rate compared to that of general population making it one of the most lethal psychiatric diseases [6] [7].

1.1. Detecting Bipolar Disorder

Several studies have focused on factors such as gender, age of onset, duration of episodes, frequency of episodes, and severity of clinical symptomatology in order

to isolate relevant criteria differentiating between these two types of depression. Postpartum affective episodes, abuse of alcohol and drugs, increased suicidality, anxiety disorders, family history of BD, hyperthymic and dominant cyclothymic temperament, frequent job changes, and unstable family relationships are known to be significantly more common in the BPD group [8]-[12]. In addition, sudden-onset depressive episodes, psychomotor retardation, diurnal mood swings, anhedonia, suicidal ideation, psychotic symptoms, atypical depression symptoms, labile mood, irritability, increased verbal output, psychomotor restlessness or retardation, cognitive dysfunctions, and incomplete remissions are suspected markers for bipolarity [12]-[14].

The delay in correct diagnosis of BD stretches up to 10 years [12] and has been a challenge for psychiatrists having had great implications for treatment and long-term prognosis, especially given the fact that nearly 40% of patients with initial depression switch to mania/hypomania during 3 to 13-year follow-up [3] [8]. In another longitudinal study following patients for 10 years, it was reported that about 5% of patients previously diagnosed with UPD had converted to mania/hypomania states [15]. To overcomplicate the diagnosis dilemma the diagnostic criteria for major depressive disorder stipulated in DSM-V and ICD-11 do not distinguish between unipolar and bipolar depression—a fact that has heavily hindered the making of the correct diagnosis. Basically, the accurate diagnosis of BPD is complicated by three factors: a) significant overlap in symptomatology between unipolar and bipolar depression; b) failure of therapists to recognize previous hypomanic symptoms and c) failure of patients to report them [16]. On one hand, prescribing antidepressant as monotherapy for BPD increases the risk of switching into opposite affective pole and leads to mixed states or initiates rapid cycles. It can also induce poor or partial response to the treatment and build up resistance to antidepressants [1] [17]. On the other hand, UPD patients unnecessarily exposed to mood stabilizers would worsen their depressive state [17]. It is a well-known fact that at least 50% of later diagnosed bipolar patients begin with a depressive episode [18] and because of that they are diagnosed as having UPD. Due to that misdiagnosis only 20% of BD patients receive the correct diagnosis within the first year of treatment [19]. All this has an enormous impact on patients' well-being, as it has been confirmed that BD patients with at least one depressive episode in the past year were more frequently absent from work, compared to patients with only manic/hypomanic episodes during the same time period [20]. Although there are screening scales for detecting bipolarity such as Mood Disorders Questionnaire (MDQ), Bipolar Depression Rating Scale (BDRS), Hypomania Symptom Checklist (HCL-32), Bipolar Spectrum Diagnostic Scale (BSDS) etc. The number of studies that have been conducted is still insufficient, and there is a strong need to develop new screening tests.

1.2. Aim of the Study

The aim of the present study is to collect data and to develop a set of predictive

criteria for the diagnosis of BD during index depressive phase, long before the manifestation of first manic/hypomanic episode has occurred. In order to achieve this task, the author compares and evaluates a set of demographic data, as well as some family diseases, ontogenetic factors relevant to the studied samples. In addition, the clinical symptomatology in both groups was systematically explored and scrutinised with the idea of developing a screening chart that could serve to distinguish BPD from UPD during index depressive episode.

2. Material and Methods

2.1. Participants and Recruitment

The study consists of two phases of 140 consecutively hospitalized patients treated at Sofia Mental Health Centre "Prof. N. Shipkovenski": 01. 2007-06. 2008 (first phase) and 10. 2016-07. 2018 (second phase). In total 23 men and 37 women with UPD were included (n = 60) with mean age 45.4 (±11.3) and respectively 23 men and 57 women (n = 80) with BPD with mean age 42.9 (±10.8).

Inclusion criteria: men and women 18 - 65 years old diagnosed either with major depressive disorder or recurrent depressive disorder, or BD I, BD II, and cyclothymic disorder presenting a current depressive episode.

Exclusion criteria: the study did not include patients with comorbid medical illnesses or other psychiatric disorders; addiction to psychoactive substances and alcohol; mental retardation IQ < 70; epilepsy or permanent neurological deficits; cognitive impairment and borderline personality disorder. Diagnostically doubtful cases, as well as those with BD III (medication-induced hypomania resulting from administration of antidepressants) were also excluded.

The study was conducted in accordance with the Declaration of Helsinki and the rules of Good Clinical Practice (ICH-GCP), and an approved study protocol was put in place (P/22/2008 and P/57/2016). All subjects provided written informed consent after a complete description of the study procedures and participated without receiving any form of payment.

2.2. Clinical Assessments

A structured clinical interview M.I.N.I PWC 5.0.0 Bulgarian Version (DSM - IV/TR) was used for the diagnoses. The Hamilton Depression Rating Scale (HDRS 17) with a total score of 17 or higher was applied to verify the diagnoses. An investigator-designed screening chart for bipolar depression (SCBPD) was administered to each patient. Both samples were tested with the Mood Disorders Questionnaire (MDQ) [Hirschfeld *et al.*, 2000] and the Bipolar Disorder Rating Scale (BDRS) [Berk *et al.*, 2007)].

2.3. Design and Procedures

First stage: the patients were diagnosed by the authors with M.I.N.I. and Hamilton Depression Rating Scale (HDRS 17) with a total score ≥ 17, following that they were retested with the same clinical tools by another experienced clinician. All

patients in the sample were interviewed in a structured manner in order to complete the SCBPD.

Second stage: Mood Disorders Questionnaire (MDQ) is a short and easy-to-use self-report scale to screen for BD. Patients complete the self-administered questionnaire, which is translated into Bulgarian. If instructions were needed during the filling out of the questionnaire, they were provided by the researchers.

