Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

# Manic Residual Symptoms Also Deserve Attention: A Symptom Network Analysis of Residual Symptoms in Bipolar Disorder

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**Background:** Lots of patients with bipolar disorder (BD) continue to have residual symptoms after treatment in their remission, BD exhibits intricate characteristics and transformation patterns in its residual symptoms, residual symptoms of different polarities and degrees can mix with and transform to each other. There is a need for further investigation of BD as a comprehensive multivariate disease system. The current research lacks network analyses focusing on BD's residual and subsyndromal symptoms.

**Methods:** 242 patients were included with bipolar disorder in remission. We compared demographic data and differences in symptoms between populations with and without residual symptoms using *t*-tests and chi-square tests, with FDR applied for multiple comparison correction. Logistic regression was used to identify influencing factors for residual symptoms. Symptom networks were compared by network analysis to analyze the relationships between different types of residual symptoms.

**Results:** Depressive residual symptoms (N=111) were more common than manic residual symptoms (n=29) in the patients included. The comparison between two groups with and without residual symptoms shows no difference in demographic data and medical history information. The main influencing factors related to residual symptoms were time from diagnosis to first treatment (OR=0.88), the first (OR=1.51) and second (OR=17.1)factors of the Mood Disorder Questionnaire (MDQ), the Quick Inventory of Depressive Symptomatology Self-Report (QIDS)(OR=5.28), the psychological(OR=0.68) and environment (OR=1.53) subscale of the World Health Organization Quality of Life Short Form (WHOQOL-BREF). There was a significant difference in network structure between the groups with and without residual symptoms (network invariance difference=0.4, p =0.025). At the same time, there was no significant difference between the groups with and without depressive residual symptoms. However, the symptom network in patients with depressive residual symptoms is more loosely structured than in those without, with symptoms exhibiting weaker interconnections. When there is no depressive or manic residual symptom, it can still form a symptom network and cause an impact on social function.

**Conclusion:** This study underscores the complexity of bipolar disorder's residual symptoms. Although it primarily manifests as loosely structured depressive residual symptoms, manic residual symptoms should not be ignored. Future research should explore network-based interventions targeting specific symptom clusters or connections to improve residual symptom management and patient outcomes.

**Keywords:** bipolar disorder, residual symptoms, influencing factors, network analysis

## Introduction

Bipolar disorder is a complex condition with recurrent episodes of depression and mania/hypomania, divided into type I and type II.[1] Individuals with BD face elevated risks of self-harm and violent behaviours.[2] Given BD's intricate and diverse clinical manifestations, semiological studies are pivotal in its research landscape. The nuanced presentation of BD, especially with depressive episodes being predominant, poses challenges in distinguishing it from unipolar depression. Furthermore, the



Received: 19 April 2024
Accepted: 10 July 2024
Published: 16 July 2024

more severe variants, like psychotic BD, can often be confounded with schizophrenia. The evolving nature of BD research symptom standardizations and diagnostic criteria underscores the pressing need for refined symptomatic investigations.[3] While there's growing attention to prodromal and mixed symptoms and tailored symptom management in BD research,[3,4] more research is needed on BD as a comprehensive multivariate disease system, with a lack of network analyses focusing on residual and subsyndromal symptoms in BD.

Residual symptoms are long-lasting disease-related symptoms that affect BD patients persistently, including their social connectivity, occupational development, and cognitive function. Residual symptoms are expected during the euthymic phase, with depressive symptoms being the most prevalent.[5,6] Residual depressive symptoms can lead to more rapid recurrences of a depressive episode, poor functioning, and poor medication adherence.[7–9] Residual manic symptoms are associated with a shorter time to manic, hypomanic, or mixed recurrences.[9] Patients with both sets of residual symptoms are more likely to have the presence of comorbid physical illness and substance abuse disorder.[10] The severity of residual symptoms can be considered a significant indicator when assessing the condition of BD. A study demonstrated the relationship between the number of lifetime BD episodes and the degree and chances of BD residual symptoms.[11] Another Study showed a correlation between residual and episodic symptoms.[12] In addition to the frequency and duration of BD episodes, residual mood symptoms have been shown to predict mood episode recurrence independently in recovered BD patients. Residual symptoms are complex, encompassing a diverse range of experiences that can significantly impact patients' lives. To better understand the correlation between residual symptoms and social function or psychotic symptoms. It is important to view them as a network.

Symptom network theory suggests that symptoms of different disorders are interconnected through various mechanisms, leading to autonomous feedback and alternative remission.[13] Symptom network analysis offers clues for diagnosis and treatment by exploring symptom correlation and treating disorders as systems rather than having a single underlying cause.[14] It has been widely used in psychiatry to explain symptoms. Network analyses reveal central depressive symptoms like death wishes and pessimism, which are essential for developing targeted late-life depression interventions.[15] Similar studies in schizophrenia show symptom independence and connections,[16] emphasizing the symptom network's role in understanding comorbidities and complex syndromes. Despite its potential, BD research lacks the ability to explore residual symptoms through network analysis, highlighting a gap this work aims to address by examining BD's residual symptom network, offering insights for better management and treatment strategies.

