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The association between low-grade inflammation and the clinical features of bipolar disorder in Han Chinese population

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ABSTRACT

Variety of evidence suggests that low-grade inflammation may be involved in the pathophysiology of bipolar disorder (BD). However, the conclusion regarding the relationship between inflammation and BD has been inconsistent. In this study, we aimed to survey the prevalence of low-grade inflammation in a large Han Chinese population with BD and assess its impact on the clinical features of BD.

430 eligible cases were drawn from patients who were admitted or had ever been admitted for BD to the inpatient service of the psychiatric department of the Third Hospital of Sun Yat-sen University. Subjects with current active physical diseases or white blood count (WBC) > 19.0×10^9/L (2 times the upper reference) were excluded. Serum C-reactive protein (CRP) levels and WBC were measured with fast blood sample. Low-grade inflammation was defined as CRP > 3 mg/L or WBC > 9.5×10^9/L(the upper reference). Clinical features of BD were collected through semi-structural interview conducted by trained interviewers with background of psychiatric education.

If defined as CRP > 3 mg/L, the prevalence of low-grade inflammation among BD was 10.1% (41/404), it was positively associated with BMI ($p = 0.012$), comorbidity of glycolipid metabolic diseases($p = 0.018$). After adjusting for BMI, it was found to be positively related to recent suicide attempt ($p = 0.03$), initiation with (hypo)manic episode($p = 0.047$), leaden paralysis ($p = 0.037$) and family history of mental disorders ($p = 0.012$), while the association between comorbidity of glycolipid metabolic diseases and low-grade inflammation disappeared ($p = 0.330$). If defined as WBC > 9.5×10^9/L, the prevalence of low-grade inflammation was 8.1% (33/409), it was positively associated with psychotic features ($p = 0.011$) and adverse life events before the onset of illness($p < 0.001$), but was not significantly influenced by BMI ($p = 0.077$).

A much lower prevalence of low-grade inflammation in BD is found among Han Chinese population than among western population. Low-grade inflammation of different definition impacts differentially on the clinical features of BD.

1. Introduction

Bipolar disorder(BD) is a common, debilitating, chronic psychiatric disease, affecting approximately 2% of the world's population (Merikangas et al., 2011). However, not much is known about its pathophysiology. Recently, a growing number of evidence indicates the involvement of immune and inflammatory pathway in BD. First, population-based cross-sectional studies have shown that higher comorbidity of metabolic syndrome, cardiovascular diseases and autoimmune diseases is found in BD compared to the general population (Osby et al., 2001; Ohaeri and Akanji, 2011; Weiner et al., 2011), implicating inflammation might be a common factor underlying both these comoribid medical diseases and BD. Further evidence stems from prospective studies showing that increased inflammatory markers during pregnancy or in childhood are associated with higher risk of developing symptoms of depression and mania subsequently in adulthood (Hayes et al., 2017; Khandaker et al., 2014, 2018). More direct evidence is that pro-inflammatory cytokines, such as soluble interleukin (IL)-2 receptor, IL-6, tumor necrosis factor-alpha (TNF-a) and C-reactive protein (CRP) are frequently reported to increase in BD (Tsai et al., 2017a; Uyanik et al., 2015; Brietzke et al., 2009; Barbosa et al., 2012; Bai et al., 2014; Cunha et al., 2008a, 2008b; Luo et al., 2016; Bai et al., 2015a) and decrease after treatment (Uyanik et al., 2015; Brietzke et al., 2009). Finally, non-steroidal anti-inflammatory drugs (NSAIDs)

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and cytokine inhibitors are found to help improve depressive symptoms in patients with depression as an adjunctive treatment (Kohler-Forsberg et al., 2017) and reduce the severity of depressive symptoms in patients with chronic inflammatory illness independently of improvement in physical illness (Kappelmann et al., 2018).

However, not all individuals with BD show evidence of inflammation. For example, only 19–47% patients with mood disorders show elevated CRP according to previous studies (Cizza et al., 2009; Raison et al., 2013; Rethorst et al., 2014; Uher et al., 2014; Wysokiński et al., 2015; Osimo et al., 2018). In addition, although case-control studies show a higher level of pro-inflammatory cytokines in BD than in healthy control, these studies do not tell to what extent the pro-inflammatory cytokines increase that has clinical meaning, especially when inconsistency regarding the difference in pro-inflammatory cytokines between BD and control is commonly seen in previous reports (Sayana et al., 2017; Munkholm et al., 2013). Finally, not all inflammatory biomarkers are elevated in patients with BD who show some evidence of inflammation (Barbosa et al., 2013, 2011; Bai et al., 2015b). Therefore, we hypothesis that inflammation only exist in some specific subpopulation of BD, and the relationship between inflammation and BD, to some extent, depends on how we define inflammation. In this study, we are going to survey the prevalence of low-grade inflammation defined by CRP or white blood count (WBC) in BD among Han Chinese population, and then assess its impact on the clinical features of BD. To our knowledge, no similar study has been done before.

