Risk Management and Healthcare Policy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical Markers of Physical Violence in Patients with Bipolar Disorder in Manic States

Xuelong Li[1–3], Yakun Gao[4], Yiyi Liu[1–3], Ying Wang[1–3,*], Qing Wu[1–3,5,*]

[1]School of Mental Health and Psychological Sciences, Anhui Medical University, Hefei, People's Republic of China; [2]Department of Psychiatry, Affiliated Psychological Hospital of Anhui Medical University, Hefei, People's Republic of China; [3]Anhui Mental Health Center, Hefei, People's Republic of China; [4]Affiliated Hospital of Weifang Medical College, Weifang, People's Republic of China; [5]Hefei Fourth People's Hospital, Hefei, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ying Wang; Qing Wu, Department of Psychiatry, Affiliated Psychological Hospital of Anhui Medical University, 316 Huangshan Road, Hefei, 230000, People's Republic of China, Tel +86-13866136686; +86-13856919530, Email wyinghf@163.com; wuqinghf@163.com

Purpose: Identifying patients with bipolar disorder (BD) in manic states (BD-M) who are at a high risk of physical violence is a matter of clinical concern. This retrospective institution-based study aimed to identify simple, rapid, and inexpensive clinical markers of physical violence in patients with BD-M.

Patients and Methods: The anonymized sociodemographic variables (sex, age, years of education, marital status) and clinical ones (weight, height, body mass index, blood pressure, the score of BRMS, number of BD episodes, psychotic symptoms, history of violence, biochemical parameters, and blood routine parameters) of 316 BD-M participants were collected, and the risk of physical violence was identified using the Brøset Violence Checklist (BVC). Difference tests, correlation analyses, and multivariate linear regression analysis were performed to identify clinical markers for the risk of physical violence.

Results: The participants were categorized into groups at low (49, 15.51%), medium (129, 40.82%), and high (138, 43.67%) risk of physical violence. The number of BD episodes, serum uric acid (UA), free thyroxine (FT4) levels, history of violence, and monocyte-to-lymphocyte ratio (MLR) differed significantly between groups (all $P<0.05$). The number of BD episodes ($r=0.152$), FT3 ($r=0.131$) and FT4 ($r=0.132$) levels, history of violence ($r=0.206$), and MLR ($r=-0.132$) were significantly correlated with the risk of physical violence (all $P<0.05$). The existence of history of violence, number of BD episodes, UA, FT4, and MLR were identified as clinical markers of the risk of physical violence in patients with BD-M (all $P<0.05$).

Conclusion: These identified markers are readily available at initial presentation and may help in the timely assessment and treatment of patients with BD-M.

Keywords: bipolar disorder, manic states, risk of physical violence, clinical makers

Introduction

Bipolar disorder (BD) is a chronic mental illness with two subcategories: bipolar I disorder, defined as the presence of manic episodes and major depressive episodes (estimated global lifetime prevalence, 0.6−1.0%), and bipolar II disorder, defined as the presence of mild manic episodes and major depressive episodes (estimated global lifetime prevalence, 0.4−1.1%). Most patients with BD have severe disease-related disabilities, reduced psychosocial functioning, and increased financial burden.[1] The onset and development of BD may be related to structural and functional brain alterations, genetic factors, social and environmental factors, and metabolic pathways.[2] Timely treatment is essential for the prognosis of the disease, while physical violence may delay it.[3]

The high risk of physical violence in patients with BD, especially in patients with bipolar disorder in manic states (BD-M), has long been a clinical concern. Physical violence is considered a core characteristic of BD-M and refers to non-accidental physical assault that intimidates or harms others and is closely related to hostility and aggression.[4,5] Physical violence is common during manic episodes of BD, resulting in a higher rate of violent crime in patients with BD than in the general

Received: 21 February 2023
Accepted: 13 May 2023
Published: 24 May 2023

population and imposes a severe burden on the occupational, social, and family functioning of patients.[6] Patients with BD are eight times more likely to engage in physical violence than the general population and are even more likely to engage in physical violence than patients with schizophrenia.[7,8] In particular, BD-M is closely associated with physical violence. A prospective study showed that patients with BD-M often exhibited significant hostility and aggression during the acute phase, including aggression toward foreign objects, others, and self. Even after adjusting for demographic and clinical differences between groups, patients with BD-M showed consistently higher levels of violent aggression than non-BD psychiatric patients and the healthy population at the 4-year follow-up.[9]

Previous studies have proposed several biomarkers of physical violence in patients with BD-M. These include serotonin and dopamine function, nicotinic acetylcholine receptor function, inflammatory markers, the function of the hypothalamic-pituitary-adrenal axis, and cortisol.[10–13] In addition, exposure to violence or being a victim of violence increases the risk of physical violence in people with mental illnesses.[14] In recent years, several studies have proposed that substance use and childhood trauma also have significant effects on the risk of physical violence.[15,16]

Previous studies on the risk of physical violence in BD-M relied on complex equipment and cumbersome and time-consuming methods to analyze the markers. Moreover, despite the high specificity of several markers, the high cost of these techniques posed a significant impediment. Therefore, this study aimed to identified inexpensive, accessible, and reproducible clinical markers by analyzing the relationship between variables and the risk of physical violence in patients with acute onset BD-M. Assessing these risks in BD-M patients in a cost-effective and objective manner will help identify the patients at high risk of physical violence in outpatient and inpatient clinics in a timely manner, thus allowing clinicians to implement effective treatment measures.