We thought symptom networks could offer a more diverse and systematic perspective on residual symptoms. Our research aims to analyze the symptom networks present in two types of BD, with and without residual symptoms. The primary objective is to excavate the central core of the BD residual symptom network, explore the influencing factors of residual symptoms, and explain the differences between the two groups. Our findings have the potential to offer a new therapeutic perspective for clinical practice and reliable management of residual symptoms.

# Participants and Methods

## Participants

This study was conducted at the Beijing Anding Hospital, Capital Medical University between December 2015 and December 2016. Beijing Anding Hospital, Capital Medical University houses a Mood Disorder Treatment Center specializing in research on affective disorders (etiology, pathogenesis, diagnosis, and treatment). This institution provides high-quality patient care and is at the forefront of depression and bipolar disorder treatment and research in China. A robust patient population exceeding 1000 annual bipolar inpatients and 20,000 annual outpatient visits facilitates clinical research recruitment at this hospital. We recruited outpatients from this hospital who met the study inclusion criteria during their clinic visits.

Following informed consent, a psychiatrist evaluated participants against pre-established eligibility criteria. Those who met the criteria were invited to participate in the study. All examinations were conducted following the principles of the Declaration of Helsinki. The Beijing Anding Hospital Ethics Committee, Capital Medical University, China, approved the study.

Inclusion Criteria: 1) Provide a written informed consent form(all independently signed); 2) Age ≥18 years and residing in Beijing during the study period; 3)Diagnosed with Bipolar I or Bipolar II Disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, DSM-IV TR) and experienced at least one mood episode in the 12 to 3 months before enrollment according to medical records (consistent with DSM-IV TR definitions of depressive, manic, hypomanic, or mixed episodes); 4) Baseline Hamilton Depression Rating Scale (HAMD-17) score ≤14, Young Mania Rating Scale (YMRS) score ≤12(according to the definition of residual symptom).

Exclusion Criteria: 1) Unable to complete patient questionnaires; 2) Experienced new mood episodes (consistent with DSM-IV TR definitions of depressive, manic, hypomanic, or mixed episodes) in the past three months; 3) Participated in an interventional clinical study in the past three months.

## Assessment Tools

We employed a comprehensive set of scales to evaluate patient symptoms across multiple dimensions, including depressive symptoms, manic symptoms, psychotic symptoms, quality of life, and insight. To assess depressive symptoms, we utilized the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS) alongside the 17-item Hamilton Depression Rating Scale (HAMD-17). Manic symptoms were evaluated using the Mood Disorder Questionnaire (MDQ) and the Young Mania Rating Scale (YMRS). For psychotic symptoms, we applied the Brief Psychiatric Rating Scale (BPRS). The quality-of-life measurement was conducted through the World Health Organization Quality of Life Short Form (WHOQOL-BREF). Lastly, the Insight and Treatment Attitude Questionnaire (ITAQ) assessed a patient's awareness and acceptance of their mental health condition, specifically focusing on their understanding of the need for treatment.

Both hetero-assessment and self-assessment forms were utilized to better assess symptoms, along with various scale factors to represent different dimensions of symptoms. According to the content of the MDQ scale, it was divided into three factors. Factor1 included items 3, 5, 6, 8, and 9, which indicated energy and high mood (MDQ1); Factor2 included items 2, 10, 1L, 12, and 13, which covered adventurous and irritable behaviours (MDQ2); Factor3 included items 1, 4, and 7. WHOQOL-BREF was divided into four domains: physical health(PHYS), psychological(PSYCH), social relationships(SOCIL), and environment(ENVIR).[17]

## Definition of Residual Symptom

The assessment of BD residual symptoms encompasses two categories: depressive and manic. For depressive symptoms, a score of 5 or above 5 on the QIDS-SR16 suggest the presence of depressive residuals, categorized into mild (6–10 points) and moderate or severe (11 points or more). A total MDQ score of 7 or more flags the presence of manic residual symptoms, three MDQ factors representing different symptom dimensions.

## Network Analysis and Statistical Analysis

We used Epidata 3.0 for double data entry and R 4.01 for data analysis. The aforementioned observational indicators are integrated into network analysis as nodes, where edges represent relationships between nodes. We aim to construct a partial correlation coefficient network to obtain the richest information. This implies that the edge between nodes A and B is the weighted connection between the two nodes after controlling for all other edges in the network. This is similar to a partial correlation coefficient, with weights ranging from −1 to 1, indicating conditional independence correlation. When constructing the network, the first step is calculating the correlation matrix and using EBICglasso for network estimation. Bootnet is used during this process to validate the results, ensuring accuracy.