2. Methods and subjects

2.1. Subjects

Cases were drawn from patients who were admitted or had ever been admitted for mood disorders to the inpatient service of the psychiatric department of the Third Affiliated Hospital of Sun Yat-sen University between July 1, 2012 and February 1, 2018. Potential participants were recommended by their treating psychiatrists and then screened with the 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). Eligible participants met the DSM-IV-TR criteria for BD. Patients with evidence of organic mental disorder were excluded. Patients who were pregnant or under steroidal or non-steroidal anti-inflammatory drugs treatment were also excluded. All the subjects were Han Chinese, aged 18 or above, had no current active physical diseases confirmed by routine clinical examination, and provided written informed consent. Totally, 430 eligible cases were recruited in this study, including 374 (87.0%) inpatients and 56 (13.0%) outpatients; 250 (58.1%) were female; 138 (32.1%) had never received any psychopharmaceutical treatment, 137 (31.9%) had not received any psychopharmaceutical treatment within 3 months prior to recruitment, and the rest (36.0%) had been under some kind of psychopharmaceutical treatment within three months prior to recruitment (detailed information was listed in the footnote of Table 1) ; the average age was 27.5 ± 11.7years. This study was reviewed and approved by the Clinical Research Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University.

2.2. Measurements

2.2.1. Definition of low-grade inflammation

In this study, we defined low-grade inflammation as a serum CRP levels > 3 mg/L.This definition originated from the US Centers for Diseases Control and Prevention and American Heart Association Guideline, which considered CRP levels over 3 mg/L as to be high (Pearson et al., 2003; Ridker, 2003). Subsequent studies further find that such CRP levels are associated with increased risk of cardiovascular diseases (Fabijanic et al., 2006) and schizophrenia (Metcalf et al., 2017). Therefore, it is well recognized and applied as the cut-off point of low-grade inflammation in later studies (Wium-Andersen et al., 2013; Osimo et al., 2018). Moreover, plenty of studies show higher CRP in BD than healthy control (Bai et al., 2015b; Aksoy et al., 2010; Cunha et al., 2008a, 2008b; Dickerson et al., 2015; De Berardis et al., 2008), indicating it is a reliable and sensitive biomarker of inflammation in BD. In addition, we also used total WBC to define low-grade inflammation. Although it is one of the most commonly checked markers of inflammation in routine clinical practice, only limited studies have demonstrated that elevated WBC is associated with BD (Merikangas et al., 2011) or some specific features of BD, such as mood symptom severity (Köhler et al., 2017). Different from Osimoa's study using the third quartile of the distribution of WBC in his sample as the cut-off point of low-grade inflammation, we defined low-grade inflammation as WBC $> 9.5 \times 10^9$/L, the upper reference of WBC. We selected such cut-off point based on the following reasons: first, it seems to be artificial to infer low-grade inflammation when WBC still falls in the normal reference; second, it is unreasonable to use the third quartile of the distribution of WBC as the cut-off point of low-grade inflammation in a sample which only comprises of cases. For example, if we used the third quartile of the distribution of WBC in our sample as the cut-off point of low-grade inflammation, the prevalence of low-grade inflammation would reach 25%, much higher than that defined as serum CRP level > 3 mg/L (10.1%). In addition, to make sure WBC $> 9.5 \times 10^9$/L represent low-grade inflammation instead of high inflammation, subjects with current active physical diseases were excluded in this study, and subjects with WBC $> 19.0 \times 10^9$/L (2 times the upper reference) were also excluded.

2.2.2. Measurement of CRP and WBC

The fasting blood samples were collected between 7:00 AM and 9:00 AM. For inpatient cases, blood drawing was arranged on the next day after admission. All the blood samples were sent to the clinical laboratory of the Third Affiliated Hospital of Sun Yat-sen University to have CRP and WBC measured within 2 h after the blood was drawn. Plasma levels of CRP were measured by immune transmission turbidimetry with a biochemical analyzer (Nippon ihua co., Ltd, Tokyo, Japan). WBC was analyzed in a automated blood cell counter (Hiesen Mikang co., Ltd, Kōbe, Japan).

2.2.3. Assessment of clinical characteristics of BD

General sociodemographic and clinical characteristics were collected via a questionnaire designed by the researchers. Severity of the current episode were evaluated with the 17-item Hamilton Depression Scale (HAMD-17) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). Atypical features were assessed by the corresponding section of the Chinese version of SCID-I (So et al., 2003) based on the patients' most severe depressive episode they had ever experienced. Psychotic features were assessed by evaluating whether the participants demonstrated any of the psychotic symptoms, including hallucination, delusion or disorganized behavior in the course of illness. Diagnosis of mental comorbidities was made according to the DSM-VI-TR based on the subjects' history of present illness and routine mental examination. Physical comorbidities were confirm

ed by reviewing the patients' previous medical history and medical records stored in our hospital's electronic medical system. History of adverse life events before the onset of BD was collected based on the subjects' self-report and brief assessment on their growth experience and family environment, when events of congenital or acquired physical disabling, being sexually abused, parents' divorce, death of loved ones, severe frustration in career development, and poverty in their childhood, were especially paid attention to since these adverse life events had been reported to be associated with the onset of BD (Paksarian et al., 2015; Bergink et al., 2016; Moraes et al., 2017; Daruy-Filho et al., 2011; Bohman et al., 2017). If a subject had experienced any of the above-mentioned adverse life events, the history of adverse

Table 1
The prevalence of low-grade inflammation among BD.

