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Research report

A predictive model for diagnosing bipolar disorder based on the clinical characteristics of major depressive episodes in Chinese population

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ABSTRACT

Background: A correct timely diagnosis of bipolar depression remains a big challenge for clinicians. This study aimed to develop a clinical characteristic based model to predict the diagnosis of bipolar disorder among patients with current major depressive episodes.
Methods: A prospective study was carried out on 344 patients with current major depressive episodes, with 268 completing 1-year follow-up. Data were collected through structured interviews. Univariate binary logistic regression was conducted to select potential predictive variables among 19 initial variables, and then multivariate binary logistic regression was performed to analyze the combination of risk factors and build a predictive model. Receiver operating characteristic (ROC) curve was plotted.
Results: Of 19 initial variables, 13 variables were preliminarily selected, and then forward stepwise exercise produced a final model consisting of 6 variables: age at first onset, maximum duration of depressive episodes, somatalgia, hypersomnia, diurnal variation of mood, irritability. The correct prediction rate of this model was 78% (95%CI: 75%–86%) and the area under the ROC curve was 0.85 (95%CI: 0.80–0.90). The cut-off point for age at first onset was 28.5 years old, while the cut-off point for maximum duration of depressive episode was 7.5 months.
Limitations: The limitations of this study include small sample size, relatively short follow-up period and lack of treatment information.
Conclusion: Our predictive models based on six clinical characteristics of major depressive episodes prove to be robust and can help differentiate bipolar depression from unipolar depression.

1. Introduction

Major depressive episodes (MDE) are common clinical condition and have substantial shared symptoms with bipolar disorder (BPD). In current clinical practice, differential diagnosis of MDE from BPD mainly depends on absence of hypomanic or manic episodes. For most patients with current depressive episodes, especially for those who experience their first visit as a depressive episode, diagnosis based on history of mood elevation might be unreliable, since it is common for these patients to intentionally or unconsciously underreport manic or hypomanic symptoms because of poor insight, stigma concern or recall bias (Perlis, 2005); and for other cases, they just have not yet experienced any manic episode (Perlis et al., 2004), though in nature they are bipolar disorder sufferers. As a consequence, misdiagnosis or delayed diagnosis is highly prevalent (Ghaemi et al., 2000; Hirschfeld et al., 2003; Morselli and Elgie, 2003), resulting in inappropriate treatment and therefore poor outcome (Goldberg and Ernst, 2002).

So far, reliable biological markers or objective indices are still unavailable to distinguish BPD from unipolar depression (UPD). Phenomenology has been the major focus of most

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studies that endeavored to differentiate these two disorders. For instance, a number of studies (Akiskal and Benazzi, 2008; Akiskal and Benazzi, 2005; Quitkin et al., 2003; Angst et al., 2006) found that atypical features, including mood reactivity, overeating or weight gain, hypersomnia, leaden paralysis, interpersonal rejection sensitivity, and absence of melancholic or catatonic features were more common in BPD than UPD (American Psychiatric Association, 2000). Other symptoms, such as psychomotor agitation (Sato et al., 2005; Akiskal and Benazzi, 2005), psychotic symptoms (Leyton and Barrera, 2010; Henry and Etain, 2010), and manic symptoms (Serretti and Olgiati, 2005; Goldberg et al., 2009; Angst et al., 2010) were also reported to be a strong diagnostic validator of bipolar nature of MDE. Some clinical characteristics like family history of BPD, early age onset, greater number of previous depressive episodes, and comorbidity of psychoactive drug abuse tend to occur more frequently with BPD (Benazzi, 2006; Goldberg et al., 2009; Oswald et al., 2007; Perlis et al., 2006). However, to what extent we can rely on these characteristics to distinguish BPD from UPD still remain to been seen, since not every subject with bipolar depression has the all above characteristics and not every subject with one or two of the above features really suffers from bipolar depression (Akiskal et al., 2008; Perlis et al., 2004). It seems unrealistic to count on a single clinical feature of MDE to differentiate BPD from UPD, while perhaps a combination of some features like these but not all due to the principle of simplicity and economy, maybe more feasible and reliable. In addition, most studies were sampled in western developed countries and studies from Asia developing countries remained scant. Therefore, in this study, we attempted to build a predictive model based on such clinical features to distinguish BPD from UPD in a Chinese MDE population through a prospective study.