Subsequently, centrality evaluations are conducted. Standard metrics for centrality include strength, closeness centrality, betweenness centrality, and expected influence. Strength refers to the sum of weighted values for all edges in which a node exists within the network. Closeness centrality is based on the reciprocal sum of the shortest distances between a node and all other nodes in the network, examining the indirect connectivity degree between this node and another. Symptoms with higher closeness centrality transmit to other symptoms more quickly due to their shorter overall paths to other symptoms. Betweenness centrality refers to the frequency of a node lying on the shortest paths between two different nodes. The shorter the path, the greater the node's influence on another. Symptoms with higher betweenness

centrality have a more significant impact on other symptoms. Expected influence estimates the sum of the original values of connection edges between each pair of nodes, considering both the weight and polarity of the edge. The higher the expected influence, the greater the centrality of the node. Thus, this study intends to evaluate the centrality of symptom networks using the four metrics above.

### Statistical Analysis

For normally distributed data, independent sample *t*-tests are used, with Cohen's d calculated to measure the effect size. For non-normally distributed continuous variables, the Mann–Whitney *U*-test is used. For count data, either the chi-square test or Fisher's exact test is used. Multiple comparisons are adjusted using the False Discovery Rate (FDR) method to obtain q-values, with q-values less than 0.05 indicating significant differences. A stepwise regression approach was employed, with variables retained in the final model based on a significance threshold of $P < 0.1$. Symptom network comparisons were conducted using the NetworkComparisonTest (NCT) package. The default multiple comparison procedure implemented in the NCT function was employed.

## Results

### Demographic Data

In this study, we included 242 patients with an average age of 34.8±11.6 years and an average total disease course of 8.7±7.3 years, with a male-to-female ratio of 79.3%. Bipolar I disorder accounted for 79% of the total, and bipolar II disorder accounted for 21%. 19% of patients had a stable physical disease, 0.8% had an unstable physical disease, 33% had a family history, 17% used antidepressants, and 27% were using double mood stabilizers. The average MDQ score of 242 patients was 3.3±3.7. One's QIDS score was missing; the average QIDS score of the others was 6.6±4.9. The QIDS missed patient was excluded from the evaluation process for residual symptoms and depression residual symptoms (Table 1). A comparative analysis of individuals with and without residual symptoms (adjusted for multiple comparisons) revealed no significant differences in demographic characteristics between the two groups. The primary difference was observed in symptom severity. And the subgroups of female and male patients showed similar results (Table S5-1, Figure S1 and Table S5-2).

In terms of residual symptoms, 124 patients had residual symptoms, 111 had depressive residual symptoms, and 29 patients had manic residual symptoms. The specific differences between depressive or mania residual symptoms were in Table S1 for mania; Table S2 for depression.

### Influencing Factors

To identify the key factors influencing residual symptoms, a logistic regression model was applied to examine the characteristics of individuals with and without residual symptoms (Table 2). It was found that the main influencing factors related to residual symptoms were time from diagnosis to first treatment, MDQ1 and 2, QIDS score, PSYCH, and ENVIR score. The results of logistic regression were not satisfactory when comparing the presence or absence of depressive and manic residual symptoms among different groups.

### Symptom Network Analysis

To investigate the influence of residual symptoms, we conducted separate symptom network analyses for three groups: patients with any residual symptoms, patients with depressive residual symptoms only, and patients without any residual symptoms. The analysis of manic residual symptoms was limited by a small sample size, and consequently, no network model could be generated. Since our observation scope did not include raw symptom data and only one single scale entry has low explanatory power, we used scale scores to represent symptom intensity and scale factors to divide symptom dimensions. Partial correlation networks for each group are shown in Figure 1. The average weights of the edges with actual weights among all possible 66 edges differed in the five groups. In the network of patients with residual symptoms, 20 edges had absolute weights greater than 0; the strongest edge was MDQ2-MDQ3. In patients without residual symptoms, nine edges had absolute weights greater than 0; the strongest edge was ENVIR-PSYCH, and the rest were ENVIR-PHYS, PHYS-SOCIL, and BPRS-YMRS. In the network of patients with depressive residual symptoms, 13 edges had absolute weights greater than 0, with the strongest edge being