Demographic and other characteristics	CRP levels > 3 mg/L (N = 404)			WBC > 9.5 × 109/L (N = 409)		
	%(n/N)	P	OR(95%CI)	%(n/N)	P	95%CI
Gender						
Male	11.3(19/168)	0.515	1.240 (0.649-2.372)	8.2(14/171)	0.940	1.028(0.500-2.112)
Female	9.3(22/236)			8.0(19/238)		
Age (year)						
< =20	9.9(13/131)	0.822	0.948(0.597-1.506)	9.0(12/134)	0.819	0.943(0.571-1.556)
20-40	11.3(24/212)			7.0(15/213)		
40-60	6.0(3/50)			11.1(6/54)		
> 60	14.3(1/7)			0.0(0/8)		
Education (year)	N = 387[a]	0.730	1.068(0.734-1.555)	N = 393[a]	0.056[*]	0.695(0.478-1.010)
< = 6	11.8(2/17)			15.8(3/19)		
6-9	10.1(8/79)			12.8(10/78)		
9-12	8.6(11/128)			7.1(9/126)		
> 12	11.7(19/163)			6.5(11/170)		
Marital status	N = 388[a]			N = 395[a]		
Never married	11.1(28/253)	0.704	reference	8.6(22/255)	0.920	reference
married	8.4(10/119)	0.860	0.871(0.188-4.034)	8.1(10/123)	0.696	1.511(0.191-11.937)
Ever-married[b]	12.5(2/16)	0.591	0.642(0.127-3.235)	5.9(1/17)	0.748	1.416(0.170-11.811)
Pharmaceutical treatment						
Under treatment	13.2(20/151)[d]	0.114	1.687(0.882-3.227)	8.4(13/155)[e]	0.853	1.071(0.517-2.220)
Without treatment	8.3(21/253)[f]			7.9(20/254)[g]		
BMI[c](mean ± SD)	21.5 ± 3.6 (N = 336)[a]	0.012[**]	1.128(1.027-1.240)	21.5 ± 3.6 (N = 342)[a]	0.077[*]	1.094 (0.990-1.209)

[a] Number of subjects with data available to be analyzed.
[b] Including widowed, divorced, and remarried.
[c] BMI: body-mass index.
[d] 151 participants had been under psychopharmaceutical treatment within 3 months prior to recruitment, including 8 under escitalopram, 9 under venlafaxine, 8 under paroxetine, 5 under duloxetine, 5 under fluoxetine,. 5 under mitrazapine, 12 under sertraline, 3 under bupropion, 58 under Quetiapine, 9 under parpiperazone, 4 under clozapine, 4 under risperdone, 21 under olanzapine, 2 under amisulpride, 57 under sodium valproate, 9 under lamotrigine, 10 under oxcarbazepine, 31 under lithium, 83 under benzodiazepine.
[e] 155 participants had been under psychopharmaceutical treatment within 3 months prior to recruitment, including 10 under escitalopram, 9 under venlafaxine, 8 under paroxetine, 5 under duloxetine, 5 under fluoxetine,. 5 under mitrazapine, 12 under sertraline, 4 under bupropion, 61 under Quetiapine, 9 under parpiperazone, 4 under clozapine, 4 under risperdone, 24 under olanzapine, 2 under amisulpride, 54 under sodium valproate, 9 under lamotrigine, 10 under oxcarbazepine, 33 under lithium, 81under benzodiazepine.
[f] 253 participants did not receive any pharmaceutical treatment currently, including 138 had never received any psychopharmaceutical treatment in their lives, and 115 had not received any psychopharmaceutical treatment within 3 months prior to recruitment.
[g] 254 participants did not receive any pharmaceutical treatment currently, including 138 had never received any psychopharmaceutical treatment in their lives, and 116 had not received any psychopharmaceutical treatment within 3 months prior to recruitment.
* $p < 0.10$.
** $P < 0.05$;***: $p < 0.05/6 = 0.0083$ (required significance level after Bonferroni correction for 6 multiple testing).

life events was coded as positivity, otherwise as negativity. Family history of mental disorders was assessed by asking the subjects or their accompanied relatives whether there was any family member with mental disorder of any kind in their first or second-degree relatives. All the above-mentioned interviews were conducted by trained psychiatrists in our study team.

2.3. Statistic analysis

Both CRP and WBC were treated as binary categorical variables based on the above-mentioned cut-off point. The prevalence of low-grade systematic inflammation was calculated according to its definition. Potential clinical features that might be associated with low-grade systematic inflammation were selected by univariate binary logistic regression with CRP or WBC as dependent variable and each clinical feature of BD as independent variable. To make sure all the potential clinical features associated with low-grade inflammation were figured out, variables with $p < = 0.10$ were considered significant. Then, multivariate logistic regression was performed to further examine these potential inflammation-related clinical features by adjusting for potential confounding factors. The final result was considered significant at $P < 0.05$ and corrected for multiple testing using a Bonferroni correction. Odds ratios and 95% confidence intervals were used to quantify the strength of associations. All data was analyzed using commercial statistical package SPSS 19.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. The association between CRP and WBC

383 participants with data on both CRP and WBC were available here. The Spearman correlation analysis using both CRP and WBC as continuous variables shown that they were significantly correlated ($p = 0.001$, $r = 0.168$). Univariate binary logistic regression using CRP as a binary dependent variable (> 3 mg/L VS. ≤ 3 mg/L) and WBC as a binary independent variable ($> 9.5 \times 10^9$/L VS. $\leq 9.5 \times 10^9$/L) also demonstrated they were significantly associated ($p = 0.018$, OR = 3.053, 95%CI = 1.216–7.667).