Materials and Methods

Study Design and Data Sources

This cross-sectional study retrospectively included 316 patients with BD who were admitted to the Anhui Mental Health Center (Hefei, China) from January 2021 to May 2022, with diagnoses of BD-M meeting criteria outlined in the 10th revision of the International Classification of Diseases (ICD-10).[17] The diagnoses were confirmed by two psychiatrists. Trained research assistants collected sociodemographic and clinical data from the electronic health records provided by the Anhui Mental Health Center prior to the patients receiving psychiatric medication within 24 hours of admission. The sociodemographic datas included the sex and age of the patients, as well as their years of education, marital status. The clinical data included, weight, height, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), the score of BRMS, number of BD episodes, psychotic symptoms, history of violence, biochemical parameters, and blood routine parameters. The history of violence was provided by the patients and their relatives. The height and weight of all the participants were measured while the patients were standing barefoot on a calibrated electronic scale, and the BMI was calculated by dividing the admission weight by the height squared.

The biochemical parameters included serum uric acid (UA), total triiodothyronine (TT3), total thyroxine (TT4), thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), total cholesterol (TC), high-density lipoprotein (HDL), triglyceride (TG). The blood routine parameters included platelet, lymphocyte, neutrophil and monocyte. The platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), and monocyte/lymphocyte ratio (MLR) were calculated manually based on the hemogram results.

The inclusion criteria were: 1) meeting the diagnostic criteria of BD based on the ICD-10, 2) any age, and 3) not receiving psychiatric medication within the last 3 months. The exclusion criteria were: 1) a history of cranial trauma, organic encephalopathy, or other psychiatric disorders (including alcohol and/or substance dependence), 2) serious physical illness, such as cardiovascular disease, 3) pregnant or lactating women, and 4) use of corticosteroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive drugs within the past 2 weeks.

A total of 653 participants were initially selected, and 319 were excluded for not meeting the inclusion criteria. Of these, 236 participants had received psychiatric medication within the last 3 months based on a diagnosis of BD, 43 had severe cardiovascular disease, 26 were diagnosed with comorbid alcohol dependence, 12 had thyroid disease, and 2 were pregnant. Finally, 316 participants were selected for analysis.

Blood Tests

The day after admission, venous blood was collected by nurses between 06:00 and 07:00 after overnight fasting (8−12 hours) and sent to the hospital laboratory within 1 hour of collection for analysis. Plasma biochemical parameters were measured with an automatic biochemistry analyzer (AU480, Beckman Coulter, Brea, CA, USA) using commercial kits (Roche, Basel, Switzerland). Blood routine analysis was performed using an automatic hematology analyzer (Mindray BC-2800, Shenzhen, China).

Psychometric Scales

Bech-Rafaelsen Mania Scale (BRMS)

The BRMS was used to assess the severity of the patients' symptoms.[18] The BRMS consists of 11 items, with each item being graded on a five-point scale (range, 0−4). The sum of the scores of each item is used as the total score. The higher the total score, the more severe the mania.

Brøset Violence Checklist (BVC)

Data regarding the risk of physical violence were collected within 2 hours of admission using the BVC. This assessment has good reliability and validity and allows for rapid and valid assessment of the risk of violence in a clinical setting.[19] The BVC is scored for the following six symptoms: irritability, confusion, physical threats, boisterousness, verbal threats, and attacks on objects. The presence of symptoms is 1, and the absence of symptoms is 0. Finally, the scores of each entry are summed, with a minimum total score of 0 and a maximum score of 6. According to standard guidelines, a total score of 0 suggests a low risk of violence. A score of 1−2 suggests that the risk is moderate and requires preventive measures. A score of ≥3 is considered high risk and requires preventive measures and a plan to manage violent attacks. Based on the BVC scores, the participants were grouped as follows: (1) Low-risk group: 49 individuals with a low risk of physical violence (BVC score, 0); (2) Medium-risk group: 129 participants with a medium risk of physical violence (BVC score, 1−2); and (3) High-risk group: 138 participants with a high risk of physical violence (BVC score, ≥3).

This study was conducted in accordance with the Declaration of Helsinki, which was revised in 1989. Protocols were reviewed and approved by the Institutional Review Board of the Anhui Mental Health Center. The requirement for written informed consent was waived due to the retrospective design of the study.