**Table 1** Difference Between Patients with or Without Residual Symptoms

| Characteristic | N | Overall, N = 241[a] | 0, N = 117[a] | 1, N = 124[a] | p-value[b] | Difference (Cohen's d)[b] | 95% CI[b,c] | q-value[d] |
|---|---|---|---|---|---|---|---|---|
| **Sex, n (%)** | 241 | | | | 0.69 | | | 0.79 |
| Male | | 107 (44%) | 54 (46%) | 53 (43%) | | | | |
| Female | | 134 (56%) | 63 (54%) | 71 (57%) | | | | |
| **Marital status, n (%)** | 241 | | | | 0.53 | | | 0.63 |
| Married | | 109 (45%) | 50 (43%) | 59 (48%) | | | | |
| Single | | 132 (55%) | 67 (57%) | 65 (52%) | | | | |
| **Using double mood stabilizers, n (%)** | 241 | 66 (27%) | 32 (27%) | 34 (27%) | >0.99 | | | >0.99 |
| **Family history, n (%)** | 241 | 80 (33%) | 39 (33%) | 41 (33%) | >0.99 | | | >0.99 |
| **Type of BD(Type I), n (%)** | 241 | | | | 0.93 | | | >0.99 |
| Bipolar I disorder | | 190 (79%) | 93 (79%) | 97 (78%) | | | | |
| Bipolar II disorder | | 51 (21%) | 24 (21%) | 27 (22%) | | | | |
| **Using antidepressant, n (%)** | 241 | 42 (17%) | 18 (15%) | 24 (19%) | 0.52 | | | 0.63 |
| **Physical disease, n (%)** | 241 | | | | 0.28 | | | 0.48 |
| No | | 194 (80%) | 99 (85%) | 95 (77%) | | | | |
| Stable disease | | 45 (19%) | 17 (15%) | 28 (23%) | | | | |
| Unstable disease | | 2 (0.8%) | 1 (0.9%) | 1 (0.8%) | | | | |
| **Working, n (%)** | 241 | | | | 0.32 | | | 0.49 |
| Employed | | 177 (73%) | 82 (70%) | 95 (77%) | | | | |
| No job | | 64 (27%) | 35 (30%) | 29 (23%) | | | | |
| **ITAQDegree, n (%)** | 241 | 203 (84%) | 101 (86%) | 102 (82%) | 0.49 | | | 0.63 |
| **BPRSDegree, n (%)** | 241 | 2 (0.8%) | 0 (0%) | 2 (1.6%) | 0.5 | | | 0.63 |
| **Age, Mean(SD)** | 241 | 34.8(11.6) | 36.5(12.6) | 33.1(10.4) | 0.025 | 3.4(0.29) | 0.44, 6.3 | 0.064 |
| **Years of education, Mean(SD)** | 241 | 13.6(3.4) | 13.7(3.6) | 13.5(3.2) | 0.74 | 0.14(0.04) | −0.71, 1.0 | 0.82 |
| **Age of first onset, Mean(SD)** | 241 | 25(9) | 25(10) | 24(9) | 0.21 | 1.5(0.16) | −0.88, 4.0 | 0.42 |
| **Total course of illness, Mean(SD)** | 241 | 9(7) | 10(8) | 8(6) | 0.058 | 1.8(0.25) | −0.06, 3.7 | 0.14 |
| **Total number of episodes, Mean(SD)** | 240 | 5.37(4.01) | 5.54(3.63) | 5.20(4.35) | 0.52 | 0.34(0.08) | −0.68, 1.4 | 0.63 |
| (Missing) | | 1 | 0 | 1 | | | | |
| **Time from first onset to diagnosis, Mean(SD)** | 240 | 5.6(6.4) | 6.1(7.1) | 5.1(5.7) | 0.22 | 1(0.16) | −0.61, 2.7 | 0.42 |
| (Missing) | | 1 | 0 | 1 | | | | |
| **Age of initial diagnosis, Mean(SD)** | 239 | 30(11) | 32(12) | 29(10) | 0.074 | 2.6(0.23) | −0.25, 5.4 | 0.16 |
| (Missing) | | 2 | 0 | 2 | | | | |
| **Time from diagnosis to first treatment, Mean(SD)** | 240 | 3.2(5.2) | 4.0(5.7) | 2.5(4.5) | 0.025 | 1.5(0.29) | 0.19, 2.8 | 0.064 |
| (Missing) | | 1 | 0 | 1 | | | | |

(*Continued*)


https://doi.org/10.2147/NDT.S466090 DovePress

**Table 1** (Continued).

| Characteristic | N | Overall, N = 241[a] | 0, N = 117[a] | 1, N = 124[a] | p-value[b] | Difference (Cohen's d)[b] | 95% CI[b,c] | q-value[d] |
|---|---|---|---|---|---|---|---|---|
| **Total number of times in hospital, Mean(SD)** | 241 | 2.63(2.41) | 2.78(2.44) | 2.48(2.39) | 0.35 | 0.29(0.94) | −0.32, 0.91 | 0.51 |
| **HAMD, Mean(SD)** | 241 | 3.2(3.4) | 1.7(2.2) | 4.6(3.7) | <0.001 | −2.9(0.12) | −3.7, −2.1 | <0.001 |
| **YMRS, Mean(SD)** | 240 | 1.63(2.42) | 1.47(2.28) | 1.79(2.55) | 0.31 | −0.32(−0.13) | −0.93, 0.29 | 0.49 |
| (Missing) | | 1 | 0 | 1 | | | | |
| **ITAQ, Mean(SD)** | 241 | 17.1(4.3) | 17.5(4.4) | 16.8(4.2) | 0.25 | 0.64(0.15) | −0.45, 1.7 | 0.46 |
| **BPRS, Mean(SD)** | 241 | 20.9(4.7) | 20.1(2.8) | 21.8(5.8) | 0.004 | −1.7(−0.37) | −2.9, −0.55 | 0.013 |
| **MDQ1, Mean(SD)** | 241 | 1.71(1.81) | 1.43(1.43) | 1.97(2.07) | 0.019 | −0.54(−0.30) | −0.99, −0.09 | 0.059 |
| **MDQ2, Mean(SD)** | 241 | 0.73(1.51) | 0.21(0.45) | 1.22(1.94) | <0.001 | −1(−0.70) | −1.4, −0.65 | <0.001 |
| **MDQ3, Mean(SD)** | 241 | 0.83(1.01) | 0.41(0.67) | 1.23(1.12) | <0.001 | −0.82(−0.88) | −1.0, −0.58 | <0.001 |
| **QIDS, Mean(SD)** | 241 | 6.6(4.9) | 2.9(1.6) | 10.0(4.6) | <0.001 | −7.1(−2.04) | −7.9, −6.2 | <0.001 |
| **WHOQOL-PHYS, Mean(SD)** | 241 | 13.22(1.99) | 14.07(1.64) | 12.41(1.97) | <0.001 | 1.7(0.91) | 1.2, 2.1 | <0.001 |
| **WHOQOL-PSYCH, Mean(SD)** | 241 | 14.02(2.68) | 15.34(1.97) | 12.77(2.67) | <0.001 | 2.6(1.09) | 2.0, 3.2 | <0.001 |
| **WHOQOL-SOCIL, Mean(SD)** | 241 | 13.70(2.66) | 14.77(2.15) | 12.69(2.70) | <0.001 | 2.1(0.85) | 1.5, 2.7 | <0.001 |
| **WHOQOL-ENVIR, Mean(SD)** | 241 | 13.78(2.24) | 14.55(2.06) | 13.06(2.17) | <0.001 | 1.5(0.7) | 0.95, 2.0 | <0.001 |