Third stage: the researcher filled in the Bipolar Disorder Rating Scale (BDRS) translated into Bulgarian language, for each patient during clinical interviewing.

Fourth stage: a statistical analysis was carried out to obtain data from the three previous phases.

Fifth stage: based on the outcome from the obtained results, a shortened version of SCBPD entitled abbreviated SCBPD (ASCBPD) has been developed.

2.4. Statistical Analyses

The data was processed with the program for statistical analysis—The IBM SPSS Statistics software 20.0. P value ($p < 0.05$) was chosen as a level of significance (α) at which the null hypothesis was rejected. The following methods were applied: Kolmogorov-Smirnov's test for samples distribution; descriptive analysis of the frequency distribution of the analysed parameters; Chui square (χ^2) test and Fisher's exact test for testing relationship between categorical variables; Student's t-test for distribution; Mann–Whitney U test for comparing two independent samples with non-normal distribution; item analysis with Cronbach's Alpha for the internal consistency of the scale; correlation analysis for reliability; Pearson's coefficient for validity of ASCBPD; Hosmer and Lemeshow's test for a logistic model; stepwise logistic regression; Receiver operating characteristic cure (ROC) to determine sensitivity and specificity of ASCBPD and the area under the curve (AUC) was also assessed by different ranges of cut off points to determine the ASCBPD's bipolar diagnosis cut off.

3. Results

3.1. Demographic Characteristics

The SCBPD consists of 69 indicators comprising a constellation of demographic characteristics parameters, somatic and psychiatric comorbidities, individual psychosocial development, onset, course, clinical symptoms, aspects of cognitive impairment, and disease remissions all aimed at picking up the specific profile of BPD. Table 1 shows the main demographic characteristics of the two studied samples.

The mean age of the sampled individuals with UPD was 45.4 (±11.3) vs 42.9 (±10.8) of those with BPD. No significant difference in the mean age was noted between the two groups of participants ($p = 0.1879$). The study results have shown that the gender ratio male vs female for UPD group was 1:1.60, whereas the same gender ratio male vs female was 1:2.47 for BPD group. The overall ratio for both diagnoses male vs female was 1:2.04.

Table 1. Demographic characteristics.

PARAMETER		Diagnosis		Total (N = 140)	X^2	df	p
		UPD (N = 60)	BPD (N = 80)				
Sex	M	23 (38%)	23 (28.8%)	46 (32.9%)	1.43	1	0.2322 ‡
	F	37 (61.7%)	57 (71.3%)	94 (67.1%)			
Level of education	Elementary	1 (1.7%)	0 (0%)	1 (0.7%)			0.3078 ₣
	Lower secondary	13 (21.7%)	11 (13.8%)	24 (17.1%)			
	Upper secondary	21 (35%)	36 (45%)	57 (40.7%)			
	Higher	25 (41.7%)	33 (41.3%)	58 (41.4%)			
Work occupation	Unemployed	20 (33.3%)	17 (21.3%)	37 (26.4%)			0.0181 ₣
	Disabled	18 (30%)	20 (25%)	38 (27.1%)			
	Employed	16 (26.7%)	39 (48.8%)	55 (39.3%)			
	Student	0 (0%)	2 (2.5%)	2 (1.4%)			
	Retired	6 (10%)	2 (2.5%)	8 (5.7%)			
Marital status	Single	10 (16.7%)	24 (30%)	34 (24.3%)			0.1196 ₣
	Married	38 (63.3%)	37 (46.3%)	75 (53.6%)			
	Divorced	9 (15%)	17 (21.3%)	26 (18.6%)			
	Widowed	3 (5%)	2 (2.5%)	5 (3.6%)			
Marriages	0.00	10 (16.7%)	23 (28.8%)	33 (23.6%)			0.0698 ₣
	1.00	45 (75%)	45 (56.3%)	90 (64.3%)			
	2.00	5 (8.3%)	8 (10%)	13 (9.3%)			
	3.00	0 (0%)	4 (5%)	4 (2.9%)			
Children	0.00	14 (23.3%)	28 (35%)	42 (30%)			0.0256 ₣
	1.00	11 (18.3%)	26 (32.5%)	37 (26.4%)			
	2.00	32 (53.3%)	23 (28.8%)	55 (39.3%)			
	3.00	2 (3.3%)	2 (2.5%)	4 (2.9%)			
	>3.00	1 (1.7%)	1 (1.3%)	2 (1.4%)			
Age mean (±SD)		45.4 (±11.3)	42.9 (±10.8)		1.32	138	0.1879 §
Age of index depressive episode mean (±SD)		29.3 (±20.0)	25.9 (±16.7)		2.16	138	0.0325 §

‡ Pearson Chi-Square; ₣ Fisher's Exact Test; § T-Test.

No significant differences such as work occupation, level of education, marital status and number of marriages were observed between the two studied groups, except for the lower age of index depressive episode of BPD group 25.9 (±16.7) vs. UPD 29.3 (±20.0) (p = 0.0325 §), the greater employment rate in the bipolar group 48.8% compared to that of UPD (26.7%) (p = 0.0181 ₣) and finally the proportion

of patients having two children 32 (53.3%) in UPD group vs 23 (28.8%) in BPD group (p = 0.0256 Ŧ).

3.2. Constellation Factors

By means of a descriptive analysis, constellation (grouped) factors with statistical significance related to the diagnosis of BPD were established (Table 2).

Table 2. Constellation factors that are significantly associated with a diagnosis of BPD.