3.2. The prevalence of low-grade inflammation

First, we calculated the prevalence of low-grade inflammation among BD with different definition. Our results shown that if defined as serum CRP levels > 3 mg/L, the prevalence of low-grade inflammation in our sample was 10.1% (41/404), while if defined as WBC $> 9.5 \times 10^9$/L, it was 8.1% (33/409). As seen in Table 1, the prevalence of low-grade inflammation, no matter in which definition, did not significantly vary with gender, age, and marital status

(p > 0.10).There was a trend that the prevalence of low-grade inflammation (defined as WBC > 9.5 × 10^9/L) decreased with education levels, but did not reach significance (p = 0.056). A larger effect was found (p = 0.044, OR = 0.468, 95%CI = 0.223-0.981) when treating education levels as a binary variable with 9 years of education as the cut-off point (equivalent to finishing basic compulsory education in China). However, the effect of education became non-significant after correcting for BMI (p = 0.350). Further analysis found that BMI was significantly associated with the prevalence of low-grade inflammation defined by CRP (p = 0.012, OR = 1.128, 95%CI = 1.027–1.240), but not that defined by WBC (p = 0.077, OR = 1.094, 95%CI = 0.990–1.209). In addition, compared to those without pharmaceutical treatment, patients under pharmaceutical treatment had a slight higher prevalence of low-grade inflammation (defined by CRP levels) (13.2% VS. 8.3%), but did not reach significance. Even after controlling for BMI, the effect of pharmaceutical treatment on the prevalence of low-grade inflammation was still not significant (p = 0.219, OR = 1.564, 95%CI = 0.766–3.192).

3.3. The association between comorbidities and the low-grade inflammation

We looked next at the association between comorbidities and the low-grade inflammation among BD. We first regressed each comorbidity on the presence of low-grade inflammation. The results were listed in table2. We found that patients with comorbidity of glycolipid metabolic diseases were more likely to be inflamed (defined as CRP levels > 3 mg/L), and subjects with recent failed suicidal attempt showed a trend for higher prevalence of low-grade prevalence (defined as CRP levels > 3 mg/L). However, after adjusting for BMI and pharmaceutical treatment, the association between glycolipid metabolic diseases and inflammation was no longer significant (p = 0.330), while the effect of recent suicidal attempt on inflammation became more obvious (p = 0.030, OR = 5.077, 95%CI = 1.168–22.077), but did not withstand sequential Bonferroni correction for multiple testing at the significance level of 0.0045 (0.05/11). No significant association was found between the above-mentioned comorbidites and the WBC-defined inflammation(p > 0.10).

3.4. The association between low-grade inflammation and the characteristics of the course of BD

We further examined the impact of low-grade inflammation on the characteristic of the course of BD. Only initiation with (hypo)manic episode was found to be slightly associated with higher risk of low-grade inflammation (defined as CRP levels > 3 mg/L) when compared to initiation with depressive episode (p = 0.051), and the association became more significant after correcting for BMI (p = 0.047, OR = 2.367, 95%CI = 1.012–5.537), but still did not withstand sequential Bonferroni correction for multiple testing at the significance level of 0.0042 (0.05/12). Apart from that, no significant effect of low-grade inflammation, no matter in which definition, was found on the characteristics of the course of BD, including onset age, number of episodes of any kind, duration of the longest episodes of any kind, duration of current episode, rapid cycling and total duration of illness (p > 0.10) (seen in Table 3).

3.5. The association between low-grade inflammation and the symptomatic features of BD

Subsequently, we assessed the effect of low-grade inflammation on the symptomatic features of BD. If defined by serum CRP levels, the low-grade inflammation was found to be positively associated with Leaden paralysis (p = 0.023, OR = 2.185, 95%CI = 1.113–4.287), and the association remained significant (p = 0.037) even after controlling for BMI and pharmaceutical treatment, but did not withstand sequential Bonferroni correction for multiple testing at the significance level of 0.0033 (0.05/15). If speaking in terms of WBC, the low-grade inflammation was discovered to be marginally related to mood reactivity (p = 0.058, OR = 0.491,95%CI = 0.235–1.024) but positively associated with psychotic features (p = 0.011,OR = 2.617, 95%CI = 1.245–5.500). The relationship between low-grade inflammation and mood reactivity became weaker (p = 0.074) after

Table 2
The association between comorbidities and the prevalence of low-grade inflammation among BD.

