

Correlation Analysis Between Disease Activity and Anxiety, Depression, Sleep Disturbance, and Quality of Life in Patients with Inflammatory Bowel Disease

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Objective: To explore the correlation between disease activity and anxiety, depression, sleep quality, and quality of life in patients with inflammatory bowel disease (IBD).

Methods: The disease activity of IBD patients was evaluated by 66 gastroenterologists from 42 hospitals in 22 provinces in China from September 2021 to May 2022. Anxiety, depression, sleep quality and quality of life of IBD patients were investigated and statistically analyzed by different scales, including Generalized Anxiety Disorder 7-item Scale (GAD-7), Patient Health Questionnaire-9 (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), and Inflammatory Bowel Disease Quality-of-Life Questionnaire (IBD-Q).

Results: A total of 2478 IBD patients were included, of which 1532 (61.8%) were in active stage and 946 (38.2%) were in remission. The proportions of active IBD with anxiety, depression, sleep disturbance, and poor quality of life were 29.5%, 29.7%, 71.1%, and 50.1%, respectively, while the proportions of remission IBD with anxiety, depression, sleep disturbance, and poor quality of life were 19.1%, 24.4%, 69.3%, and 17.4%, respectively. IBD patients who also had anxiety, depression, sleep disturbances and poor quality of life had 80 cases (8.46%) in remission and 114 cases (7.44%) in active stage, with 54 cases (9.18%) in mild activity, 51 cases (6.95%) in moderate activity and 9 cases (4.49%) in severe activity. IBD patients with different disease activity levels differed in GAD-7 scores, PHQ-9 scores, PSQI scores, and IBD-Q scores (all $P < 0.001$). In IBD patients, anxiety, depression, and sleep disturbance, which interact with each other, can further aggravate their disease activity (all $P < 0.001$).

Conclusion: Anxiety, depression, sleep disturbances, and quality of life are strongly correlated with disease activity in IBD patients, and IBD patients with psychological disturbances are most often in the active stage and have a poor quality of life.

Keywords: inflammatory bowel disease, disease activity, anxiety, depression, sleep quality, quality of life, survey

Introduction

Inflammatory bowel disease (IBD) is a systemic, autoimmune and recurrent chronic nonspecific inflammatory disease of the intestine that requires lifelong monitoring and treatment, and whose pathophysiological mechanisms are not yet

understood, known as the “green cancer”.¹ IBD, which mainly includes ulcerative colitis (UC), Crohn’s disease (CD) and Inflammatory Bowel Disease Unclassified (IBD-U), has affected more than 6.8 million people worldwide and its incidence and prevalence are increasing worldwide.^{2,3} Long-term drug maintenance is the foundation of IBD treatment.

In recent years, the social pressure on patients has gradually increased and the problem of mental health disorders has become more serious due to various factors, and the disease activity of patients with IBD would be influenced.^{4,5} Anxiety/depression is at least twice as prevalent in IBD as in the general population, and depression accounts for approximately 34.7% of IBD active patients and 19.9% of IBD remission patients.^{6,7} The brain-gut axis is the link between the physiological connection between the human central nervous system and the gastrointestinal tract, and psychological disorders may affect gastrointestinal function by generating a stress response, which leads to activation of the hypothalamic–pituitary–adrenal axis exacerbating the intestinal inflammatory response. In addition, reduced bacterial diversity and pro-inflammatory bacterial microbiota are associated with IBD disease activity,⁸ and may modulate brain development, function, and behavior through immune, endocrine, and neural pathways of the brain-gut-microbiota axis.⁹

This study is the first large-sample study in China to collect basic information from IBD patients through a multicenter and to assess the correlation between mental health status and quality of life of IBD patients through relevant scales. It mainly analyzes the clinical data of patients with active and remitting IBD, further analyzes the correlation between anxiety, depression, sleep disorders and quality of life and disease activity, and aids patients and clinicians in monitoring and treating IBD activity, and also strengthens the correct understanding of mental health status and the importance of psychological treatment for IBD patients, so as to achieve early screening and treatment of psychological disorders at the early stage of the disease.