PARAMETER		Diagnosis		Total (N = 140)	X^2	df	p
		UPD (N = 60)	BPD (N = 80)				
Bipolar spectrum family loading[a]	No	55 (91.7%)	61 (76.3%)	116 (82.9%)	5.74	1	0.0166 ‡
	Yes	5 (8.3%)	19 (23.8%)	24 (17.1%)			
Artistic family background	*No*	59 (98.3%)	51 (63.8%)	110 (78.6%)	24.36	1	0.0000 ‡
	Yes	1 (1.7%)	29 (36.3%)	30 (21.4%)			
Hypothyroidism family loading	*No*	59 (98.3%)	64 (80%)	123 (87.9%)	10.80	1	0.0010 ‡
	Yes	1 (1.7%)	16 (20%)	17 (12.1%)			
Thyroid pathology	No	54 (90%)	61 (76.3%)	115 (82.1%)	4.42	1	0.0355 ‡
	Yes	6 (10%)	19 (23.8%)	25 (17.9%)			
Obesity	No	50 (83.3%)	53 (66.3%)	103 (73.6%)	5.15	1	0.0233 ‡
	Yes	10 (16.7%)	27 (33.8%)	37 (26.4%)			
Migraine	No	56 (93.3%)	61 (76.3%)	117 (83.6%)	7.29	1	0.0069 ‡
	Yes	4 (6.7%)	19 (23.8%)	23 (16.4%)			
Alcohol abuse in the family	No	48 (80%)	49 (61.3%)	97 (69.3%)	5.66	1	0.0173 ‡
	Yes	12 (20%)	31 (38.8%)	43 (30.7%)			
Hypersensitivity (*highly sensitive person*)	*No*	40 (66.7%)	19 (23.8%)	59 (42.1%)	25.90	1	0.0000 ‡
	Yes	20 (33.3%)	61 (76.3%)	81 (57.9%)			
Early puberty	No	60 (100%)	74 (92.5%)	134 (95.7%)			0.0374 Ŧ
	Yes	0 (0%)	6 (7.5%)	6 (4.3%)			
Truancy/absence from work	*No*	60 (100%)	67 (83.8%)	127 (90.7%)			0.0006 Ŧ
	Yes	0 (0%)	13 (16.3%)	13 (9.3%)			
Physical aggression and violence	*No*	60 (100%)	74 (92.5%)	134 (95.7%)			0.0374 Ŧ
	Yes	0 (0%)	6 (7.5%)	6 (4.3%)			
Alcohol abuse	*No*	60 (100%)	65 (81.3%)	125 (89.3%)			0.0001 Ŧ
	Yes	0 (0%)	15 (18.8%)	15 (10.7%)			
Practicing extreme sports	No	60 (100%)	74 (92.5%)	134 (95.7%)			0.0374 Ŧ
	Yes	0 (0%)	6 (7.5%)	6 (4.3%)			
Age of index depressive episode	before age of 25	25 (41.7%)	47 (58.8%)	72 (51.4%)	4.01	1	0.0453 ‡
	after age of 25	35 (58.3%)	33 (41.3%)	68 (48.6%)			

Continued

Number of depressive episodes	≤3	24 (40%)	15 (18.8%)	39 (27.9%)	7.70	1	0.0055 ‡
	>3	36 (60%)	65 (81.3%)	101 (72.1%)			
Evening brightening and activity invigoration	*No*	53 (88.3%)	8 (10%)	61 (43.6%)	85.57	1	0.0000 ‡
	Yes	7 (11.7%)	72 (90%)	79 (56.4%)			
Frequent job changes	*No*	59 (98.3%)	58 (72.5%)	117 (83.6%)	16.67	1	0.0000 ‡
	Yes	1 (1.7%)	22 (27.5%)	23 (16.4%)			
Decay in job productivity	No	50 (83.3%)	48 (60%)	98 (70%)	8.89	1	0.0029 ‡
	Yes	10 (16.7%)	32 (40%)	42 (30%)			
Dismissal from work	No	59 (98.3%)	71 (88.8%)	130 (92.9%)			0.0434 ₣
	Yes	1 (1.7%)	9 (11.3%)	10 (7.1%)			
Complete clinical remissions	No	20 (33.3%)	69 (86.3%)	89 (63.6%)	41.46	1	0.0000 ‡
	Yes	40 (66.7%)	11 (13.8%)	51 (36.4%)			
Residual clinical remissions (partial)	No	40 (66.7%)	35 (43.8%)	75 (53.6%)	7.24	1	0.0071 ‡
	Yes	20 (33.3%)	45 (56.3%)	65 (46.4%)			
Mood alternation (*switching to the opposite mood pole*)	*No*	60 (100%)	57 (71.3%)	117 (83.6%)			0.0000 ₣
	Yes	0 (0%)	23 (28.8%)	23 (16.4%)			
Mood fluctuations	*No*	55 (91.7%)	4 (5%)	59 (42.1%)	105.62	1	0.0000 ‡
	Yes	5 (8.3%)	76 (95%)	81 (57.9%)			
Impulsiveness	*No*	60 (100%)	55 (68.8%)	115 (82.1%)	22.83	1	0.0000 ‡
	Yes	0 (0%)	25 (31.3%)	25 (17.9%)			
Staying up late	*No*	53 (88.3%)	17 (21.3%)	70 (50%)	61.72	1	0.0000 ‡
	Yes	7 (11.7%)	63 (78.8%)	70 (50%)			
Irritability	*No*	44 (73.3%)	13 (16.3%)	57 (40.7%)	46.28	1	0.0000 ‡
	Yes	16 (26.7%)	67 (83.8%)	83 (59.3%)			
Mood reactivity	*No*	48 (80%)	24 (30%)	72 (51.4%)	34.31	1	0.0000 ‡
	Yes	12 (20%)	56 (70%)	68 (48.6%)			
Increased verbal output (*talkativeness*)	*No*	58 (96.7%)	34 (42.5%)	92 (65.7%)	44.65	1	0.0000 ‡
	Yes	2 (3.3%)	46 (57.5%)	48 (34.3%)			
Anhedonia	*No*	22 (36.7%)	48 (60%)	70 (50%)	7.47	1	0.0063 ‡
	Yes	38 (63.3%)	32 (40%)	70 (50%)			
Increased motor drive (*restlessness*)	*No*	49 (81.7%)	40 (50%)	89 (63.6%)	14.85	1	0.0001 ‡
	Yes	11 (18.3%)	40 (50%)	51 (36.4%)			

‡ Pearson Chi-Square; ₣ Fisher's Exact Test; a The most significant statistic parameters are highlighted by italics.