2. Methods

2.1. Sample

This study sample consisted of 344 cases treated initially for major depressive episode (MDE) in the psychiatric department of the Third Affiliated Hospital of Sun Yat-sen University, between July, 2006 and July, 2009. Patients with a psychiatric or physical disorder that prevented them from being interviewed or undermined their ability to provide accurate information, and those who declined participation in the study or refused to provide informed consent were excluded.

2.2. Instrument

Chinese version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) Axis 1 Disorders (SCID-I) (So et al., 2003) was used for diagnostic interview. General sociodemographic and clinical characteristics were collected via a questionnaire designed by the researchers. Variables in regard to characteristics of MDE included age at first onset, number of depressive episode, maximum duration of depressive episode, family history of mental disorder, season of onset, and trigger factors. As for features of the worst depressive episode, the following symptoms of interest were confirmed based on the results of SCID and clinical interviews: hypersomnia, weight gain, retardation, fatigue, anxiety, somatosization, somatalgia, suicide risk, psychotic symptoms, and diurnal variation of mood. The suicide risk was treated as ordinal variable, divided into 5 levels: 1 = no suicidal ideation, 2 = suicidal ideation but no suicidal plan, 3 = suicidal plan but no suicidal attempt, 4 = once suicidal attempt and 5 = more than once suicidal attempts. The other abovementioned symptoms were seen as binary variables: yes or no.

2.3. Procedure

Prior to the start of this study, 3 senior psychiatrists (ZJB, GNH, and WXL) attended a training program focused on SCID, self–compiled questionnaires and the detection of switch. At the end of the program, their kappa coefficient reached 0.92 in terms of interrater reliability. Throughout the whole study period, all diagnostic interview and assessments were performed by these three psychiatrists, who already constituted a special committee responsible for these tasks.

Potential participants for this study were found by reviewing the archive records and clinical outpatient files. The cases were included if they had been or would like to be followed up by the psychiatrists of our department. All the participants submitted written inform consent. At the study entry, SCID-I was performed for each participants to establish an initial diagnosis meeting with the criteria of DSM-IV-TR. Sociodemographic and clinical characteristics and features of the worst depressive episode were collected using the self-compiled questionnaire. The participants were then followed up for 1 year, being interviewed by one of the three senior psychiatrists for at least six times with a flexible interval of 1–2 months via telephone or face to face talking. In each interview, if suspected switch was detected, the patients' relatives or friends who knew well about them were asked to provide additional information, and then all the data about this patient was submitted to the committee, who would decide whether the patient had experienced a switch according to the criteria of DSM-IV-TR. To insure the quality and objectivity of switch detection, those who did not complete 1 year follow-up or did not regularly follow up for more than 6 times within the year were excluded. At the end of study, the committee reviewed the 1-year medical records and came up with a final diagnosis.

During the study period, all treatment decisions or changes in treatment medications such as dose reduction, dose augmentation, or switch strategies were made by their treating psychiatrists. This study was carried out under naturalistic clinical settings and no treatment information was obtained.

2.4. Statistical analysis

2.4.1. Statistical methodology

Logistic regression was performed to select potential predictive factors and build a final predictive model. The final model was internally validated using bootstrapping methods. All data were analyzed using commercial statistical package SPSS 18.0 (SPSS, Inc., Chicago, IL), except predictive

value, and correct prediction rate calculated by Visual FoxPro 9.0 (Microsoft Company).

2.4.2. Development of a model to predict BPD

The final diagnosis meeting with the criteria of DSM-IV-TR at the end of 1-year follow-up was used as the gold criteria to separate UPD from BPD. All the potential risks factors collected in this study were compared one by one between UPD and BPD by using unconditional univariate binary logistic regression. Variables with P values less than 0.10 were included in an initial predictive model. Then a forward stepwise logistic regression was performed to build a final predictive model and a p value less than 0.05 was seen significant to predict the association of a certain characteristic with diagnosis. Receiver operator characteristic (ROC) curves were constructed by plotting the sensitivity against 1-the specificity. The area under the curve (AUC) was calculated for each ROC plot and cut-off values for the prediction of BPD were determined by maximizing the Youden's index, i.e. sensitivity + specificity-1. Accuracy of using the optimal cut-off values was assessed by the sensitivity, specificity, predictive values and likelihood ratios. Their 95% confidence intervals were obtained by 100 bootstrap samples.

2.4.3. Validation of the predictive model

The dataset was subject to 100-fold bootstrapping validation. For each of the 100 samples, coefficients for each predictor variable were calculated. The 100 coefficient sets were then used to derive predictor functions on 100 replicates of the original data. The correct prediction of BPD was calculated and ROC curves were plotted for each of the 100 outputs. The distribution of areas under the ROC curve and the correct prediction rate, in terms of 95% CI, were then assessed.