Methods

Study Design and Patient Population

This is a national multicenter cross-sectional survey on the correlation between disease activity and the mental psychological state, and quality of life in IBD patients in China, conducted by the Psychology Club of IBD Group of Gastroenterology Society of Chinese Medical Association and the Chinese Association for Mental Hygiene from September 2021 to May 2022. Uniformly trained investigators explained to eligible patients the purpose, methods, voluntary participation, and harmlessness of the results of the survey, and obtained informed consent, during which standardized speech techniques were used. In this study, IBD patients were investigated by an online survey platform system. Sixty-six gastroenterologists from 42 hospitals in 22 provinces (autonomous regions and municipalities) in China participated in this study, and a total of 2478 valid questionnaires were included, including 1532 patients in active stage (967 with UC and 565 with CD) and 946 patients in remission (404 with UC and 542 with CD).

Inclusion criteria: patients diagnosed with IBD according to the consensus opinion on the diagnosis and treatment of IBD formulated by the Chinese Society of Gastroenterology in 2018;⁹ age ≥ 18 years; patients who could understand and agree to be surveyed (willingness to accept physician management and psychological aspects of the survey, submission to management of medication adherence, etc.).

Study Assessments and Data Collection

General Information Collection

The general clinical data of IBD patients were collected, and 66 attending physicians with extensive work experience from 42 hospitals nationwide were trained to refine the scores of the patients, and the modified Mayo score and CDAI score were used to assess the disease activity of UC and CD, respectively. Modified Mayo score and CDAI score are currently the most commonly used clinical indicators to evaluate disease activity and efficacy. The modified Mayo score: <2 is considered in remission, 3–5 is mild activity, 6–10 is moderate activity, and 11–12 is severe activity;¹⁰ the CDAI score: <150 is clinical remission, 150–220 is mild activity, 219–450 is moderate activity, and >450 is severe activity.¹¹

Generalized Anxiety Disorder 7-Item Scale (GAD-7) and Patient Health Questionnaire-9 (PHQ-9)

GAD-7 is a widely used anxiety screening scale and has been validated in several studies with a sensitivity of 89% and specificity of 82%.¹² It includes 7 entries, each with a score of 0 to 3 and a total score between 0 and 21. PHQ-9 is

a widely used international universal depression screening scale with 88% sensitivity and 88% specificity.¹³ It consists of nine main entries, each with a score of 0 to 3 and a total score between 0 and 27. Ten points were taken as the cut-off point in this study. The score ranges for anxiety and depressive symptom severity in the results of both GAD-7 and PHQ-9 are as follows: minimal symptoms (0–4), mild,^{5–9} moderate,^{10–15} and severe (15+) symptoms. In addition, the GAD-7, PHQ-9 and PSQI are simple to operate and have been validated by domestic and international studies to have reliable diagnostic sensitivity and specificity for anxiety disorders, depression and sleep disorders and are also widely used in various studies in China.^{14–17}

Pittsburgh Sleep Quality Index (PSQI)

PSQI is used to evaluate the sleep quality of the subjects in the last 1 month. There are 7 dimensions and 9 entries with a total score between 0 and 21, where a score higher than 5 indicates a sleep quality problem, 0 to 5 indicates good sleep quality, 6 to 10 indicates moderate sleep quality, 11 to 15 indicates poor sleep quality, and 16 to 21 indicates very poor sleep quality.

Inflammatory Bowel Disease Quality-of-Life Questionnaire (IBD-Q)

IBD-Q has been widely used to evaluate the quality of life of IBD patients, including 4 dimensions of bowel symptoms, systemic symptoms, emotional ability, and social ability, with a total of 32 items.¹⁸ Each item is divided into 7 levels, counting from 1 to 7, with 1 indicating the most severe degree and 7 indicating the least severe degree. The total score ranged from 32 to 224, and the higher the total score, the better the patient's quality of survival.