The results obtained from BPD group (Table 2) showed a positive familial burden for bipolar disorders [(BAD I; BAD II, cyclothymic disorder); 23.8%; p = 0.0166 ‡)], artistic/colourful relatives [(hyperthymic temperament); 36.3%; p = 0.0000 ‡)] and hypothyroidism (20%; 0.0010 ‡). Significant differences were

reported between the unipolar and bipolar groups regarding comorbidities with thyroid pathology [(hyper/hypothyroidism); (p = 0.0355 ‡)], obesity (p = 0.0233 ‡), migraine (p = 0.0069 ‡) and alcohol abuse (p = 0.0173 ‡). Early onset of puberty, truancy or absence from work, physical aggression, and inclination to extreme sports and undertaking risky endeavours are typical characteristics of the bipolar group (Table 2). In 58.8% of patients with BPD, the onset of depression was before the age of 25 with 81.3% of them experiencing more than three depressive episodes. Interestingly, over half of BPD patients (56.3%) do not achieve complete remission. Frequent job changes (27.5%; p = 0.0000 ‡), dismissal from work (11.3%; 0.0434 ₣), decline in professional skills (40%; p = 0.0029 ‡) were more common in the BPD group and testify for significant cognitive dysfunctions (Table 2). Clinical symptoms such as mood swings, staying up late, evening chronotype (evening mood lightening and energy invigoration), affective fluctuations, mood reactivity, irritability, psychomotor restlessness, anhedonia, increased verbal output have shown significant differences between the studied groups and clearly underline the specific profile of BPD (Table 2). In order to identify more specific indicators with statistical significance related to diagnosis of BPD, the obtained data were subjected to item analysis and 15 indicators were selected (see Table 2; the selected indicators are highlighted in italics). These prioritized factors were chosen on the basis of a subgroup item analysis that has shown that some factors had a stronger correlation with the diagnosis of BPD than the others (see Table 3). From now on, the selected indicators will be called the abbreviated screening card for bipolar depression—ASCBPD.

3.3. Reliability and Validity of ASCBPD

In order to determine the reliability (internal consistency) of the ASCBPD, correlation analysis was applied (Table 3).

Table 3. Internal consistency of ASCBPD.

Item	Mean (difficulty)	Corrected item-total correlation (discrimination)	Cronbach's alpha if item deleted
Artistic family background	0.2	0.35	0.87
Hypersensitivity (highly sensitive person)	0.6	0.47	0.86
Truancy	0.1	0.44	0.86
Aggression	0.1	0.34	0.87
Alcohol abuse	0.1	0.46	0.86
Evening mood brightening and activity invigoration	0.6	0.68	0.85
Frequent job changes	0.2	0.37	0.86

Continued

Mood alternation	0.2	0.55	0.86
Mood variability	0.6	0.78	0.84
Impulsiveness	0.2	0.56	0.86
Staying up late	0.5	0.63	0.85
Irritability	0.6	0.59	0.85
Mood reactivity	0.5	0.51	0.86
Talkativeness	0.3	0.48	0.86
Restlessness	0.4	0.44	0.86

The high Cronbach's alpha coefficient (0.87) and relatively low inter-item correlation (0.30) indicate a good internal consistency of the ASCBPD. The difficulty [Mean (difficulty)] of the individual items is within the limits (0.1 ÷ 0.9). The discrimination coefficients [Corrected Item-Total Correlation (discrimination)] are relatively high around 0.4 and above this value. All this confirms the reliability of the discrimination chart that was studied.

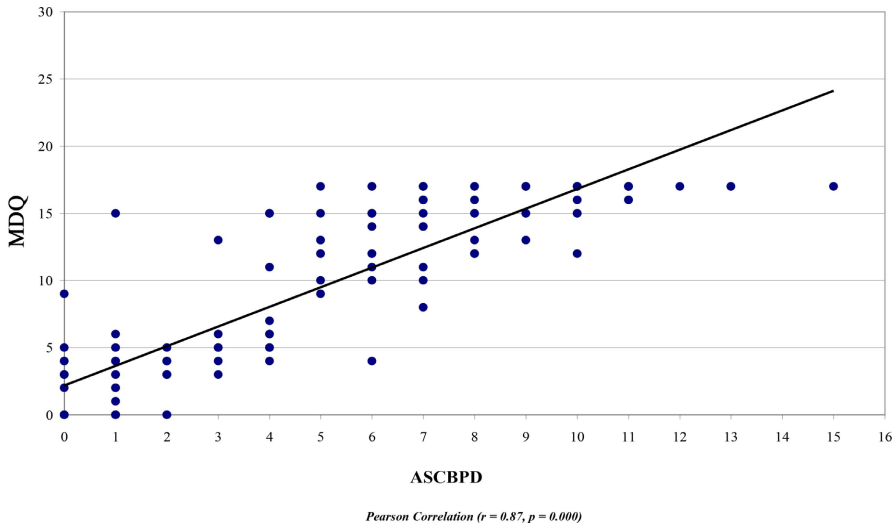
To establish validity of ASCBPD, a correlation was sought between ASCBPD and MDQ, and ASCBPD and BDRS respectively (as the investigators are looking for a concise outline of this article, the results of MDQ and BDRS will not be presented separately, but would be available on a request). Table 4 shows the Pearson's correlation coefficient and the p value measuring the correlation between the compared scales.