Comorbidities	CRP levels > 3 mg/L (N = 401)			WBC > 9.5 × 109/L (N = 404)		
	%(n/N)	P	OR(95%CI)	%(n/N)	P	OR(95%CI)
physical comorbidites						
Inflammatory or Autoimmune disease[a]	7.0(5/71)	0.344	0.625(0.236-1.653)	10.7(8/75)	0.359	1.481(0.640-3.425)
Cyst or hyperplasia[b]	13.5(7/52)	0.399	1.455((0.609-3.477)	5.6(3/54)	0.473	0.639(0.188-2.172)
Thyroid diseases[c]	0.0(0/18)	0.998	0.000(0.000-∞)	5.9(1/17)	0.739	0.705(0.091-5.490)
Glycolipid metabolic diseases[d]	25.0 (6/24)	0.018**	3.286(1.224-8.818)	11.5(3/26)	0.502	1.539(0.437-5.424)
Cardiovascular diseases[e]	9.5(2/21)	0.922	0.928(0.208-4.137)	9.1(2/22)	0.854	1.152(0.257-5.157)
Mental comorbidities						
OCD	11.1(3/27)	0.864	1.115(0.321-3.877)	7.1(2/28)	0.855	0.871(0.197-3.843)
Anxiety disorders[f]	5.6(1/18)	0.517	0.509(0.066-3.926)	0.0(0/18)	0.998	0.000(0.000-∞)
Eating disorders[g]	16.7(2/12)	0.667	1.307(0.386-4.425)	10.0(1/10)	0.976	1.026(0.191-5.501)
Somatoform disorders	17.2(5/29)	0.406	0.421(0.055-3.246)	6.7(2/30)	0.773	0.804(0.183-3.535)
Attempted suicide[h]	30.0 (3/10)	0.051*	4.015((0.997-16.172)	10.0(2/10)	0.179	2.976 (0.605-14.625)
Psychoactive substance abuse[i]	8.7(2/23)	0.812	0.835(0.189-3.697)	12.0(3/25)	0.458	1.614(0.457-5.703)

***: p < 0.05/11 = 0.0045 (required significance level after Bonferroni correction for 11 multiple testing).
[a] Including all kinds of asymptomatic infectious diseases, allergic rhinitis, urticaria, eczema, psora, asthma, and irritable bowel syndrome.
[b] Including all the benign cyst, nodule, polyp and well-healed cancer.
[c] Including Grave's diseases, thyroiditis, thyroid cyst, thyroid nodule, thyroid cancer., primary hypothyroidism.
[d] Including diabetes mellitus, impaired glucose tolerance, and hepatic adipose infiltration.
[e] Including hypertension, lacunar cerebral infarction, aneurism, phlebangioma, atherosclerosis, and varicosity.
[f] Including panic disorder, generalized anxiety disorder, and social phobia.
[g] Including bulimia nervosa and anorexia nervosa.
[h] Failed suicide attempt in the last two weeks.
[i] Including 5 with ever psychoactive substance abuse and 17 with current cigarette or alcohol abuse.
* p < 0.10.
** P < 0.05.

Table 3
The association between low-grade inflammation and the characteristics of the course of BD.

Characteristics of the course	CRP levels > 3 mg/L (N = 404)			WBC > 9.5 × 10^9/L (N = 409)		
	%(n/N)	P	OR(95%CI)	%(n/N)	P	OR(95%CI)
Onset age (mean ± SD) (year)	23.0 ± 11.4	0.828	0.997(0.997-1.028)	22.8 ± 11.2	0.883	0.998(0.965-1.031)
Sate of first episode	N = 387[c]			N = 393[c]		
Depressive	7.3 (14/191)	0.139	reference	9.4(18/192)	0.605	reference
(hypo)manic	14.6(15/103)	0.051*	2.155 (0.996-4.663)	8.9 (9/101)	0.896	0.946(0.409-2.188)
mixed	11.8 (11/93)	0.213	1.696 (0.738-3.897)	6.0 (6/100)	0.323	0.617(0.237-1.607)
Number of depressive episodes Median (min-max)	1.0(0-90)	0.915	1.003 (0.948-1.062)	2.0(0-90)	0.631	0.969(0.851-1.103)
Duration of depressive episode[a] (mean ± SD) (day)	186.8 ± 321.0	0.668	1.000 (0.999-1.001)	196.2 ± 345.7	0.664	1.000(0.998-1.001)
Number of (hypo)manic episodes Median (min-max)	1.0(0-90)	0.663	1.008 (0.972-1.045)	1.0(0-90)	0.856	1.004(0.962-1.048)
Duration of (hypo)manic episode[a] (mean ± SD) (day)	153.1 ± 2545.4	0.263	1.001 (0.999-1.003)	135.4 ± 198.1	0.103	0.996(0.992-1.001)
Number of mixed episode Median (min-max)	1.0(0-6)	0.102	1.319 (0.947-1.837)	1.0(0-6)	0.888	0.967(0.606-1.543)
Duration of mixed episode[a] (mean ± SD) (day)	550.6 ± 1012.1	0.184	0.999 (0.998-1.000)	565.0 ± 1058.0	0.987	1.000(0.999-1.000)
Duration of current episode (mean ± SD) (day)	338.78 ± 739.4	0.227	0.999 (0.998-1.000)	345.0 ± 769.2	0.707	1.000(0.999-1.000)
Rapid cycling[b]	7.8(4/51) (N = 375)[c]	0.485	0.681 (0.232-2.001)	10.9(6/55) (N = 381)[c]	0.419	1.474(0.575-3.777)
Duration of illness Median (min-max) (year)	2.5(0.02-38)	0.195	1.030 (0.985-1.077)	3.0(0.02-38)	0.521	1.018(0.965-1.073)
History of postpartum episode	7.2(2/22) (N = 78)[d]	0.772	1.300 (0.221-7.663)	8.7(2/23) (N = 81)[d]	0.557	1.746(0.272-11.199)

P < 0.05;*: p < 0.05/12 = 0.0042 (required significance level after Bonferroni correction for 12 multiple testing).
[a] Based on the longest episode the patient had ever experienced.
[b] Defined as ≥4 episodes /year.
[c] Number of subjects with data available to be analyzed.
[d] Only female subjects who had given birth were included in the analysis.
* p < 0.10.