2.4.4. Determination of optimal cut-off point for age at first onset and maximum duration of depressive episode

A receiver-operating characteristic curve was plotted and calculated with diagnosis as dependent variable and age at first onset or maximum duration of MDE as independent variable respectively, and then the cut-off point was determined by maximizing the Youden's index.

3. Results

3.1. Comparison of the dropout group and the rest

By the end of study, there were totally 76 (22.1%) patients who dropped out for varieties of reasons, including 37(10.8%) for lack of efficacy or adverse event, 21(6.1%) for noncompliance, 13(3.8%) for lost to follow up, and 5 (1.5%) for patients' decision. Among the dropout group, less proportion of participants experienced anxiety but more had spring or summer onset ($p<0.05$). No significance was found in other characteristic features observed in this study between the dropout group and the rest ($p>0.05$). Given there is no eminent features in dropout group, this group is not involved in the subsequent statistical analysis.

3.2. Comparison of initial diagnosis and final diagnosis

As expected, initial misdiagnosis was quite common in this study. Both underdiagnosis and overdiagnosis of bipolar depression existed in clinical practice (Table 1).

3.3. Comparison of sociodemographic and clinical features of BPD and UPD

Table 2 showed that subjects with BPD experienced more frequently hypersomnia, psychotic symptoms, and irritability, while symptoms like neurotic anxiety, somatosization, somatalgia, fatigue and diurnal variation of mood were more common in subjects with UPD than those with BPD. Compared with subjects with UPD, subjects with BPD had an earlier age at first onset; more likely abused psychoactive drug, showed higher risk of suicide, and had shorter duration of a single depressive episode.

3.4. Predictive model for diagnosing BPD from MDE

Stepwise forward logistic regression built a final predictive model for BPD, BPDII, and BPD, respectively; the predictive factors of each model were listed in Table 3. Table 4 showed their cut-off points, predictive values and likelihood ratios. The ROC for each model was presented in Figs. 1, 2 and 3, respectively.

3.5. Optimal cut-off point for age of illness onset and maximum duration of depressive episode

To explore the optimal cut-off point for age of illness onset and maximum duration of depressive episode, two receiver-operating characteristic curves were plotted and calculated. The cut-off point was determined by maximizing the Youden's index. As a consequence, the optimal cut-off point for age of illness onset was 28.5 years (less than 28.5 years old, greater possibility for bipolar depression and vice versa), where the sensitivity was 0.714, the specificity was 0.776. The area under curve for this model was 0.794 ($P=0.028$, 95%CI: 0.739–0.849); the optimal cut-off point for maximum duration of depressive episode was 7.5 months (less than 7.5 months, greater possibility for bipolar depression and vice

Table 1
Comparison of initial diagnosis with final diagnosis.

Initial diagnosis	Final diagnosis	N of cases	percentage (%)
UDP (111)	UDP	84	75.7
	BPI	2	8
	BPII	25	22.5
BPI (30)	UDP	0	0
	BPI	30	100
	BPII	0	0.0
BPII (127)	UDP	15	11.8
	BPI	7	5.5
	BPII	105	82.7
Total (268)	Agreed with initial diagnosis	216	80.6
	Disagreed with initial diagnosis	52	19.4

Table 2
Comparison of sociodemographic and clinical features of BPD and UPD[a].