Table 4. Correlation between ASCBPD, MDQ and BDRS.

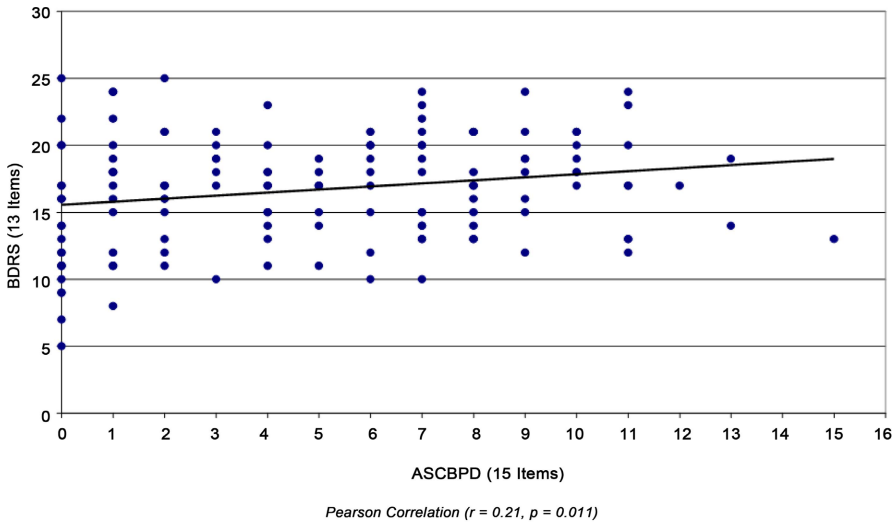
Relationship between:	Pearson correlation	p
ASCBPD/MDQ	0.87	0.0000
ASCBPD/BDRS	0.01	0.8618

A strong linear correlation was found (r = 0.87, p = 0.000) with the MDQ scale (Figure 1(a)) and no linear correlation (r = 0.01, p = 0.862) with the BDRS. A careful analysis of the individual BDRS items revealed 13 factors that showed a significant difference (p = 0.0103 T-test) between the UPD and BPD groups (the overall mean values were: 15.6 (±4.6) for UPD and 17.4 (±3.4) for BPD). In fact, the BDRS items that were dropped, such as hypersomnia, change in appetite, reduction in energy or activity, anxiety, worthlessness, suicidal ideation, and guilt, were symptoms that were more typical of classic unipolar depression. The fact that only 13 out of a total of 20 indicators included in the BDRS had shown a significant association with a diagnosis of BPD meant that the larger proportion of the patients in the studied bipolar sample were patients with both depressive and mixed symptoms. In the present study, the 13 items from BDRS have shown a weak, but significant linear correlation with the ASCBPD (r = 0.21, p = 0.011) [(r = 0.21, r =

0.011; Figure 1(b))], were a combination of cognitive dysfunctions, psychological symptoms and mixed symptoms. This means that the observed depressive picture cannot be defined as a classic unipolar depression, but rather as a dynamic three-factor symptomatic pattern. Basically, BPD contains a mixture of symptoms that can be placed in three main groups: a) psychological depressive symptoms; b) somatic depressive symptoms and c) mixed symptoms. The combination of these three symptom domains can form different clinical profiles of BPD. This fact has demonstrated once again that bipolar depression does not have uniformity and represents a heterogeneous group of symptoms depending on the subtype of BD - BD I or BD II, cyclothymia or subclinical mixed phases. The question of the modifying role of temperamental predisposition in shaping the depressive pictures of BPD also remains open, debatable and intriguing.



(a)



(b)

Figure 1. (a) Linear correlation of ASCBPD with MDQ; (b) Linear correlation of ASCBPD with BDRS (13 items).

3.4. Logistic Regression Model and Accuracy

ASCBPD items were incorporated as predictors in a stepwise logistic regression with diagnosis bipolar vs unipolar depression. As a result of stepwise logistic regression, only those with significant regression coefficients ($p < 0.05$) remained in the model (Table 5).

Table 5. Logistic regression model.

Parameters	B[a]	S.E.[b]	Wald[c]	DF[d]	Sig.[e]	Exp[f] (B)	95% C.I. for EXP (B)[g]	
							Lower	Upper
Evening mood brightening and activity invigoration	3.55	1.02	12.16	1	0.0005	34.69	4.73	254.56
Frequent job changes	4.78	1.68	8.13	1	0.0044	119.46	4.46	3199.86
Mood fluctuation	3.77	0.94	16.21	1	0.0001	43.56	6.94	273.50
Staying up late	2.59	1.11	5.46	1	0.0195	13.31	1.52	116.76
Constant	−4.73	0.98	23.08	1	0.0000	0.01		

[a]beta coefficient; [b]Standard error; [c]Wald test; [d]Degrees of freedom; [e]significance; [f]exponential value of B; [g]confidence interval.

The Hosmer–Lemeshow's test used to assess the goodness of fit and calibrate the logistic regression models reported a good fit of the applied logistic model ($\chi^2 = 2.56$; $p = 0.6347$).

3.5. A Receiver Operating Characteristic (ROC) Curve Analysis

The obtained results from the logistic regression were subjected to a receiver operating characteristic (ROC) curve analysis. ROC curve permits the definition of the accuracy (sensitivity and 1-specificity) of ASCBPD (Table 6).

Table 6. Sensitivity and specificity of the ASCBPD.