Study Size

The sample size needed for the questionnaire survey was calculated according to the principles of international psychometrics and questionnaire design. If the number of items in the questionnaire increases, the recommended sample size will increase, that is, 5–20 times the number of items in the questionnaire. If N is the number of questionnaire items in this study, the sample size is at least $5N$. In addition, about 10% of the questionnaires may be withdrawn or invalid, so the sample size needs to be $5.5N$. Therefore, the sample size should be greater than 451. Considering the large population and other confounding factors in our country, we try to expand the sample size when conducting the study. Therefore, 2478 questionnaires were finally included in the study.

Statistical Analysis

SPSS 27.0, GraphPad prism, and Excel 2021 software were used for data entry, statistical analysis, and visualization in this study. Count data were expressed as frequencies and percentages using the cross-tabulated χ^2 test or Fisher's exact test. The measurement data that conformed to normal distribution were expressed as $\bar{X} \pm S$, and t -test or non-parametric test was used. The test level for this study was $\alpha = 0.05$, and $P < 0.05$ was considered a statistically significant difference.

Results

Clinical Characteristics of IBD Patients of Different Disease Activity

A total of 2478 patients with IBD were included, including 1371 (55.33%) with UC and 1107 (44.67%) with CD. A total of 1532 (61.8%) and 946 (38.2%) patients with IBD were in the active and remission stages, respectively, and 967 (70.5%) and 565 (51.4%) patients with UC and CD, respectively, were in the active stage. Age and gender were associated with disease activity in IBD patients (both $P < 0.05$). The mean age of patients with IBD in the active stage was 38.57 ± 12.48 years, and the proportion of women in the active stage was higher than in the remission stage (39.8% vs 33.9%) (Table 1).

Anxiety, Depression, Sleep Quality and Quality of Life in IBD Patients of Different Disease Activity

As shown in Table 2 and Table 3 and Figures 1 and 2, the proportion of anxiety in active stage was significantly higher than that in remission (IBD: 29.4% vs 19.1%, $P < 0.001$; UC: 31.4% vs 21.0%, $P < 0.001$; CD: 25.8% vs 17.7%, $P = 0.001$), and

Table I General Clinical Features with Remission and Activity in Patients of Inflammatory Bowel Disease

| | IBD | | | | UC | | | | CD | | | |
|--------|--------------|---------------|--------------|-------|-------------|--------------|---------------|-------|-------------|---------------|---------------|-------|
| | All | Remission | Activity | p | All | Remission | Activity | p | All | Remission | Activity | p |
| Age | 37.96±12.544 | 36.98±12.591 | 38.57±12.481 | 0.002 | 41.64±12.59 | 42.44±12.826 | 41.31±12.483 | 0.131 | 33.40±10.88 | 32.91±10.748 | 33.87±10.998 | 0.141 |
| Gender | | | | 0.004 | | | | 0.592 | | | | 0.205 |
| Male | 1547(62.4) | 625(66.1) | 922(60.2) | | 754(55.00) | 227(56.2) | 527(54.5) | | 793(71.6) | 398(73.4) | 395(69.9) | |
| Female | 931(37.6) | 321(33.9) | 610(39.8) | | 617(45.00) | 177(43.8) | 440(45.5) | | 314(28.4) | 144(26.6) | 170(30.1) | |
| Weight | 61.51±11.76 | 61.961±11.539 | 61.23±11.893 | 0.133 | 62.57±11.81 | 63.0±11.935 | 62.396±11.756 | 0.388 | 60.19±11.57 | 61.187±11.183 | 59.235±11.869 | 0.005 |

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; *P*, *P* value.