Statistical Analysis

All statistical analyses were performed using Stata 17.0 (StataCorp LP, College Station, TX, USA). The normality of continuous variables was tested using the *Kolmogorov Smirnov* test. Continuous variables with a normal distribution are expressed as the mean ± standard deviation (SD), and those with a non-normal distribution are expressed as the median and interquartile range (25th and 75th percentiles). Categorical data are expressed as n(%). One-way analysis of variance or the *Kruskal–Wallis H*-test was used to analyze intergroup differences in continuous variables, and the chi-squared test was used to analyze intergroup differences in categorical data. Spearman rank correlation coefficients were used to evaluate correlations between the risk of physical violence and sociodemographic and clinical variables. Multiple linear regression analysis was used to identify predictive variables that were significantly correlated with the risk of physical violence. All statistically significant variables were added to the model simultaneously to avoid overlooking any potential associations. All *P*-values were two-sided, and *P*-values of < 0.05 were considered statistically significant.

Results

Differences in Baseline Characteristics of Sociodemographic Variables

This study included 316 participants with a mean age of (36.27±13.80) years in the low-risk group, (35.47±12.74) years in the medium-risk group, and (35.53±11.97) years in the high-risk group. There were no significant between-group differences in age, sex, marital status, and years of education (all $P>0.05$) (Table 1).

Table 1 Comparison of Baseline Characteristics of Sociodemographic Data

Variables	Low-Risk Group (n=49)	Medium-Risk Group (n=129)	High-Risk Group (n=138)	*P*
Sex				0.910
Female	23 (46.94%)	56 (43.41%)	62 (44.93%)	
Male	26 (53.06%)	73 (56.59%)	76 (55.07%)	
Marital status				0.392
Unmarried	21 (42.86%)	65 (50.39%)	55 (39.86%)	
Married	21 (42.86%)	53 (41.09%)	69 (50.00%)	
Divorced / Widowed	7 (14.29%)	11 (8.53%)	14 (10.14%)	
Education (years)	10.51±4.29	10.36±3.83	10.66±3.90	0.970
Age (years)	36.27±13.80	35.47±12.74	35.53±11.97	0.947

Abbreviation: Education, years of education.

Differences in Baseline Characteristics of Clinical Variables

The number of BD episodes, UA, FT4, MLR, and history of violence were significantly different among the three groups (all $P<0.05$). Among them, the UA and history of violence were significantly different between the low-risk and medium-risk groups (all $P<0.05$). The UA, MLR, and history of violence were significantly different between the low-risk and high-risk groups (all $P<0.05$). In addition, the number of BD episodes, FT4, and history of violence were significantly different between the medium-risk and high-risk groups (all $P<0.05$). However, there were no significant between-group differences in duration of BD, education, TT3, TT4, TSH, FT3, BMRS, age, BMI, SBP, DBP, blood glucose, TC, HDL, TG, NLR, PLR, and psychotic symptoms (all $P>0.05$) (Table 2)?

Table 2 Comparison of Baseline Characteristics of Clinical Data

Variables	Low-Risk Group (n=49)	Medium-Risk Group (n=129)	High-Risk Group (n=138)	*P*
History of violence				**<0.001**
No	29 (59.18%)	86 (66.67%)	56 (40.58%)	
Yes	20 (40.82%)	43 (33.33%)	82 (59.42%)	
Psychotic symptoms				0.531
No	24 (48.98%)	64 (49.61%)	77 (55.80%)	
Yes	25 (51.02%)	65 (50.39%)	61 (44.20%)	
BMI (kg/m^2)	24.71±4.27	24.43±3.93	25.04±4.27	0.316
Episodes (n)	3 (2, 5)	3 (2, 5)	4 (2, 6)	**0.006**
Duration (years)	9.95±8.66	10.39±9.35	10.62±9.54	0.893
UA (μmol/L)	325.96±64.03	359.47±85.53	368.01±104.98	**0.039**
TT3 (ng/mL)	1.13±0.29	1.19±0.28	1.26±0.42	0.207
TT4 (μg/dL)	1.33 (1.17, 1.54)	1.30 (1.11, 1.50)	1.39 (1.16, 1.79)	0.155
TSH (μIU/mL)	2.20±1.51	2.48±2.19	2.11±1.74	0.365
FT3 (pg/mL)	3.31±0.67	3.47±0.87	3.70±1.04	0.066
FT4 (ng/dL)	3.29 (2.77−3.60)	3.38 (2.92, 3.84)	3.49 (3.01, 4.09)	**0.021**
BRMS	20.76±10.50	22.92±10.03	23.35±9.23	0.274
BMI (kg/m^2)	24.71±4.27	24.43±3.93	25.04±4.27	0.316
SBP (mmHg)	123.35±11.61	123.71±11.06	123.35±10.81	0.970
DBP (mmHg)	78.88±6.36	79.62±7.99	79.63±8.09	0.758
Blood glucose (mmol/L)	5.18±1.71	5.17±1.38	5.55±1.85	0.194
TC (mmol/L)	4.36±0.96	4.04±0.92	4.17±0.88	0.206
HDL (mmol/L)	1.26±0.34	1.22±0.35	1.22±0.27	0.716

(*Continued*)

Table 2 (Continued).