Classification table		Diagnosis	Predictable diagnosis		Percentage correct
			UPD	BPD	
Step 1[a]	*Specificity*	UPD	55	5	91.67
	Sensitivity	BPD	4	76	95
	Overall percentage				93.57
Step 2[b]	*Specificity*	UPD	55	5	91.67
	Sensitivity	BPD	4	76	95
	Overall percentage				93.57
Step 3[c]	*Specificity*	UPD	59	1	98.33
	Sensitivity	BPD	6	74	92.5
	Overall percentage				95
Step 4[d]	*Specificity*	UPD	58	2	96.67
	Sensitivity	BPD	4	76	95
	Overall percentage				**95.71**

[a]mood fluctuation: [b]hypersensitivity + mood fluctuation; [c]hypersensitivity + mood fluctuation + staying up late; [d]hypersensitivity + mood fluctuation + staying up late + frequent job changes.

Sensitivity shows that the model correctly classifies 76 out of 80 cases (95.00%) as bipolar depression. Specificity that 58 out of 60 cases (96.67%) were correctly classified as unipolar depression. The overall percentage of correctly predicted cases by the model was 95.71. ROC curve was built based on the applied logistic model. The total area under the curve is 0.985 (Figure 2).

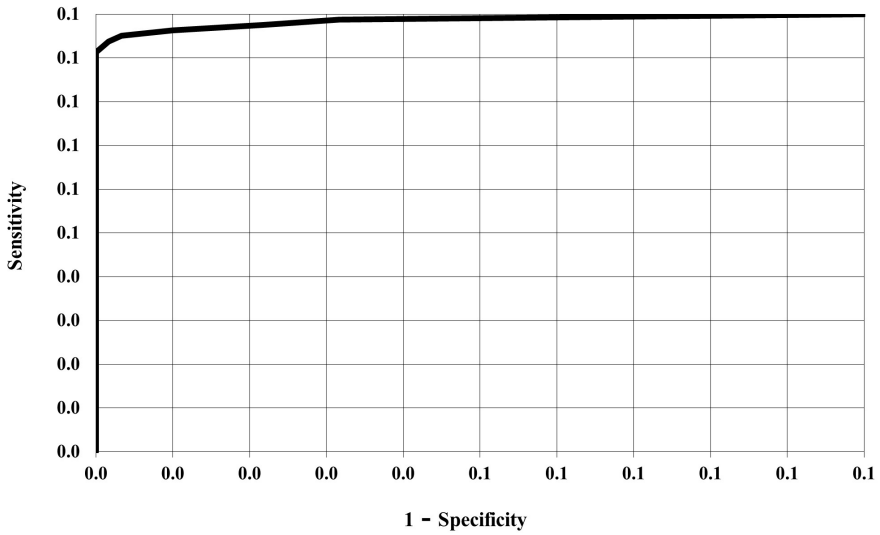


Figure 2. Sensitivity and specificity of ASCBPD assessed by ROC curve.

After the accuracy of ASCBPD was determined, the area under the ROC curve (AUC) was assessed by different ranges of cut off points to determine the bipolar diagnosis (Table 7).

Table 7. Results for area under the ROC curve of ASCBPD assessed by different ranges of cut off points.

Cut off	Area under the curve	Std. Error	p	95% confidence interval for the area	
				Lower bound	Upper bound
Cut off 2	0.894	0.032	0.0000	0.831	0.957
Cut off 3	0.938	0.025	0.0000	0.889	0.986
Cut off 4	**0.942**	0.022	0.0000	0.898	0.985
Cut off 5	0.892	0.029	0.0000	0.835	0.949
Cut off 6	0.838	0.034	0.0000	0.770	0.905

Figure 3 represents the ROC curve and AUC of ASCBPD assessed by different ranges of cut off points.

The ROC analysis concluded that at cut off 4 the AUC was the largest. This allows us to predict the following cut offs for ASCBPD serving as diagnostic criteria: the cut off between 0 ÷ 4 points stand for UPD diagnosis and that of more than 4 points for BPD diagnosis.

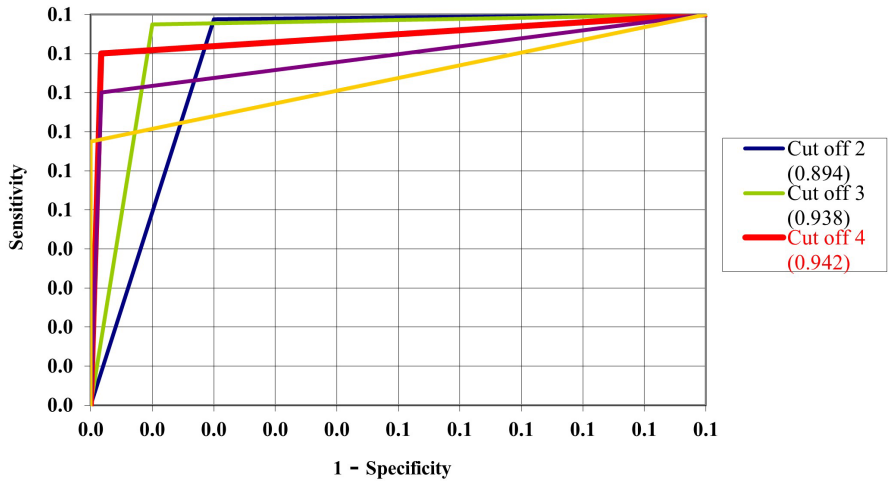


Figure 3. Assessment of the area under the curve (AUC) of ASCBPD at different ranges of cut off points.

4. Discussion

4.1. Demographic Characteristics

The mean age of the unipolar group in this study was 45.4 (±11.3) years, which was higher than that of the bipolar group of 42.9 (±10.8) years - a fact that is consistent with most studies [16] [21]-[23]. The age of the index depressive episode in the group of bipolar patients was found to be 25.9 (±16.7) years, which was lower than in the unipolar group 29.3 (±20.0) years, which corresponds to the results of most studies [12] [24] [25]. In both groups, the prevalence of depression in women was higher, which was confirmed in most studies [26] [27], but not all. [28]. Demographic indicators such as level of education, employment, family status, number of marriages and number of children, except for more children in the subgroup with two children of the UPD group (53.3%) compared to the BPD group (28.8%), did not show other significant differences. These results contradict some of the other studies [16] [29] [30].