Features	UPD 99 (100%)	BPD			OR[b]		
		BPI	BPII	Total			
		36 (100%)	133 (100%)	169 (100%)	BPD	BPI	BPII
Female gender	65 (65.6)	15 (41.7)	85 (63.9)	100 (59.2)	1.501	2.676	1.080
Family history of mental disorder[c]	20 (20.2)	12 (33.3)	34 (25.6)	46 (27.2)	1.372	1.975	1.357
Comorbidity of anxiety disorder[d]	31 (31.3)	9 (25.0)	36 (27.1)	45 (26.6)	0.713	0.731	0.814
Comorbidity of psychoactive drug abuse	3 (3.0)	5 (13.9)	12 (9.0)	17 (10.0)	5.916*	7.823*	4.810*
Trigger factors	42 (42.4)	7 (19.4)	43(32.3)	50 (29.6)	0.627	0.328*	0.648
Season of onset					1.033	1.050	0.978
Spring	45 (45.5)	21 (58.3)	66 (49.6)	87 (51.5)			
Summer	24 (24.2)	4 (11.1)	26 (19.5)	30 (17.8)			
Autumn	12 (12.1)	6 (16.7)	14 (10.5)	20 (11.8)			
Winter	18 (18.2)	5 (13.9)	16 (12.0)	21 (12.4)			
Risk of suicide[e]					1.241*	1.024	1.282*
1	29 (29.3)	12 (33.3)	31 (23.3)	43 (25.4)			
2	46 (46.5)	16 (44.4)	55 (41.4)	71 (42.0)			
3	12 (12.1)	2 (5.6)	20 (15.0)	22 (13.0)			
4	8 (8.1)	3 (8.3)	10 (7.5)	13 (7.7)			
5	4 (4.0)	3 (8.3)	17 (12.8)	24 (14.2)			
Atypical symptoms							
Hypersomnia	5 (5.1)	12 (33.3)	25 (18.8)	37 (21.9)	5.781**	9.400**	4.352**
Weight gain	0 (0.0)	1 (2.8)	8 (6.0)	9 (5.3)	0.953	5.0	1.0
Psychotic symptoms	6 (6.1)	8 (22.2)	29 (21.8)	37 (21.9)	3.907**	4.429**	4.322**
Diurnal variation of mood	52 (52.5)	10 (27.8)	43 (32.3)	53 (31.4)	0.464**	0.348*	0.432**
Fatigue	95 (95.6)	29 (80.6)	118 (88.7)	137 (81.1)	0.257*	0.174**	0.331*
Irritability	30 (30.3)	28 (77.8)	84 (63.2)	112 (66.3)	4.247**	8.050**	3.943**
Neurotic anxiety	68 (68.7)	14 (38.9)	62 (46.6)	76 (45.0)	0.355**	0.290**	0.398**
Somatosization	50 (50.6)	8 (22.2)	39 (29.3)	47 (27.8)	0.357**	0.280**	0.407**
Somatalgia	23 (23.2)	4 (11.1)	17 (12.8)	21 (12.4)	0.395**	0.413	0.484*
	X ± s	X ± s	X ± s	X ± s			
Age at illness onset (year)	36.8 ± 12.5	23.6 ± 10.9	24.6 ± 8.8	24.4 ± 9.4	0.906**	0.887**	0.900**
Maximum duration of MDE (month)	9.4 ± 9.5	3.4 ± 4.2	5.9 ± 5.6	5.4 ± 5.5	0.930**	0.830**	0.937**
Single MDE(%)	48(48.5)	21(57.9)	81(61.1)	99(58.6)	1.571	1.053	1.093

Note: * P<0.05; **P<0.01.
[a] The categorization was based on the final diagnosis.
[b] all compared with UPD; OR>1,less possibility of UPD;OR<1,greater possibility of UPD.
[c] Mental disorder here included psychotic disorder and mood disorder.
[d] Anxiety disorder here consisted of generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, phobia, somatization disorder.
[e] Risk of suicide was leveled as: 1 = no suicidal ideation; 2 = suicidal ideation but no suicidal plan; 3 = suicidal plan but no suicidal attempt; 4 = once suicidal attempt; 5 = more than once suicidal attempts.

versa), where the sensitivity was 0.381, the specificity was 0.836. The area under curve for this model was 0.619 (p = 0.036, 95%CI: 0.549–0.690).

4. Discussion

A correct timely diagnosis of bipolar depression remains a big challenge nowadays for clinicians (Ghaemi et al., 2000; Hirschfeld et al., 2003; Morselli and Elgie, 2003). Therefore, many strategies such as identifying possible markers for BPD among depression symptoms (Benazzi, 2006), exploring hypomanic symptoms questionnaires (Forty et al., 2009; Hirschfeld et al., 2000) were brought up. However, as this study and other studies (Akiskal et al., 1995; Akiskal and Benazzi, 2005; Coryell et al., 1995; Fiedorowicz et al., 2011; Holma et al., 2008; Simpson et al., 2002) showed that the diagnosis of UPD and BPD based on a single interview was instable over time. Thus, evaluation on any new diagnostic strategy for distinguishing BPD from UPD defined by a single diagnostic structural interview was questionable. As this study and previous literatures showed the rate of patients that moved from the diagnosis of UPD to that of BPD was 12.5%–30%, depending on the length of observation and the definition of BPD (Angst et al., 2003). Besides, underdiagnosis or overdiagnosis of BPD was also common in this study and other reports (Lopez et al., 2008; Zimmerman et al., 2010). Therefore, it is reasonable and necessary to further confirm the diagnosis by follow-up visits.