Variables	Low-Risk Group (n=49)	Medium-Risk Group (n=129)	High-Risk Group (n=138)	*P*
TG (mmol/L)	1.36±0.82	1.26±0.77	1.26±0.64	0.583
NLR	2.65±1.73	2.67±1.53	2.43±1.42	0.398
PLR	0.26±1.11	0.29±0.19	0.24±0.09	0.171
MLR	127.78±47.85	112.34±43.61	109.35±43.96	**0.023**

Note: Statistically significant *P*–values are shown in bold.
Abbreviations: Episodes, number of BD episodes; Duration, duration of BD; UA, uric acid; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglyceride; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio.

Correlation Between Variables and Risk of Physical Violence

All variables were selected for analysis of the correlation with the risk of physical violence after confirming that they have no multicollinearity. The correlation coefficient of the number of BD episodes (r=0.152, P=0.007), FT3 (r=0.131, P=0.019), FT4 (r=0.132, P=0.019), history of violence (r=0.206, P<0.001), and MLR (r=−0.132, P=0.019) were significant in the correlation coefficient matrix (Table 3)?

Table 3 Correlation Between Variables and Risk of Physical Violence

Variables	N	*r*	*P*
Episodes	316	0.152	**0.007**
Duration	316	0.025	0.653
Education	316	0.014	0.810
UA	316	0.107	0.058
TT3	316	0.082	0.146
TT4	316	0.104	0.064
TSH	316	−0.070	0.216
FT3	316	0.131	**0.019**
FT4	316	0.132	**0.019**
BRMS	316	0.070	0.216
Age	316	0.003	0.961
BMI	316	0.048	0.391
SBP	316	−0.005	0.932
DBP	316	0.042	0.458
Blood glucose	316	0.102	0.071
TC	316	0.008	0.891
HDL	316	−0.014	0.808
TG	316	0.033	0.562
NLR	316	−0.052	0.356
PLR	316	−0.093	0.100
MLR	316	−0.132	**0.019**
History of violence (Yes)	316	0.206	**<0.001**
Male sex	316	0.003	0.952
Marital status	316	0.445	0.426
Psychotic symptoms (Yes)	316	−0.061	0.284

Note: Statistically significant *P*–values are shown in bold.
Abbreviations: Episodes, number of BD episodes; Duration, duration of BD; Education, years of education; UA, uric acid; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; BRMS, Bech-Rafaelsen Mania scale; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglyceride; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio.

Table 4 Multivariate Logistic Regression Analysis of Variables Associated with the Risk of Physical Violence

Variables	B	*β*	*P*	95% CI
History of violence (Yes)	0.278	0.194	**<0.001**	0.125−0.431
Episodes	0.019	0.115	**0.035**	0.001−0.037
UA	0.001	0.136	**0.012**	0.000−0.002
FT4	0.017	0.122	**0.026**	0.002−0.033
MLR	−0.002	−0.111	**0.041**	−0.003−0.000

Notes: R^2=0.101; Statistically significant *P*–values are shown in bold.
Abbreviations: Episodes, number of BD episodes; UA, uric acid; FT4, free thyroxine; MLR, monocyte/lymphocyte ratio; OR, odds ratio; CI, confidence interval.

Potential Clinical Markers for Risk of Physical Violence in Patients with BD-M

All statistically significant variables were added to the model of multivariate linear regression analysis after confirming that they have no multicollinearity. The following variables were found to be statistically significant: the existence of history of violence (B=0.278, *β*=0.194, *P*<0.001, 95% CI 0.125−0.431), number of BD episodes (B=0.019, *β*=0.115, *P*=0.035, 95% CI 0.001–0.037), UA (B=0.001, *β*=0.136, *P*=0.012, 95% CI 0.000−0.002), FT4 (B=0.017, *β*=0.122, *P*=0.026, 95% CI 0.002−0.033), and MLR (B=−0.002, *β*=−0.111, *P*=0.041, 95% CI −0.003−0.000) (Table 4)?

Discussion

In the current study, we evaluated easily obtainable clinical markers of risk of physical violence in patients with BD-M, which can facilitate the follow-up and observation of these patients. There were significant differences in the history of physical violence, number of BD episodes, UA, FT3, FT4, TT4, and MLR in patients with BD-M with different levels of risk of physical violence. Additional analysis of the above factors revealed that the presence of a history of violence, more frequent episodes of BD, and higher serum UA levels were associated with a higher risk of physical violence in all patients with BD-M, regardless of sex. In contrast, there was an inhibitory effect of MLR on the risk of physical violence.