4.2. Constellation Factors

The constellation factors associated with the diagnosis of BPD such as family genetic loading with bipolar spectrum (BAR I, BAR II, cyclothymic disorder and hyperthymic temperament), hypothyroidism [31] [32], alcohol abuse [11] [13] [24] especially with an underlying dominant cyclothymic temperament, comorbidities such as hypo/hyperthyroidism, obesity and migraine are all in line with the obtained results from the studies in the field. Most studies have shown that the association between BD and migraine is most significant among patients with BAR II, especially females [33]. All of the above-mentioned indicators differ statistically between unipolar and bipolar groups. Frequent job changes and a sense of subjective professional failure, individual's hypersensitivity to external stimulation and interpersonal relationships, truancy, inclination towards extreme sports, and undertaking of risky activities, as well as aggression, were found to be

significant characteristics associated with bipolarity [13]. In the present study, not only the lower age of index depressive episode was confirmed, but also the greater number of depressive episodes during the illness course, which has been confirmed in most studies [18] [34] [35]. Despite modern treatment methods, in the Zurich follow-up study only 16% of BPD patients met criteria for complete recovery, with 52% continuing to have relapses [36]. This study also concluded that the rate of incomplete remissions in the bipolar group 56.3% were twice as many as those in the unipolar group 33.3% ($p = 0.0071$ ‡). This can be explained by a more severe baseline dysregulation of the behavioural activation system in the brain of bipolar patients [19]. The most common symptoms of partial remissions are social dysfunctions, maladaptive attitudes, hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA) [in addition to depression, HPA-axis hyperactivity has also been implicated in the development of various cardiometabolic, inflammatory, endocrine, and neural disorders], and shortened REM sleep latency [37] accompanied by mood swings, irritability, and insomnia. These findings were supported by the fact that a long-term follow-up of BD patients had shown that 45% of their lifetime was affected by depression occupying on average 72% of it [38].

Nearly two-thirds of bipolar patients in remission complain of cognitive dysfunctions, but there is no perfect match between what patients report and what is assessed by neuropsychological tests. In the present study, frequent job changes, dismissal and decline in professional skills were more frequent in the BPD group and were indicators of significant and more global cognitive impairment such as deficits in psychomotor speed, verbal memory (retention and reproduction), selective attention/inhibitory control, and working memory. These cognitive dysfunctions in BD are present not only during symptom exacerbations (more than 50% of the euthymic bipolar patients present some level of cognitive dysfunction), but also during the prodromal and residual phases. A possible explanation for this is that subjective cognitive impairment may be more closely related to persistent subthreshold depressive symptoms or to the treatment side effects [39]. Ultimately, the cognitive dysfunctions in BD patients lead to social isolation, illness aggravation, executive dysfunctions and a reduced quality of life [12] [40] [41].

4.3. Differences between BD and MDD

The most important part of the constellation factors are clinical symptoms. These include evening chronotype (evening invigoration and surge of energy), mood alternation, mood swings, impulsivity, staying up late, irritability, mood reactivity, increased verbal output (logorrhoea), increased motor drive, impulsivity, and anhedonia. The study has also confirmed that anhedonia (63.3% in UPD vs 40% in BPD; $p = 0.0063$ ‡) could play a role in discriminating between unipolar and dipolar depressed patients, as it had previously been reported [42]. On the whole, these symptoms can be attributed to a mixed depression and can be conceptualised as a symptomatic continuum between unipolar depression and mania, with variable expressions of bipolarity representing different dimensions of underlying pathophysiological mechanisms [42] [43] and genetic vulnerability expressed by

the endophenotypes. The endophenotypes refer to traits present in unaffected individuals that can be interpreted as a marker of disease predisposition, *i.e.*, a genetic substrate potentially linked to the illness.

All these clinical characteristics (see Table 2) derived from the study (essentially cross-sectional parameters) have been confirmed in the great majority of other studies [12] [21] [44]-[47].

4.4. ASCBPD Serving as a Screening Tool

ROC curve is drawn up based on the used logistic model. The sensitivity of ASCBPD showed that the model correctly classified 76 of 80 cases (95.00%) as BPD and specificity correctly classified 58 of 60 cases (96.67%) as UPD. The overall percentage of correctly predicted cases by the model was 95.71. The high sensitivity of the test is associated with a low rate of false negatives, *i.e.*, of affected people misidentified as healthy. AUC is of 0.985. The applied analysis found that at cut off 4 the AUC was the largest 0.942. This allows us to define the following diagnostic cut offs based on the score of the ASCBPD: for diagnosis of UPD 0 ÷ 4 points and for that of BPD > 4 points.

5. Conclusion

Clinical symptoms such as diurnal variation in mood and energy, mood reactivity, mood swings, impulsivity, mood alternation, increased motor drive and verbal output during depressive episode can serve to distinguish bipolar from unipolar depression. Factors such as artistic family background and family history of hypothyroidism also increase the possibility of having "hidden" bipolarity during the index depressive episode. Frequent job changes, decline in professional skills, hypersensitivity, truancy and frequent absence from work, along with alcohol abuse seem to be specific predictors of bipolar diathesis. Last but not least is the rate of partial remissions which are more frequent in the bipolar than in unipolar patients' group.

6. Future Directions for Research

Future directions in the accurate diagnosis of BPD are laboratory tests and rapidly developing brain imaging methods (s/f MRI, PET, and SPECT). Studies based on genetic data for the whole genome will allow the discovery of genetic markers for BPD, which will allow the differentiation of depression subtypes using polygenic risk scores. These studies could be designed to capture genetic differences between UPD and BPD, and not only between common affective disorders [15].