Table 2 Anxiety, Depression, Sleep Quality, and Quality of Life in IBD Patients in Activity Compared with in Remission

| | IBD | | | | UC | | | | CD | | | |
|----------------------|------------|-----------|------------|--------|-----------|-----------|-----------|--------|-----------|-----------|-----------|--------|
| | All | Remission | Activity | P | All | Remission | Activity | P | All | Remission | Activity | P |
| Anxiety | | | | <0.001 | | | | <0.001 | | | | 0.001 |
| No (GAD-7<10) | 1847(74.5) | 765(80.9) | 1082(70.6) | | 982(71.6) | 319(79.0) | 663(68.6) | | 865(78.1) | 446(82.3) | 419(74.2) | |
| Yes (GAD-7≥10) | 631(25.5) | 181(19.1) | 450(29.4) | | 389(28.4) | 85(21.0) | 304(31.4) | | 242(21.9) | 96(17.7) | 146(25.8) | |
| Symptom Severity | | | | <0.001 | | | | 0.002 | | | | <0.001 |
| Minimal | 976(39.4) | 405(42.8) | 571(37.3) | | 539(39.3) | 172(42.6) | 367(38.0) | | 437(39.5) | 233(43.0) | 204(36.1) | |
| Mild | 871(35.1) | 360(38.1) | 511(33.4) | | 443(32.4) | 147(36.4) | 296(30.5) | | 428(38.7) | 213(39.3) | 215(38.1) | |
| Moderate | 397(16.1) | 125(13.2) | 272(17.7) | | 246(17.9) | 54(13.4) | 192(19.9) | | 151(13.6) | 71(13.1) | 80(14.2) | |
| Severe | 234(9.4) | 56(5.9) | 178(11.6) | | 143(10.4) | 31(7.7) | 112(11.6) | | 91(8.2) | 25(4.6) | 66(11.7) | |
| Depression | | | | <0.001 | | | | <0.001 | | | | 0.032 |
| No (PHQ-9<10) | 1741(70.3) | 715(75.6) | 1026(67.0) | | 941(68.6) | 307(76.0) | 634(65.6) | | 800(72.3) | 408(75.3) | 392(69.4) | |
| Yes (PHQ-9≥10) | 737(29.7) | 231(24.4) | 506(33.0) | | 430(31.4) | 97(24.0) | 333(34.4) | | 307(27.7) | 134(24.7) | 173(30.6) | |
| Symptom Severity | | | | <0.001 | | | | 0.001 | | | | 0.002 |
| Minimal | 1032(41.6) | 426(45.0) | 606(39.6) | | 588(42.9) | 188(46.5) | 400(41.4) | | 444(40.1) | 238(43.9) | 206(36.5) | |
| Mild | 709(28.6) | 289(30.5) | 420(27.4) | | 353(25.7) | 119(29.5) | 234(24.2) | | 356(32.2) | 170(31.4) | 186(32.9) | |
| Moderate | 422(17.1) | 149(15.8) | 273(17.8) | | 243(17.7) | 59(14.6) | 184(19.0) | | 179(16.2) | 90(16.6) | 89(15.8) | |
| Severe | 315(12.7) | 82(8.7) | 233(15.2) | | 187(13.6) | 38(9.4) | 149(15.4) | | 128(11.6) | 44(8.1) | 84(14.9) | |
| Sleep disturbance | | | | 0.145 | | | | 0.842 | | | | 0.069 |
| No (PSQI≤5) | 717(28.9) | 290(30.7) | 427(27.9) | | 376(27.4) | 109(27.0) | 267(27.6) | | 341(30.8) | 181(33.4) | 160(28.3) | |
| Yes (PSQI>5) | 1761(71.1) | 656(69.3) | 1105(72.1) | | 995(72.6) | 295(73.0) | 700(70.4) | | 766(69.2) | 361(66.6) | 405(71.7) | |
| Sleep quality | | | | <0.001 | | | | 0.032 | | | | <0.001 |
| Good | 987(39.8) | 412(43.6) | 575(37.5) | | 542(39.5) | 173(42.8) | 369(38.2) | | 445(40.2) | 239(44.1) | 206(36.5) | |
| Medium | 1073(43.3) | 417(44.1) | 656(42.8) | | 579(42.2) | 176(43.6) | 403(41.7) | | 494(44.6) | 241(44.5) | 253(44.8) | |
| Poor | 353(14.2) | 102(10.7) | 251(16.4) | | 215(15.7) | 46(11.4) | 169(17.5) | | 138(12.5) | 56(10.3) | 82(14.5) | |
| Very poor | 65(2.6) | 15(1.6) | 50(3.3) | | 35(2.6) | 9(2.2) | 26(2.7) | | 30(2.7) | 6(1.1) | 24(4.2) | |
| Quality of life | | | | <0.001 | | | | <0.001 | | | | <0.001 |
| Poor (IBD-Q<169) | 933(37.7) | 165(17.4) | 768(50.1) | | 578(42.2) | 71(17.6) | 507(52.4) | | 355(32.1) | 94(17.3) | 261(46.2) | |
| Not poor (IBD-Q≥169) | 1545(62.3) | 781(82.6) | 764(49.9) | | 793(57.8) | 333(82.4) | 460(47.6) | | 752(67.9) | 448(82.7) | 304(53.8) | |