Physical violence is considered a serious public health problem with negative effects on individuals and society and can even result in crime.[20,21] BD-M is a recurrent disease; therefore, timely assessment of the patient's risk of physical violence is of great importance for treatment and prognosis. However, the complex assessment process and the stigma associated with the disease can delay the identification of patients at high risk of physical violence to some extent, thus preventing their timely and effective treatment.[22,23] Moreover, physical violence is notoriously difficult to predict in clinical settings, and it may be difficult for staff to know what a patient is thinking or trying to do if the patient is intellectually disabled or motivated by an internal logic known only to themselves.[4] To help meet these challenges, we analyzed rapidly available clinical data to explore easily obtainable clinical markers of the risk of physical violence. Our findings may help develop a method for the timely assessment of the risk of physical violence in acute patients with BD-M.

We found that a history of violence was a risk factor for physical violence in patients with BD-M, which is consistent with the results of previous studies.[18] Previous study have found that patients with acute psychiatric disorders with history of physical violence (especially within 1 month) exhibit significant rates of violent behavior after hospitalization, and researchers hypothesize that history of violent behaviors reflected significant hostility of patients, predisposing the patients to resort to violent behaviors in resistance.[19] A recent study found that patients with BD experience difficulties in identifying, expressing, and processing their negative states, and therefore it is difficult to effectively comply with their emotions and relate them to behaviors that are consistent with their goals. For this reason, they may tend to express their thoughts and emotions through violent behavior toward others.[24] Based on these factors, we hypothesized that a history of physical violence reflects the high risk of physical violence in patients with BD-M.

The increased number of BD episodes was associated with a higher risk of physical violence in patients with BD-M. This association may be related to abnormalities in the nervous and endocrine systems of patients. A neuroanatomical study has found that the greater the number of manic episodes, the greater the degree of prefrontal cortex thinning in

patients and may lead to emotional dysregulation.[25] The relationship between the prefrontal cortex and the risk of physical violence revealed that aggression can be modulated by stimulating the ventral lateral prefrontal cortex.[26] In addition, several studies in recent years have reported alterations in the functional connections between the anterior cingulate gyrus and the amygdala and caudate nucleus during the first manic episode.[27,28] Patients with multiple episodes of BD exhibit hypoactivation in areas, such as the bilateral ventral lateral prefrontal cortices and amygdala networks in the prefrontal-striatal-amygdala circuit.[29] Abnormalities in the amygdala and prefrontal cortical connectivity are closely associated with the regulation of irritability, which in turn promotes the emergence of physical violence.[30,31] Thus, we hypothesized that as the number of BD episodes increases, the risk of physical violence may increase due to a decline in the patient's ability to control physical violence.

Furthermore, we identified serum UA level as a clinical marker for the risk of physical violence in patients with BD-M; precisely, patients with a higher risk of physical violence exhibited higher serum levels of UA. A previous study proposed an association between BD-M and high levels of UA, showing that serum UA levels were significantly lower in patients in remission than in those not in remission.[32] Meanwhile, serum UA was higher in patients before and after treatment than in healthy controls, suggesting that serum UA levels may be a potential marker for patients with BD-M.[33] Abnormal serum UA levels in patients with BD-M are thought to be associated with purinergic system dysfunction and adenosine neurotransmission. This hypothesis is supported by the effectiveness of allopurinol treatment in alleviating manic symptoms in patients with BD in the acute phase.[34,35] One study reported an association between UA levels and the risk of physical violence in patients with BD-M.[36] A follow-up study reported that serum UA levels were positively associated with physical violence in patients with BD-M, and the levels decreased with improvement in manic symptoms.[37] Based on these findings, UA is thought to be an effective predictive marker of physical violence in patients with BD-M.[38]

In recent years, several studies have validated the inflammatory mechanisms involved in the pathophysiology of BD-M. Accordingly, low-cost, highly reproducible, and easily accessible markers of inflammation (such as NLR, PLR, and MLR) are increasingly being used in the study of BD.[39] Growing evidence suggests that patients with BD-M have higher values of NLR, PLR, and MLR and lower levels of lymphocytes than the healthy population and patients with other types of mental illnesses, implying a more pronounced level of inflammation in BD-M.[40,41] After analyzing the three inflammatory markers, we found that MLR may be an independent protective factor against the risk of physical violence in patients with BD-M. In contrast, NLR and PLR had negligible effects on this risk. The severity of BD-M has been shown to be strongly correlated with abnormal MLR values.[42] Monocytes are an important component of the innate immune response and play a regulatory role in the production and release of inflammatory factors (such as interleukin 1 and TNF-α).[43] Elevated serum TNF-α levels are also closely associated with high levels of aggression in patients with mental disorders.[44] However, although patients with BD-M exhibited elevated MLR, their increased dopamine function may also downregulate the functional activity of monocytes and macrophages and inhibit TNF-α production.[45,46] Taken together, MLR may play a protective role in the risk of physical violence in patients with BD-M by inhibiting the release of pro-inflammatory cytokine.