7. Limitations

1) The study did not distinguish between BD subtypes I and II. A more precise division between the two subtypes would have given more insight into specificities of BPD related to BD I and BD II. This particularly holds true for BD II symptoms, as they present closest to UPD, which can be a difficulty in the diagnostic assessment

therefore, using an evidence-based screening tool is the most effective intervention for early diagnosis both for the clinician and the patient [48]. 2) The duration of depressive episodes was not reported. 3) The main limitation is the sample size.

Acknowledgements

I would like to tank to all my colleagues working at Mental Health Centre "N. Shipkovensky" Sofia, Bulgaria, for their kind and friendly support during the research period.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction.

Conflicts of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix

Abbreviated Screening Scale for Bipolar Depression (ABSD)

GENERAL INSTRUCTIONS

The implications of timely rapid assessments allow for prompt interventions that have shown to halt or prevent mental health conditions to worsen and by means of that to reducing risk of emergency situations. ASCBPD is a screening tool that serves to differentiate bipolar from unipolar depression. The individual items of the ASCBPD assess the likelihood of bipolarity during the index depressive episode.

The chart contains 15 items. Since it is based on a dichotomous model, the possible answers are only: **Yes**, which is marked 1 point or **No**, respectively marked 0 point. The maximum possible score is 15 points. Higher scores indicate a greater likelihood of bipolar depression.

Items included are based either on subjective data (patients' responses – e.g. regarding evening chronotype and hypersensitivity or personal history data such as - presence of artistic/accented relatives; frequent job changes; skipping school and breaking from work), or objective assessment of the clinicians (e.g. clinical symptoms) or a combination of both. When the examiner's assessment diverges from what the subject has reported, e.g. there is a discrepancy between subjective and objective findings, the preference is given to the objective observation of the interviewer.

The chart does not assess the severity of depression and serves entirely for screening purposes *i.e.*, differentiating UPD from BPD.

Assessment of clinical symptoms should be based on the subject's current mental status. Assessment should, if possible, avoid the interference of environmental factors or side effects from the treatment (if there is a clear pharmacological cause for given symptoms, such as logorrhoea and irritability due to prescribed antidepressants, then the symptoms should be assessed carefully).

The enlisted questions are a rough guide and should be contextualized to the individual's clinical situation.

The score is drawn from a clinical interview executed either in clinical or in outpatient settings. The assessment can start with a general statement addressing the main issues of the evaluation.

"I'm going to ask you a few questions about some symptoms you may have or you have already had. When answering, please keep in mind that we are only focusing on how you are feeling now or have been in the last two to three weeks.

For the questions that concern information about your family, personal development and psychological wellbeing, the requested information covers a long period of time, facts and specific circumstances, therefore, please try to answer as accurately and objectively as possible.

Once a cut off of >4 points has been detected the patient needs to undergo more vigorous clinical assessment and a collateral information has to be sought out (interviewing key informants, taking more in-depth his personal history, asking for

all medical examinations that have been done so far and also scrutinising the whole medical documentation).

Abbreviated Screening Chart for Bipolar Depression (ASCBPD)

1) **Family history for artistic/accentuated relatives:** (relatives with stormy biographies, artistic professions, accentuated personalities, unusual hobbies, generally thrill seekers and hedonists).

No/Yes

2) **Hypersensitivity or a Highly Sensitive Person:** [(psychological and sensory hypersensitivity)]. Extreme sensitivity to sensory stimulation: touch, sight, hearing, taste, and smell. It can also have a major impact on both emotional and behavioural responses of the individual.

No/Yes

3) **Truancy:** (frequent absences from school, skipping classes, taking permanent sick days).

No/Yes

4) **Physical aggression:** (assaults, self-arguments, fights).

No/Yes

5) **Alcohol abuse:** [(alcohol abuse refers to excessive consumption of alcohol that can create dangerous consequences for the consumer and others)].

No/Yes

6) **Evening chronotype:** [in addition to the shifts in circadian rhythm, additional features such as brightening of mood and surge of energy in the late evening hours are also included].

No/Yes

7) **Frequent job changes:** [failure to keep a job; the reasons behind this behaviour should be explored – e.g. not coping with the job (cognitive aspect), or not following the rules of the workplace (behavioural problems) or regular drinking, etc.]

No/Yes

8) **Mood alternation:** (sudden shift to the opposite affective pole; all questions about frequency and contextual precipitating stimuli such as external circumstances, alcohol or drug abuse should be carefully explored). By definition the mood alternation is independent of all these triggering events and occurs spontaneously.

No/Yes

9) **Mood fluctuations:** (subjectively or objectively reported mood swings).

No/Yes

10) **Impulsivity:** (subjectively or objectively reported inability to inhibit the flow of intrusive thoughts or necessity to act immediately under the pressure of

circumstances).

No/Yes

11) **Staying up late:** [(falling asleep in the early hours of the day (burning both sides of the candle) due to evening chronotype)].

No/Yes

12) **Irritability:** [(patients report feeling annoyed or grumpy or the clinician spots in patient's behaviour (most often both) temper tantrums, excessive moodiness, sharp remarks and offensive comments)].

No/Yes

13) **Emotional reactivity:** (this is a relief of a depressed mood in response to actual or potential positive events; at the same time, it could also be manifested by overreacting with despair to some minor negative events).

No/Yes

14) **Increased verbal output:** (perceptible increase in rate or quantity of speech or pressure of speech).

No/Yes

15) **Motor agitation:** (subjectively reported or observed increased motor activity).

No/Yes

Cut-offs:

(0 ÷ 4) diagnosis of UPD

(>4) diagnosis of BPD