**Notes**: [a] Median (SD) OR n(Frequency); [b] Pearson's Chi-squared test; Welch Two Sample *t*-test; [c] CI = Confidence Interval; [d] False discovery rate correction for multiple testing.

**Abbreviations**: QIDS, the 16-item Quick Inventory of Depressive Symptomatology Self-Report; HAMD-17, 17-item Hamilton Depression Rating Scale; MDQ, the Mood Disorder Questionnaire; YMRS, the Young Mania Rating Scale; BPRS, the Brief Psychiatric Rating Scale; WHOQOL, the quality-of-life measurement was conducted through the World Health Organization Quality of Life Short Form; PHYS, physical health; PSYCH, psychological; SOCIL, social relationships; ENVIR, environment; ITAQ, the Insight and Treatment Attitude Questionnaire. Logistic regression shows that there was not enough difference in basic information between the groups, and doesn't constitute a confounding factor.


https://doi.org/10.2147/NDT.S466090 DovePress

**Table 2** Logistic Regression Between Patients with or Without Residual Symptoms

| Characteristic | OR[a] | 95% CI[a] | p-value |
|---|---|---|---|
| **Time from diagnosis to first treatment** | 0.88 | 0.72, 1.01 | **0.067** |
| **MDQ1** | 1.51 | 0.99, 2.47 | **0.059** |
| **MDQ2** | 17.1 | 5.17, 75.4 | **<0.001** |
| **QIDS** | 5.28 | 3.24, 10.4 | **<0.001** |
| **PSYCH** | 0.68 | 0.44, 0.98 | **0.041** |
| **ENVIR** | 1.53 | 1.02, 2.42 | **0.039** |

**Note**: [a] OR = Odds Ratio, CI = Confidence Interval.
**Abbreviations**: QIDS, the 16-item Quick Inventory of Depressive Symptomatology Self-Report; MDQ, the Mood Disorder Questionnaire; WHOQOL, the quality-of-life measurement was conducted through the World Health Organization Quality of Life Short Form; PSYCH, psychological factor of WHOQOL; ENVIR, environment factor of WHOQOL.

MDQ2-MDQ3 and the remaining stronger edges being MDQ1-MDQ2, PSYCH-SOCIL, PSYCH-PHYS, HAMD-QIDS, HAMD-BPRS. In the network of patients without depressive residual symptoms, 18 edges had absolute weights greater than 0, the strongest edge was MDQ2-MDQ3, and the remaining stronger edges were SOCIL-PHYS and ENVIR-PSYCH. In the network of patients without residual manic symptoms, 29 edges had absolute weights greater than 0; the strongest edge was QIDS-PSYCH, while the other stronger ones were HAMD-PSYCH, PSYCH-SOCIL, SOCIL-ENVIR, PSYCH-PHYS, QIDS-HAMD, HAMD-BPRS, MDQ3-YMRS, PSYCH occupied an important central position in the entire network.

## Comparison of Networks

For the comparison of the symptom networks of BD patients with residual and those without residual symptoms, the network invariance test resulted in a test statistic of 0.400, with a p-value of 0.025. In the global strength invariance test, the global strength per group was found to be 3.632 for BD patients with residual symptoms and 1.312 for those without residual symptoms. The test statistic was 2.320, with a p-value of 0.002. The Edge Invariance Test and Centrality Invariance Test are presented in Table S3-1 and Table S3-2, respectively. And differences in centrality structure: 50% of nodes had strength differences, with HAMD, MDQ1, and QIDS having significant differences in strength ($P < 0.001$), 33% had expected influence differences ($P < 0.05$), and there was a general difference in closeness, with significant differences in BPRS closeness ($P < 0.01$), intergroup betweenness is relatively consistent. The comparison revealed differences between the two networks on a structural level: the maximum difference in any edge weight was 0.40 ($P < 0.05$), indicating a different overall structure. 4 out of 23 edges have different weights in the two networks (all $P < 0.05$): MDQ1-MDQ2, MDQ2-MDQ3, HAMD-QIDS, and MDQ1-QIDS. Also, global strength differed between the two networks (patients with residual symptoms: 3.63, patients without residual symptoms: 1.312, $P < 0.005$), which means that the symptom network of patients with residual symptoms has denser overall connections and higher sensitivity to symptom mapping and transformation. In comparison, the network of those without residual symptoms has weaker overall connections, and the impact of individual symptoms on the overall network is relatively weak.