Similar to previous studies, the present study found serum FT4 levels to be a risk factor for physical violence in patients with BD-M. A positive correlation between serum T3 and T4 levels and physical violence has also been demonstrated in several studies.[47,48] Acar et al explored thyroid hormone levels in 208 prisoners and found that higher T3 and T4 levels were associated with a tendency to commit violent crimes among manic patients.[49] They suggested that stressful environmental conditions may affect the hypothalamic-pituitary-thyroid axis and lead to aggression through the increase of thyroid hormone levels.

Limitations

This study had some limitations. First, due to its cross-sectional nature, the present study could not elucidate a temporal causal relationship between clinical markers and the risk of physical violence in patients with BD-M. Second, blood indicators may be influenced by other factors that we could not consider, such as the patients' cardiovascular status and dietary patterns. Third, the study did not distinguish BD-I and BD-II types, which may affect the accuracy of the study. Finally, the effect of harmful substance abuse on the risk of violence has been described.[50] The limitations of this retrospective study left patients' smoking and drinking histories under-collected, which may have biased the assessment of physical violence risk. This needs to be considered, collected, and analyzed in future studies.

Conclusion

Physical violence seriously affects the diagnosis and treatment of patients with BD-M. The potential clinical markers reported in this study, including a history of physical violence, number of BD episodes, UA levels, FT4 levels, and MLR, may be predictive of a high risk of physical violence in patients with BD-M. These data are reliable and inexpensive to obtain in most clinical settings. As such, the early collection of these data may help identify BD-M patients (in both outpatient and inpatient settings) who are at high risk of physical violence, thus allowing clinicians to implement effective treatment measures in a timely manner.

Acknowledgments

We would like to thank the Anhui Mental Health Center for providing data support for this study. Without the support of the hospital, this work would not have been possible.

Funding

This research was funded by the Hefei Health Applied Medicine Research Project (grant number Hwk2021yb015) and the Hospital Project of Hefei Fourth People's Hospital (grant numbers 2019001, HFSY2022YB08 and HFSY2022ZD11). The funders had no role in the study design; in the collection, analysis, or interpretation of the data; in the writing of the manuscript; or in the decision to submit the article for publication.

Disclosure

The authors report no conflicts of interest in this work.

References

1. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet*. 2020;396:1841–1856. doi:10.1016/S0140-6736(20)31544-0
2. Scaini G, Valvassori SS, Diaz AP, et al. Neurobiology of bipolar disorders: a review of genetic components, signaling pathways, biochemical changes, and neuroimaging findings. *Braz J Psychiatry*. 2020;42:536–551. doi:10.1590/1516-4446-2019-0732
3. Maier W, Hauth I, Berger M, et al. [Interpersonal violence in the context of affective and psychotic disorders]. *Nervenarzt*. 2016;87(1):53–68. German. doi:10.1007/s00115-015-0040-6
4. Lawrence RE, Rolin SA, Looney DV, et al. Physical assault in the psychiatry emergency room. *J Am Acad Psychiatry Law*. 2020;48:484–495. doi:10.29158/JAAPL.200022-20
5. Pan YZ, Xie XM, Tang YL, et al. A comparison of aggression between patients with acute schizophrenia and mania presenting to psychiatric emergency services. *J Affect Disord*. 2022;296:493–497. doi:10.1016/j.jad.2021.09.071
6. Latalova K. Bipolar disorder and aggression. *Int J Clin Pract*. 2009;63:889–899. doi:10.1111/j.1742-1241.2009.02001.x
7. Corrigan PW, Watson AC. Findings from the National Comorbidity Survey on the frequency of violent behavior in individuals with psychiatric disorders. *Psychiatry Res*. 2005;136:153–162. doi:10.1016/j.psychres.2005.06.005
8. Volavka J. Violence in schizophrenia and bipolar disorder. *Psychiatr Danub*. 2013;25:24–33.
9. Ballester J, Goldstein B, Goldstein TR, et al. Prospective longitudinal course of aggression among adults with bipolar disorder. *Bipolar Disord*. 2014;16:262–269. doi:10.1111/bdi.12168
10. Seo D, Patrick CJ, Kennealy PJ. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. *Aggress Violent Behav*. 2008;13:383–395. doi:10.1016/j.avb.2008.06.003
11. Picciotto MR, Lewis AS, van Schalkwyk GI, et al. Mood and anxiety regulation by nicotinic acetylcholine receptors: a potential pathway to modulate aggression and related behavioral states. *Neuropharmacology*. 2015;96:235–243. doi:10.1016/j.neuropharm.2014.12.028
12. Castle R, Bushell WC, Mills PJ, et al. Global correlations between chronic inflammation and violent incidents: potential behavioral consequences of inflammatory illnesses across socio-demographic levels. *Int J Gen Med*. 2021;14:6677–6691. doi:10.2147/IJGM.S324367
13. Chichinadze K, Chichinadze N, Gachechiladze L, et al. The role of androgens in regulating emotional state and aggressive behavior. *Rev Neurosci*. 2012;23(2):123–133. doi:10.1515/revneuro-2012-0026
14. Sariaslan A, Lichtenstein P, Larsson H, et al. Triggers for violent criminality in patients with psychotic disorders. *JAMA Psychiatry*. 2016;73(8):796–803. doi:10.1001/jamapsychiatry.2016.1349
15. Drachman R, Colic L, Sankar A, et al. Rethinking "aggression" and impulsivity in bipolar disorder: risk, clinical and brain circuitry features. *J Affect Disord*. 2022;303:331–339. doi:10.1016/j.jad.2022.02.047
16. Adiguzel V, Ozdemir N, Sahin SK. Childhood traumas in euthymic bipolar disorder patients in Eastern Turkey and its relations with suicide risk and aggression. *Nord J Psychiatry*. 2019;73:490–496. doi:10.1080/08039488.2019.1655589
17. Kaltenboeck A, Winkler D, Kasper S. Bipolar and related disorders in DSM-5 and ICD-10. *CNS Spectr*. 2016;21:318–323. doi:10.1017/S1092852916000079
18. Li Q, Zhong S, Zhou J, et al. Delusion, excitement, violence, and suicide history are risk factors for aggressive behavior in general inpatients with serious mental illnesses: a multicenter study in China. *Psychiatry Res*. 2019;272:130–134. doi:10.1016/j.psychres.2018.12.071
19. Amore M, Menchetti M, Tonti C, et al. Predictors of violent behavior among acute psychiatric patients: clinical study. *Psychiatry Clin Neurosci*. 2008;62:247–255. doi:10.1111/j.1440-1819.2008.01790.x