Table 4
The association between low-grade inflammation and the symptomatic features of BD.

Symptomatic features	CRP levels > 3 mg/L (N = 404)			WBC > 9.5 × 109/L (N = 409)		
	%(n/N)	P	OR(95%CI)	%(n/N)	P	OR(95%CI)
Atypical feature	N = 388[a]			N = 393[a]		
Mood reactivity	9.2(25/273)	0.517	0.791(0.389-1.607)	6.4(18/280)	0.058*	0.491(0.235-1.024)
Increased appetite	10.7(9/84)	0.749	1.138(0.516-2.508)	9.6(8/83)	0.570	1.276(0.551-2.953)
Weight gain	12.5(8/64)	0.427	1.400(0.610-3.213)	8.2(5/61)	0.981	1.012(0.374-2.739)
hypersomnia	12.5(13/104)	0.280	1.480(0.727-3.213)	7.1(7/98)	0.683	0.834(0.349-1.993)
Leaden paralysis	14.5(20/138)	0.023**	2.185(1.113-4.287)	8.9(12/135)	0.688	1.166(0.552-2.463)
Reject sensitivity	11.1(21/189)	0.405	1,331(0.679-2.609)	6.9(13/188)	0.396	0.727(0.349-1.517)
Psychotic feature	8.3(7/84)	0.537	0.765(0.326-1.792)	14.8(13/88)	0.011**	2.617(1.245-5.500)
Current episode	N = 399[a]			N = 404[a]		
remission	13.0 (6/46)	0.906	reference	4.3(2/46)	0.245	reference
depressive	9.4(17/181)	0.466	0.691(0.256-1.865)	10.7(19/177)	0.202	2.646(0.593-11.796)
(hypo)manic	11.1(4/36)	0.791	0.833(0.216-3.208)	11.4(4/35)	0.245	2.839(0.489-16.475)
Mixed	10.3(14/136)	0.607	0.765(0.276-2.123)	5.5(8/146)	0.764	1.275(0.261-6.230)
HAMD-17 total scores (mean ± SD)	18.4 ± 9.4	0.696	1.007(0.973-1.041)	17.9 ± 9.6	0.487	1.013(0.976-1.053)
HAMD-anxiety somatization (mean ± SD)	4.8 ± 3.3	0.435	1.039(0.944-1.142	4.7 ± 3.3	0.818	0.987(0.887-1.100
HAMD-cognitive deficit (mean ± SD)	18.4 ± 9.4	0.443	1.050(0.92-1.191)	3.8 ± 2.6	0.249	1.085(0.945-1.246)
HAMD-retardation (mean ± SD)	5.3 ± 3.1	0.810	0.987(0.890-1.095)	5.2 ± 3.1	0.416	1.047(0.937-1.169)
HAMD-weight loss (mean ± SD)	0.3 ± 0.6	0.986	0.995(0.577-1.717)	0.3 ± 0.6	0.860	0.946(0.507-1.765)
HAMD-sleep disturbance (mean ± SD)	2.7 ± 2.1	0.918	1.008(0.866-1.173)	2.8 ± 2.1	0.303	1.092(0.924-1.290)
YMRS total score(mean ± SD)	11.1 ± 10.4	0.833	1.003(0973-1.173)	11.4 ± 10.4	0.710	1.006(0.973-1.041)

[a] Number of subjects with data available to be analyzed.
* p < 0.10.
** P < 0.05;***: p < 0.05/15 = 0.0033 (required significance level after Bonferroni correction for 15 multiple testing).

adjusting for BMI and pharmaceutical treatment, while the association between inflammation and psychotic features were more significant (p = 0.008, OR = 2.962, 95%CI = 1.335–6.572) after correcting for BMI and pharmaceutical treatment, but still did not withstand sequential Bonferroni correction for multiple testing at the significance level of 0.0033 (0.05/15). Other than these symptoms, no other symptomatic features, including HAMD-17 or YMRS total scores, the 5 sub-domains scores of HAMD-17, weigh gain, increased appetite, reject sensitivity, hypersomnia, and states of current episode, were found to be associated with low-grade inflammation (p > 0.10) (seen in Table 4).