Network comparisons between BD patients with depressive residuals and those without residuals revealed no significant differences in overall network structure (test statistic = 0.244, p = 0.404). Similarly, the global strength of symptom connections did not differ significantly between the groups (depressive residuals: 2.532; no depressive residuals: 2.854; test statistic = 0.322, p = 0.709). Results for the Edge Invariance Test and Centrality Invariance Test are presented in Tables S4-1 and S4-2, respectively. There were differences in the centrality structure: the closeness was generally different (all $P < 0.05$), and the depressive residual symptoms network had a more compact central tendency. In addition, 16.7% of nodes had a difference in strength and 8.3% in expected influence, and 25% of nodes' betweenness showed differences (all $P < 0.05$). The comparison revealed differences between the two networks on a structural level: the maximum difference in any edge weight was 0.24 ($P < 0.05$), indicating an overall structural difference. Among the 23 edges, 3 have different weights in the two networks (all $P < 0.05$): HAMD-YMRS and PSYCH-ENVIR. The global strength of the two is close to the same (patients with depressive residual symptoms: 2.53 and patients without depressive

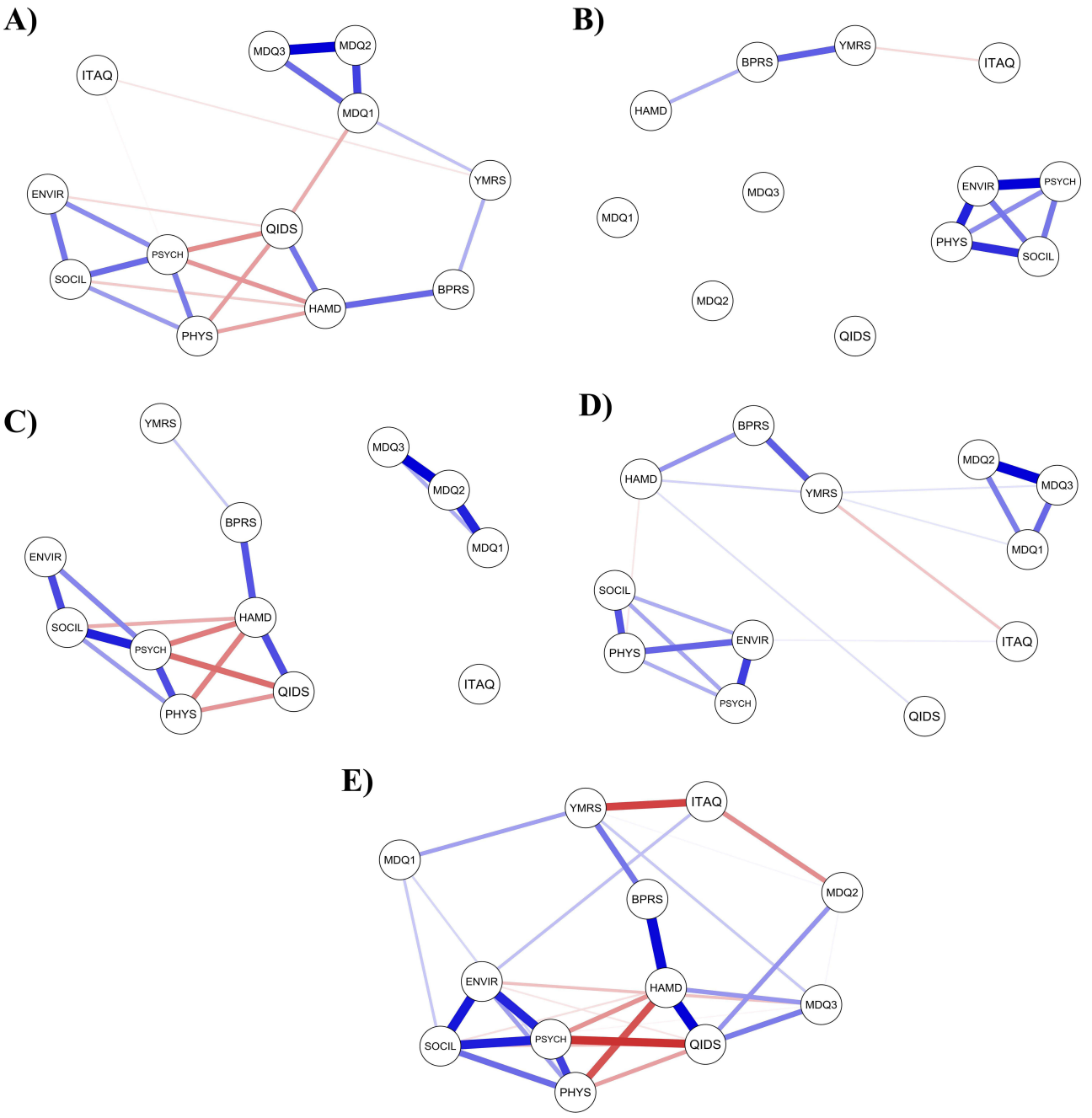


**Figure 1** The symptom network of patients with different types of residual symptoms.
**Note**: (**A**) With residual symptoms (**B**) Without residual symptoms (**C**) With depressive residual symptoms (**D**) Without depressive residual symptoms (**E**) Without manic residual symptoms.
**Abbreviations**: QIDS, the 16-item Quick Inventory of Depressive Symptomatology Self-Report; HAMD-17, 17-item Hamilton Depression Rating Scale; MDQ, the Mood Disorder Questionnaire; YMRS, the Young Mania Rating Scale; BPRS, the Brief Psychiatric Rating Scale; WHOQOL, The quality-of-life measurement was conducted through the World Health Organization Quality of Life Short Form; PHYS, physical health; PSYCH, psychological; SOCIL, social relationships; ENVIR, environment; ITAQ, the Insight and Treatment Attitude Questionnaire.

residual symptoms: 2.85, P=0.41). The global strength of the symptom network for patients with residual symptoms is higher. Still, there was not a significant difference, indicating that the symptom network connection of the population with depressive residual symptoms is even looser than that of the population without it.

## Discussion

To the best of our knowledge, this is the first study to conduct network analysis on the residual symptoms of BD patients, and we have constructed network models to carry on the intergroup comparison. 124 out of 241 patients had residual symptoms, accounting for 51.5%. Among them, depressive residual symptoms were the main residual symptoms, which is consistent with the results of previous studies. It is noteworthy that the population exhibiting residual manic symptoms was too small to develop a network model for manic symptoms. Individuals with residual symptoms, regardless of whether they are depressive or manic, exhibited stronger symptom network connections compared to those without residual symptoms. Interestingly, when