Abbreviations: GAD-7, Generalized Anxiety Disorder 7-item Scale; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; IBD-Q, Inflammatory Bowel Disease Quality-of-Life Questionnaire; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; P, P value.

Table 3 Anxiety, Depression, Sleep Quality, and Quality of Life in IBD Patients in Mild, Moderate, Severe Activity

| | IBD (n = 1532) | | | | | UC (n = 967) | | | | | CD (n = 565) | | | | |
|----------------------|----------------|-----------|-----------|-----------|--------|--------------|-----------|-----------|-----------|--------|--------------|-----------|-----------|----------|--------|
| | All | Mild | Moderate | Severe | P | All | Mild | Moderate | Severe | P | All | Mild | Moderate | Severe | P |
| Anxiety | | | | | 0.011 | | | | | 0.051 | | | | | 0.243 |
| No (GAD-7<10) | 1082(70.6) | 422(71.8) | 530(72.2) | 130(61.9) | | 663(68.6) | 258(69.9) | 324(70.1) | 81(59.6) | | 419(74.2) | 164(74.9) | 206(75.7) | 49(66.2) | |
| Yes (GAD-7≥10) | 450(29.4) | 166(28.2) | 204(27.8) | 80(38.1) | | 304(31.4) | 111(30.1) | 138(29.9) | 55(40.4) | | 146(25.8) | 55(25.1) | 66(24.3) | 25(33.8) | |
| Symptom Severity | | | | | 0.040 | | | | | 0.082 | | | | | 0.758 |
| Minimal | 571(37.3) | 209(35.5) | 295(40.2) | 67(31.9) | | 367(38.0) | 130(35.2) | 192(41.6) | 45(33.1) | | 204(36.1) | 79(36.1) | 103(37.9) | 22(29.7) | |
| Mild | 511(33.4) | 213(36.2) | 235(32.0) | 63(30.0) | | 296(30.6) | 128(34.7) | 132(44.5) | 36(26.5) | | 215(38.1) | 85(38.8) | 103(37.9) | 27(36.5) | |
| Moderate | 272(17.8) | 98(16.7) | 127(17.3) | 47(22.4) | | 192(19.9) | 69(18.7) | 90(19.5) | 33(17.2) | | 80(14.2) | 29(13.2) | 37(13.6) | 14(18.9) | |
| Severe | 178(11.6) | 68(11.6) | 77(10.5) | 33(15.7) | | 112(11.6) | 42(11.4) | 48(10.4) | 22(16.2) | | 66(11.7) | 26(11.9) | 29(10.7) | 11(14.9) | |
| Depression | | | | | 0.017 | | | | | 0.02 | | | | | 0.588 |
| No (PHQ-9<10) | 1026(67.0) | 396(67.3) | 507(69.1) | 123(58.6) | | 634(65.6) | 245(66.4) | 314(68.0) | 75(55.1) | | 392(69.4) | 151(68.9) | 193(71.0) | 48(64.9) | |
| Yes (PHQ-9≥10) | 506(33.0) | 192(32.7) | 227(30.9) | 87(41.4) | | 333(34.4) | 124(33.6) | 148(32.0) | 61(44.9) | | 173(30.6) | 68(31.1) | 79(29.0) | 26(35.1) | |
| Symptom Severity | | | | | 0.060 | | | | | 0.203 | | | | | 0.387 |