20. Freitag S, Kapoor S, Lamis DA. Childhood maltreatment, impulsive aggression, and suicidality among patients diagnosed with bipolar disorder. *Psychol Trauma*. 2022;14:1256–1262. doi:10.1037/tra0001218
21. Eggink E, de Waal MM, Goudriaan AE. Criminal offending and associated factors in dual diagnosis patients. *Psychiatry Res*. 2019;273:355–362. doi:10.1016/j.psychres.2019.01.057
22. Varshney M, Mahapatra A, Krishnan V, et al. Violence and mental illness: what is the true story? *J Epidemiol Commun Health*. 2016;70 (3):223–225. doi:10.1136/jech-2015-205546
23. Li DJ, Lin CH, Wu HC. Factors predicting re-hospitalization for inpatients with bipolar mania--A naturalistic cohort. *Psychiatry Res*. 2018;270:749–754. doi:10.1016/j.psychres.2018.10.073
24. Candini V, Ghisi M, Bianconi G, et al. Aggressive behavior and metacognitive functions: a longitudinal study on patients with mental disorders. *Ann Gen Psychiatry*. 2020;19:36. doi:10.1186/s12991-020-00286-3
25. Abe C, Ching CRK, Liberg B, et al. Longitudinal structural brain changes in bipolar disorder: a multicenter neuroimaging study of 1232 individuals by the ENIGMA Bipolar Disorder Working Group. *Biol Psychiatry*. 2022;91:582–592. doi:10.1016/j.biopsych.2021.09.008
26. Gallucci A, Riva P, Romero Lauro LJ, et al. Stimulating the ventrolateral prefrontal cortex (VLPFC) modulates frustration-induced aggression: a tDCS experiment. *Brain Stimul*. 2020;13(2):302–309. doi:10.1016/j.brs.2019.10.015
27. Lippard ETC, Weber W, Welge J, et al. Variation in rostral anterior cingulate functional connectivity with amygdala and caudate during first manic episode distinguish bipolar young adults who do not remit following treatment. *Bipolar Disord*. 2021;23:500–508. doi:10.1111/bdi.13025
28. Lu CF, Wu YT, Teng S, et al. Genetic predisposition and disease expression of bipolar disorder reflected in shape changes of the anterior limbic network. *Brain Sci*. 2019;9:240. doi:10.3390/brainsci9090240
29. Borgelt L, Strakowski SM, DelBello MP, et al. Neurophysiological effects of multiple mood episodes in bipolar disorder. *Bipolar Disord*. 2019;21:503–513. doi:10.1111/bdi.12782
30. Stoddard J, Tseng WL, Kim P, et al. Association of irritability and anxiety with the neural mechanisms of implicit face emotion processing in youths with psychopathology. *JAMA Psychiatry*. 2017;74:95–103. doi:10.1001/jamapsychiatry.2016.3282
31. Hein S, Barbot B, Square A, et al. Violent offending among juveniles: a 7-year longitudinal study of recidivism, desistance, and associations with mental health. *Law Hum Behav*. 2017;41:273–283. doi:10.1037/lhb0000241
32. Yang X, Tao H, Xiao L, et al. Increased serum C3 and decreased UA in patients of bipolar disorder in Chinese Han population. *Front Psychiatry*. 2018;9:381. doi:10.3389/fpsyt.2018.00381
33. Chen JX, Zhang LG, Liu KZ, et al. Patients with drug-naive bipolar disorder in remission after 8 weeks of treatment had decreased serum uric acid concentrations. *Front Psychiatry*. 2019;10:767. doi:10.3389/fpsyt.2019.00767
34. Bartoli F, Crocamo C, Dakanalis A, et al. Purinergic system dysfunctions in subjects with bipolar disorder: a comparative cross-sectional study. *Compr Psychiatry*. 2017;73:1–6. doi:10.1016/j.comppsych.2016.09.011