examining depressive residual symptoms in isolation, patients with these symptoms displayed weaker network connections compared to those without. Additionally, symptom network connectivity was associated with both social functioning and psychotic symptoms regardless of depressive or manic residual symptom status. These findings highlight the importance of considering both depressive and manic residual symptoms, as focusing on either alone may overlook their respective impacts on social functioning and psychotic symptoms.However, the relationship between depressive residual symptoms is weaker, and the predictability between each other is comparatively worse. These findings also illustrate the distinct nature of residual depressive symptoms and their connections with other symptoms. Previous research indicates that this could be linked to alterations in large-scale functional brain networks associated with BD's residual depressive symptoms, potentially manifesting as a decline in the flexibility in cognitive control, salience detection, and emotion processing.[18] The presence of a loosely structured network of symptoms may be linked to disrupted brain connectivity correlates. In logistic regression, the main influencing factors related to residual symptoms were time from diagnosis to first treatment, MDQ1, MDQ2, QIDS score, PSYCH score, and ENVIR score. The p-value of MDQ2 and QIDS score was less than 0.001, indicating that in the entries of the MDQ scale, MDQ1 and 2 have a higher diagnostic and risk advisory value for residual symptoms, and the predictive value of MDQ2 is higher than MDQ1. MDQ2 focuses on adventurous and irritable behaviors. Although there were fewer individuals with manic residual symptoms compared to those with residual depression, both MDQ1 and the QIDS score were significantly correlated factors, and the Odds Ratio of MDQ1 is the highest, more significant than the OR value of the QIDS score, indicating its strongest correlation. Therefore, it can be considered that the patient's adventurous and irritable behaviors were major risk factors for BD residual symptoms. Although there are more patients with depressive residual symptoms, mania remained less than depression; symptoms such as manic irritability have a higher transformation efficiency towards residual symptoms and are more likely to lead to recurrence; patients with residual irritability and other manic symptoms may be more likely to exhibit depressive residual symptoms, which reflects the mixed symptoms and polarity transformation of BD symptoms. However, MDQ2 is not a central structure based on the network models. In patients with or without depressive residual symptoms, MDQ2 only has a strong association with MDQ1 and MDQ3. The manic symptom triangle of MDQ has a positive correlation with YMRS in the network of depressive residual symptoms, although not strong. The comparison of manic factors in depressive residual symptoms network analysis and the correlation analysis of residual symptoms reflects that manic factors play a crucial role in the residual symptom network but are not strongly reflected in the residual depression system; perhaps it will show more importance in the manic residual symptom system.