3.6. The difference in etiology between BD patients with and without low-grade inflammation

Finally, we explored whether there was any difference in etiology between BD patients with and without low-grade inflammation. We first compared the prevalence of the appointed adverse life events

between BD patients with and without low-grade inflammation. We found that there was no significant difference in the prevalence of adverse life events before the onset of illness between patients with and without low-grade inflammation defined by CRP (12.8% VS. 8.5%, $p = 0.439$), but if the low-grade inflammation was defined as WBC $> 9.5 \times 10^9$/L, the prevalence of adverse life events before the onset of illness was found to be higher in patients with low-grade inflammation than those without inflammation(27.3% VS. 7.4%, $p < 0.001$, OR = 4.674, 95%CI = 1.983–11.017), and the association became more significant ($p < 0.001$, OR = 5.447, 95%CI = 2.126–13.959) after controlling for BMI and pharmaceutical treatment. Then, we examined the difference in family history of mental disorders between patients with and without low-grade inflammation. If the low-grade inflammation was defined as CRP levels > 3 mg/L, it was found to be associated with a higher risk of family history of mental disorders (18.8%VS. 8.5%, $p = 0.024$, OR = 2.317, 95%CI = 1.115–4.815), and the effect was larger ($p = 0.012$, OR = 2.772, 95%CI = 2.550–6.417) after correcting for BMI. However, if the low-grade inflammation was defined as WBC $> 9.5 \times 10^9$/L, no significant difference was found (8.6% VS. 5.5%, $p = 0.378$).

4. Discussion

4.1. The prevalence of low-grade inflammation in BD

As previously expected, only a small percentage of BD (about 10%) is found to be associated with low-grade inflammation in our study. However, this prevalence is much lower than that reported in western countries (ranging from 28.2% to 40.4%) (Osimo et al., 2018; Wysokinski et al., 2015; Wium-Andersen and Nielsen, 2013; Wium-Andersen et al., 2016)(Wysokinski et al., 2015). Many factors might contribute to this difference: first, the participants in western studies are much older than the subjects in our study. For example, the average age of the participants in Osimo's study is 39 years and in Wysokiński's study is 50.3 years, while in our study, it is 27.5 years. Although no significant association is found between age and inflammation after excluding patients with active physical diseases in our study, if patients with comorbidity of active physical diseases were included, age was found to influence the prevalence of low-grade inflammation in Osimo's study (Osimo et al., 2018) and in general population (Wium-Andersen et al., 2016); second, all the participants had been stayed in hospital for a period of time and taking variety of medications in Osimo's study, while in our study, most of the participants were newly admitted to hospital. More importantly, more than 60% of the participants in our study were drug-naïve. Although anti-inflammatory effect has been reported in mood stabilizers, including lithium (Sluzewska et al., 1997), valproate (Yuen et al., 2010), and atypical antipsychotics (McNamara et al., 2011; Sobiś et al., 2015), both Osimo's study and our study show a trend for higher prevalence of low-grade inflammation among patients under pharmaceutical treatment compared to those without pharmaceutical treatment, implicating the effect of mood stabilizers on inflammation is more complicated than it seems to be. For example, it is well-known that lithium might lead to the increase of WBC, and atypical antipsychotics, especially at high dose, are reported to trigger inflammation (Meyer et al., 2009; McNamara et al., 2011). In addition, looser entry criteria might be another factor that leads to higher prevalence of inflammation in the western studies (Osimo et al., 2018) (Wysokinski et al., 2015), especially including patients with comorbidity of active physical diseases might be a major factor. Finally, difference in ethnicity might also play a part in the gap of prevalence of low-grade inflammation between the western studies and our study. Although no study has been done to compare the prevalence of low-grade inflammation between the westerners and the Orientals, Osimo's study (Osimo et al., 2018) suggests that ethnicity itself might lead to the difference in the prevalence of low-grade inflammation, and genetic studies (Reiner et al., 2012; Martinez-Calatrava et al., 2007; Dehghan et al., 2011) further confirm this view.

4.2. Clinical features associated with low-grade inflammation in BD

In this study, several clinical features of BD are found to be associated with low-grade inflammation. One is (Wium-Andersen and Nielsen, 2013; Queissner et al., 2018)recent suicide attempt, which is in line with Courtet's report (Courtet et al., 2015) that increased CRP levels are associated with a lifetime history of suicide attempt among depressed inpatients. Although only recent suicide attempt was paid attention to in this study, Courtet's study found that the increased CRP levels seemed to be independent of the time gap between suicide attempt and CRP sampling, and therefore was regarded as a trait marker for suicide vulnerability. On the contrary, in another study (Dickerson et al., 2017), inflammation, in terms of specific markers of gastrointestinal inflammation, was only found to be associated with recent suicide attempt but not a past suicide attempt history, while if in terms of CRP, inflammation was only found to be associated with a past, but not recent suicide attempt history. However, the small sample size and including all kinds of suicide attempt but not just actual suicide attempt in Faith Dickerson's study decrease its power of test (Dickerson et al., 2017).

A second clinical feature of BD that is found to be associated with low-grade inflammation in this study is adverse life events before the onset of illness, which is partly consistent with the finding from previous studies (Moraes et al., 2017; Danese et al., 2007) that childhood maltreatment is associated with adult inflammation. However, this association is found only when inflammation is defined by WBC. If inflammation is defined with CRP, the relationship between childhood maltreatment and inflammation is no more significant. A system review (Coelho et al., 2014) has pointed out that, in the previous studies, the conclusion regarding the relationship between childhood maltreatment and adult inflammation is inconsistent. Possible reason for this inconsistency may be lack of control for potential confounding factors. For example, in a cross-sectional study (Aas et al., 2017), the association between childhood maltreatment and inflammation among patients with schizophrenia or BD disappeared after controlling for BMI. However, in a study which examined the association between childhood maltreatment and inflammation with both CRP and WBC, increased WBC was more significantly related to childhood maltreatment than increased CRP (Danese et al., 2007). Combined with our finding, it is reasonable to believe that WBC is better than CRP to reflect the relationship between childhood maltreatment and inflammation among BD.