This study's findings about the clinical distinctions between BPD and UPD were mostly in line with previous studies (Akiskal and Benazzi, 2008; Goldberg et al., 2009; Oswald et al., 2007; Perlis et al., 2006). However, this study took a further step to find out to what extent these distinctions can predict BPD or UPD, which was more practical in guiding the diagnosis of BPD and UPD. Moreover, only six variables (only five if BPDI and BPDII were separately calculated) were involved in the predictive model, making data collecting more economic and easier. Compared with the previous model (Akiskal et al., 1995; Perlis et al., 2006), the predictive power of this model was a little smaller. One possible explanation is that Perlis's study only involved subjects with BPDIin their BPD group, while most cases in the BPD group of this study were patients with BPDII. As this study and other research (Akiskal et al., 1995) showed,

Table 3
Stepwise forward logistic regression model for BPD, BPD, or BPDII versus UPD.

	Independent variables	B	Wald	P value	OR
Model 1	Age of onset	−0.072	22.979	<0.001	0.930
(UPD vs. BPD)	Maximum duration of episode	−0.073	9.350	0.002	0.930
	Hypersomnia	1.405	6.113	0.013	4.077
	Somatalgia	−1.381	10.810	0.001	0.251
	Diurnal of mood	−0.719	4.879	0.027	0.487
	Irritability	1.113	11.485	0.001	3.043
	Constant	2.938	26.967	<0.001	18.887
Model 2					
(UPD vs. BPI)	Trigger factors	−1.413	4.502	0.034	0.243
	Age of onset	−0.070	5.8302	0.016	0.933
	Maximum duration of episode	−0.195	8.346	0.004	0.822
	Hypersomnia	2.404	9.524	0.002	11.0683
	Irritability	1.562	7.208	0.007	4.770
	Constant	1.215	1.5298	0.216	3.372
Model 3					
(UPD vs. BPII)	Age of onset	−0.089	29.131	<0.001	0.915
	Maximum duration of episode	−0.069	7.854	0.005	0.9335
	Diurnal of mood	−0.973	8.024	0.005	0.378
	Irritability	1.047	9.129	0.003	2.849
	Somatalgia	−1.129	6.382	0.012	0.3239
	Constant	3.590	33.481	<0.001	36.216

subjects with BPDIIwere more difficult to be distinguished from UPD than those with BPDI; meanwhile, the previous models included too many variables (12 variables in Perlis's study and 23 in Akiska's study), and many of them had to be collected through questionnaires. Such increase in the predictive power was at the cost of more effort in collecting information.

It has been a controversial topic about the association of atypical features of depression and BPD. In this study, on one hand, some atypical features like hypersomnia, irritability were found to be strongly associated with BPD, consistent with previous studies (Akiskal and Benazzi, 2005); on the other hand, not every atypical feature, e.g. weight gain, had such association, in line with the study by Seemuller et al. (2008). Differences in sample and methodology may contribute to these contrary results, since in this study, the prevalence of weight gain was so low that the small sample size of this study might not be big enough to detect their difference; while in Seemuller's study, diagnosis without validation by follow-up might make underdiagnosis of BPD highly possible (Ghaemi et al., 2000). Another explanation for this might be the continuous distribution of atypical features between depression and BPD (Akiskal and Benazzi, 2008). Whatsoever, the abovementioned results suggest that caution should be exercised when distinguishing depression and BPD by atypical depressive symptoms.

It is widely acknowledged that subjects with BPD have an earlier age at first onset than those with UPD (Benazzi, 2006; Goldberg et al., 2009; Oswald et al., 2007; Perlis et al., 2006). But when it comes to classification, the problem is what the cut-off point is. An international survey found a mean age at onset of 18.1 for the US cohort of patients with bipolar disorder, versus 25.6 for the US cohort of patients with unipolar depressive disorder (Weissman et al., 1996). Therefore, 25 years old was

Table 4
Optimal cut-off values by maximizing Youden index and their accuracies for BPD derived from whole study population and validated with 100-fold bootstrap.