The low cohesion and within-network predictability of depressive residual symptoms may be related to the characteristics of the depressive symptoms themselves, which may damage their function of perception, experience, and expression; it is consistent with previous studies[10] showed that poor insight in BD is consistently associated with higher residual depression and manual symptoms and a higher level of cognitive impairment and disability. Since the impairment of insight is also a part of the BD depressive residual symptom system, the low aggregation of the network model caused by it was initially a part of the symptom system characteristics, given the high cohesion in residual symptoms network relative to no residual symptom network and the significant correlation outcome of MDQ anxiety factors in influencing factor analysis. The curative effects could be more apparent when the overall residual symptoms and the manic residual symptom targets were aimed at; clinical doctors can also manage symptoms more efficiently. Our results emphasized the bidirectional characteristics of the BD residual symptom system, which is a highly cohesive system, but once viewed as mania and depression two parts, the presentation differs. At the same time, we emphasized the complex role that individual symptoms may play in the overall burden of patients' psychosocial symptoms.

In previous research on the symptom network of BD, several studies have demonstrated consistency with our findings. Owing to differing methods in classifying symptom nodes and analyzing symptom components, our research serves to complement these studies. For instance, studies have revealed that within the symptom network structure of BD, depressive and manic symptoms exhibit abnormally low and high energy levels, respectively.[19] The energy imbalance is central to the symptoms, potentially elucidating the loosely structured residual depressive symptom network we observed and the high correlation with other nodes of MDQ factors. Another study has shown that mood lability and irritability are not the central symptoms but represent potential warning signs of emergent episodes of either polarity.[20] It's consistent with our research, which emphasizes the risk-warning role of irritability in BD, this is accordant in both the onset and remission. A Study have shown that agitation followed by irritability were the central and highly interconnected nodes in the symptom network of major depressive episodes across BD and major depressive disorder diagnosis.[21] It might show a connection between irritable manic symptoms and depressive disorder. But in the general, it is suggested that the symptom structure of BD is mainly characterized by depressive symptoms. Although manic symptoms are secondary, they can reflect the activity of BD, which has a considerable risk-warning value and the necessity for attention, especially irritability.

Our results can also be combined with the previous research to expand the comprehensive management of BD residual symptoms. Studies show that interventions targeting activity like behavioral activation may improve residual inter-episode mood symptoms;[22] our research further suggested that symptom management can be approached from the patients' physical-mental state or each opposite of manic and depressive symptoms. Although the total score of BD residual symptoms can serve as an indicator of psychosocial symptoms, clinical doctors should evaluate the symptoms separately and consider the potential causes and solutions of each symptom from a patient-central perspective, which may occur in the context of psychotherapy; it can also guide decision-making for the treatment of comorbidities and the management of drug side effects.

Our study's strengths included expanding the research on BD residual symptoms and exploring network analysis and risk factors for BD residual symptoms. Our study brought in and compared multiple groups and divided the symptoms of patients into several parts: depression evaluated by oneself and others, psychiatric symptoms, physical symptoms, social experience, and three factors of manic symptoms. We used the symptom systems to assess the levels in a multidimensional and balanced manner and explored the network structure.

Our results ought to be interpreted in light of the following limitations: the results are limited due to only a portion of patients having residual symptoms, with depression remaining as the main symptom. The sample size of BD patients with manic residual symptoms is relatively tiny, and there was no symptom network analysis for patients with manic residual symptoms. Manic symptoms were an essential part of BD. Even if low-level manic residual symptoms are mixed in with residual symptoms dominated by depression, this portion of residual manic symptoms may also accelerate the overall progression and recurrence of the BD disease, which is also demonstrated by the MDQ factor as the risk factor for residual symptoms. It is necessary to research this aspect of the disease, especially if a balanced sample size can be achieved or by specifically targeting individuals with residual manic symptoms through network analysis. In that case, we may be able to compensate for the lack and consummate the results. The cross-sectional design of the study precludes the determination of causal relationships between the variables examined. Longitudinal studies with repeated assessments would be better suited to establish causal inferences. While the study's generalizability may be limited by its single-center, cross-sectional design and lack of detailed information on excluded participants, the consistency of the findings across different measures suggests that the observed effects are robust and unlikely to be significantly influenced by these limitations. Future research should consider conducting multicenter, longitudinal studies across diverse populations to further enhance the generalizability of the findings and obtain more precise effect size estimates. Our study used the DSM-IV diagnostic system as the standard to ensure consistent diagnoses among the included patients. It's important to note that other diagnostic systems, such as ICD-10, ICD-11, and CCMD, may have different definitions of remission. There may be differences in residual symptoms, and corresponding outcomes that merit further investigation.

## Conclusion

Our findings highlight the complexity of residual symptoms in bipolar disorder and underscore the importance of considering the interconnectedness of symptoms when developing treatment strategies. We especially suggested highlighting the

importance of considering both depressive and manic residual symptoms. Future research should focus on exploring network-based interventions that target specific symptom clusters or connections to improve the management of residual symptoms and enhance overall patient outcomes.

## Acknowledgments

This study is supported by Beijing Municipal Administration of Hospitals Incubating Program, (Grant no. PZ2023032). However, the funding sources had no role in the design of the study, the collection, analysis, interpretation of data, or in writing the manuscript.

## Disclosure

The authors report no conflicts of interest in this work.

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