35. Weiser M, Burshtein S, Gershon AA, et al. Allopurinol for mania: a randomized trial of allopurinol versus placebo as add-on treatment to mood stabilizers and/or antipsychotic agents in manic patients with bipolar disorder. *Bipolar Disord*. 2014;16:441–447. doi:10.1111/bdi.12202
36. Bartoli F, Crocamo C, Bava M, et al. Testing the association of serum uric acid levels with behavioral and clinical characteristics in subjects with major affective disorders: a cross-sectional study. *Psychiatry Res*. 2018;269:118–123. doi:10.1016/j.psychres.2018.08.039
37. Chatterjee SS, Ghosal S, Mitra S, et al. Serum uric acid levels in first episode mania, effect on clinical presentation and treatment response: data from a case control study. *Asian J Psychiatr*. 2018;35:15–17. doi:10.1016/j.ajp.2018.04.030
38. Bao P, Jing J, Yang WH, et al. Violence-related behaviors among adolescents and its association with cognitive emotion regulation strategies. *World J Pediatr*. 2016;12:82–87. doi:10.1007/s12519-015-0014-6
39. Fusar-Poli L, Natale A, Amerio A, et al. Neutrophil-to-lymphocyte, platelet-to-lymphocyte and monocyte-to-lymphocyte ratio in bipolar disorder. *Brain Sci*. 2021;11:58. doi:10.3390/brainsci11010058
40. Ozdin S, Usta MB. A comparison of inflammatory markers in manic and euthymic states of bipolar disorder. *Nord J Psychiatry*. 2021;75:124–129. doi:10.1080/08039488.2020.1807048
41. Kirlioglu SS, Balcioglu YH, Kalelioglu T, et al. Comparison of the complete blood count-derived inflammatory markers in bipolar patients with manic and mixed episodes. *Bratisl Lek Listy*. 2019;120:195–199. doi:10.4149/BLL_2019_051
42. Dadouli K, Janho MB, Hatziefthimiou A, et al. Neutrophil-to-lymphocyte, monocyte-to-lymphocyte, platelet-to-lymphocyte ratio and systemic immune-inflammatory index in different states of bipolar disorder. *Brain Sci*. 2022;12:1034. doi:10.3390/brainsci12081034
43. Pfau ML, Menard C, Russo SJ. Inflammatory mediators in mood disorders: therapeutic opportunities. *Annu Rev Pharmacol Toxicol*. 2018;58:411–428. doi:10.1146/annurev-pharmtox-010617-052823
44. Barzman D, Eliassen J, McNamara R, et al. Correlations of inflammatory gene pathways, corticolimbic functional activities, and aggression in pediatric bipolar disorder: a preliminary study. *Psychiatry Res*. 2014;224:107–111. doi:10.1016/j.pscychresns.2014.07.009
45. Ashok AH, Marques TR, Jauhar S, et al. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. *Mol Psychiatry*. 2017;22:666–679. doi:10.1038/mp.2017.16
46. In SW, Son EW, Rhee DK, et al. Modulation of murine macrophage function by methamphetamine. *J Toxicol Environ Health A*. 2004;67:1923–1937. doi:10.1080/15287390490514589
47. Eklund J, Alm PO, Af Klinteberg B. Monoamine oxidase activity and tri-iodothyronine level in violent offenders with early behavioural problems. *Neuropsychobiology*. 2005;52:122–129. doi:10.1159/000087557
48. Sinai C, Hirvikoski T, Nordstrom AL, et al. Thyroid hormones and adult interpersonal violence among women with borderline personality disorder. *Psychiatry Res*. 2015;227:253–257. doi:10.1016/j.psychres.2015.03.025
49. Acar H, Ulgen A. Relationship between thyroid hormone levels and crime type: a controlled study in prisoners. *Int J Endocrinol*. 2020;2020:9172134. doi:10.1155/2020/9172134
50. Chester DS, DeWall CN. Aggression is associated with greater subsequent alcohol consumption: a shared neural basis in the ventral striatum. *Aggress Behav*. 2018;44:285–293. doi:10.1002/ab.21751