A third clinical feature of BD that is found to be associated with low-grade inflammation in this study is family history of mental disorders. More importantly, this association is found to be independent of BMI. As far as we know, no study has ever reported such association before. Considering heredity may play a role in the determination of CRP levels (Miljkovic et al., 2011; Lakka et al., 2006), we speculate that inherited increased CRP levels may be associated with susceptibility for mental disorders.

Other clinical features of BD that are found to be associated with low-grade inflammation in this study include initiation with (hypo) manic episode, leaden paralysis, and psychotic features. But these associations depend on how we define low-grade inflammation. If in terms of serum CRP levels > 3 mg/L, low-grade inflammation is positively associated with initiation with (hypo)manic episode and leaden paralysis. While if in terms of WBC $> 9.5 \times 10^9$/L, low-grade inflammation is positively associated with psychotic features. To our knowledge, this has not been examined before either. This differential effect means that using only CRP to define low-grade inflammation may not be enough to fully reflect the relationship between inflammation and BD, especially when the effect of BMI, a major confounding factor, is ignored. Thus part of the difficulty in finding consistent relationship between inflammation and BD may reflect difficulties in identifying

appropriate measures for analysis.

Contrary to previous studies reporting an association between elevated CRP and the number of affective episodes (Queissner et al., 2018), severity of current manic symptoms (Queissner et al., 2018; Dickerson et al., 2007; Tsai et al., 2017b), comorbid substance use disorder (Goldstein et al., 2015), longer illness duration (Goldstein et al., 2015) among BD, we do not find any association between low-grade inflammation and quantity of affective episodes, state or severity of current affective episode, comorbid substance use disorder and duration of illness in BD. In fact, inconsistence regarding the abovementioned relationships has been existed. For example, a meta-analysis (Fernandes et al., 2016) does not support the extent of the increases in CRP concentrations in mania and depression is related to symptom severity, the association between elevated pro-inflammatory markers and illness duration can not be replicated by several studies (Queissner et al., 2018; Tsai et al., 2001; Cetin et al., 2012).Furthermore, in Queissner's study, the correlation between levels of high-sensitive CRP and number of affective episodes is found only in female BD patients but not in male ones. Theses inconsistencies, on one hand, might be partly attributed to the differences in methods of study, such as strategies of sampling, indicators of inflammation, ways of statistics. On the other hand, these inconsistencies might reflect the heterogeneity of BD and the difficulty in finding a consistent, valid measure of inflammation.

4.3. Strengths and limitations

This study has several strengths. It comprises of one of the largest sample of BD patients ever examined. More importantly, all the subjects were Han Chinese, most of them were young and drug-naïve, and active physical diseases were excluded, which provided us a good sample with great homogeneity. In addition, as many clinical features of BD as possible were collected through face-to-face semi-structural interview by well-trained interviewers with clinical background to make sure the BD sample well-defined. Finally, all the blood samples were treated in the same way and in the same laboratory, thus minimized the effect of measurement deviation. However, our findings are subject to several limitations. First, its cross-sectional design limits causal conclusions regarding the relationship between inflammation and BD. Second, the clinical features of BD were reported retrospectively, therefore we can not rule out the possibility that biased recall shaped the pattern of results we have observed. Third, all kinds of adverse life events before the onset of illness were combined together in our study, therefore we can not tell which kind of adverse life event, when they happen in life, and how serious they are do really matter in the process of inflammation. Fourth, the family history of mental disorders was reported by the participants or their healthy family members, we can not estimate how valid the diagnosis in the relatives is. Correspondingly, we treated the family history of mental disorders as a binary categorical variable, which may cause unspecific error in estimates of the effect size that we observe. Fifth, distinction was not make between current and past parameters for some clinical features, such as atypical features, psychotic features. Although the conclusion about whether the serum levels of CRP or WBC vary over the course of illness has been conflicting (Fernandes et al., 2016; Jacoby et al., 2016), caution should be exercised when interpreting their relationship. Finally, participants in our study were identified because they sought treatment in our hospital, a general hospital, therefore we can not comment on the extent to which our finding can be generalized to patients who do not seek treatment or seek treatment in other hospitals, especially in mental hospital.

5. Conclusion

In summary, this is the largest study to date that surveys the prevalence of low-grade inflammation in BD and examines its impact on the clinical features of BD. This study finds a much lower prevalence of low-grade inflammation in BD among Han Chinese population than that reported in western studies and identifies several clinical features of BD that are associated with low-grade inflammation. These findings provide further evidence that BD is a disease of great heterogeneity and enrich the knowledge about the relationship between BD and low-grade inflammation. Given that low-grade inflammation is found in numerous psychiatric and medical conditions, it is unlikely to serve as a diagnostic biomarker that can distinguish BD from other mental disorders. However, since the relationships between low-grade inflammation between some specific clinical features of BD are established, the indexes of inflammation can be used as auxiliary diagnostic biomarkers to classify BD and therefore improve the precision of diagnosis of BD. Moreover, future comparison of treatment response between BD with and without low-grade inflammation, will help explore and guide the accurate treatment of BD.

Conflicts of interest

All authors report no biomedical financial interests or potential conflicts of interest

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