	Prediction for BPD		Prediction for BPI		Prediction for BPII	
	Value	95% CI	Value	95% CI	Value	95% CI
Total study population						
Optimal cut-off	0.68	0.30	0.46			
Sensitivity	0.75	0.65–0.93	0.86	0.72–1.00	0.85	0.62–0.93
Specificity	0.83	0.63–0.92	0.86	0.67–0.99	0.65	0.60–0.90
PPV	87 %	79%–93%	68 %	47%–96%	75 %	67%–91%
NPV	67 %	63%–87%	95 %	89%–100%	78 %	64%–89%
PLR	4.26	2.45–9.36	5.94	2.93–45.09	2.43	2.10–6.57
NLR	0.31	0.10–0.40	0.16	0.00–0.32	0.23	0.11–0.43
100 fold bootstrap						
AUC	0.85	0.80–0.90	0.93	0.87–0.98	0.82	0.75–0.89
CPR	78 %	75%–86%	86 %	75%–96%	76 %	72%–82%

Note: PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative predictive ratio; AUC: area under curve; CPR: correct prediction rate.

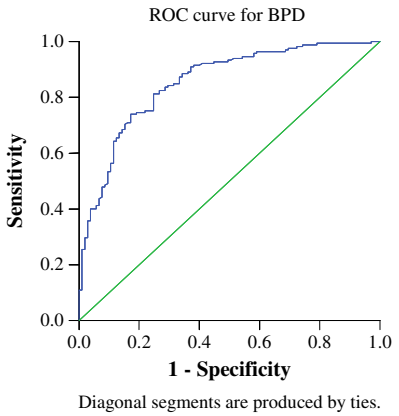

Fig. 1. ROC curve for model 1 (UPD versus BPD).

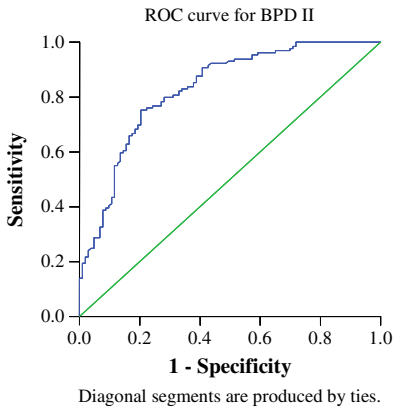

Fig. 3. ROC curve for model 3 (UPD versus BPD II).

generally used as the cut-off point of age at first onset to distinguish BPD from UPD. But in China, such epidemic survey is not yet available. From the perspective of statistical analysis, 28.5 years old was chosen as the cut-off point in this study. Whether this finding can be generalized to the whole Chinese population is still unclear considering the small sample size and its limited representativeness. As for the index depressive episode duration, this study suggested that bipolar depressions were shorter than unipolar depression, consistent with previous several studies (Furukawa et al., 2000; Mitchell et al., 1992; Roy-Byrne et al., 1985). Nevertheless, two large scale studies found no difference between unipolar and bipolar depression in episode length (Coryell et al., 1987; Kessing and Mortensen, 1999).The differences might be due to changes in episode length over time (Berghofer et al., 1996). Besides, this study only observed the maximum duration of depressive episode, which might be one of the reasons why the cut-off point of episode length in this study was longer than that reported byAkiskal and Benazzi (2005). The retrospective way the data about episode length was collected might be another reason.

There are several limitations in this study. First, the follow-up period is relatively short, especially for those at their first depressive episode. Second, selection bias is inevitable because the sample of our patients consisted mainly of those from Southern China. Such a sample may not be representative for Chinese depressive patients in general. In addition, the high expulsion rate might also contribute to the selection bias, although it seemed to have little impact on the predictive model since no significance was found in the distribution of the six variables included in the logistic model between the dropout group and the rest. Third, information on the anti-depressant drug used for treatment was not obtained during our study period, so the predictive value of a certain anti-depressant drug cannot be inferred in this study.

In conclusion, a predictive model with six clinical characteristic variables including age at first onset, maximum duration of depressive episodes, somatalgia, hypersomnia, diurnal variation of mood, and irritability, may be feasible and reliable to predict BPD from MDD in Chinese patients with current depression episode.

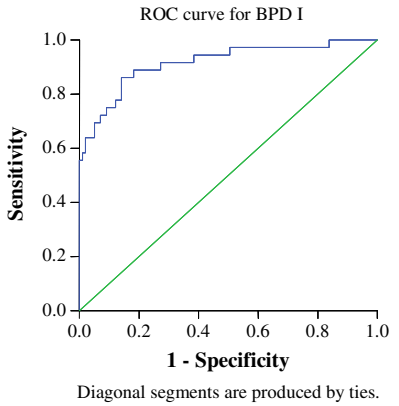

Fig. 2. ROC curve for model 2 (UPD versus BPD I).

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Conflict of interest

None to declare.

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