| Minimal | 606(39.6) | 238(40.5) | 303(41.3) | 65(31.0) | | 400(41.4) | 155(42.0) | 199(43.1) | 46(33.8) | | 206(36.5) | 83(37.9) | 104(38.3) | 19(25.7) | |
| Mild | 420(27.4) | 158(26.9) | 204(27.8) | 58(27.5) | | 234(24.2) | 90(24.4) | 115(24.9) | 29(21.3) | | 186(32.9) | 68(31.1) | 89(32.7) | 29(39.2) | |
| Moderate | 273(17.8) | 99(16.7) | 130(17.7) | 44(21.0) | | 184(19.0) | 67(18.2) | 85(18.4) | 32(23.6) | | 89(15.8) | 32(14.6) | 45(16.5) | 12(16.2) | |
| Severe | 233(15.2) | 93(15.8) | 97(13.6) | 43(20.5) | | 149(15.4) | 57(15.4) | 63(13.6) | 29(21.3) | | 84(14.9) | 36(16.4) | 34(12.5) | 14(18.9) | |
| Sleep disturbance | | | | | 0.056 | | | | | 0.077 | | | | | 0.583 |
| No (PSQI≤5) | 427(27.9) | 163(27.7) | 219(29.8) | 45(21.4) | | 267(27.6) | 103(27.9) | 137(29.7) | 27(19.9) | | 160(28.3) | 60(27.4) | 82(30.1) | 18(24.3) | |
| Yes (PSQI>5) | 1105(72.1) | 425(72.3) | 515(70.2) | 165(78.6) | | 700(72.4) | 266(72.1) | 325(70.3) | 109(80.1) | | 405(71.7) | 159(72.6) | 190(69.9) | 56(75.7) | |
| Sleep quality | | | | | <0.001 | | | | | <0.001 | | | | | 0.458 |
| Good | 575(37.5) | 225(38.3) | 288(39.2) | 62(29.5) | | 369(38.2) | 147(39.8) | 183(39.6) | 39(28.7) | | 206(36.5) | 78(35.6) | 105(38.6) | 23(31.1) | |
| Medium | 656(42.8) | 266(45.2) | 312(42.5) | 78(37.1) | | 403(41.6) | 162(43.9) | 194(42.0) | 47(34.6) | | 253(44.8) | 104(47.5) | 118(43.4) | 31(41.9) | |
| Poor | 251(16.4) | 78(13.3) | 118(16.1) | 55(26.2) | | 169(17.5) | 51(13.8) | 78(16.9) | 40(29.3) | | 82(14.5) | 27(12.3) | 40(14.7) | 15(20.3) | |
| Very poor | 50(3.3) | 19(3.2) | 16(2.2) | 15(7.1) | | 26(2.7) | 9(2.4) | 7(1.5) | 10(7.4) | | 24(4.2) | 10(4.6) | 9(3.3) | 5(6.7) | |
| Quality of life | | | | | <0.001 | | | | | <0.001 | | | | | <0.001 |
| Poor (IBD-Q<169) | 768(50.1) | 235(40.0) | 384(52.3) | 149(71.0) | | 507(52.4) | 149(40.4) | 262(56.7) | 96(70.6) | | 261(46.2) | 86(39.3) | 122(44.9) | 53(71.6) | |
| Not poor (IBD-Q≥169) | 764(49.9) | 353(60.0) | 350(47.7) | 61(29.0) | | 460(47.6) | 220(59.6) | 200(43.3) | 40(29.4) | | 304(53.8) | 133(60.7) | 150(55.1) | 21(28.4) | |

Abbreviations: GAD-7, Generalized Anxiety Disorder 7-item Scale; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; IBD-Q, Inflammatory Bowel Disease Quality-of-Life Questionnaire; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; P, P value.

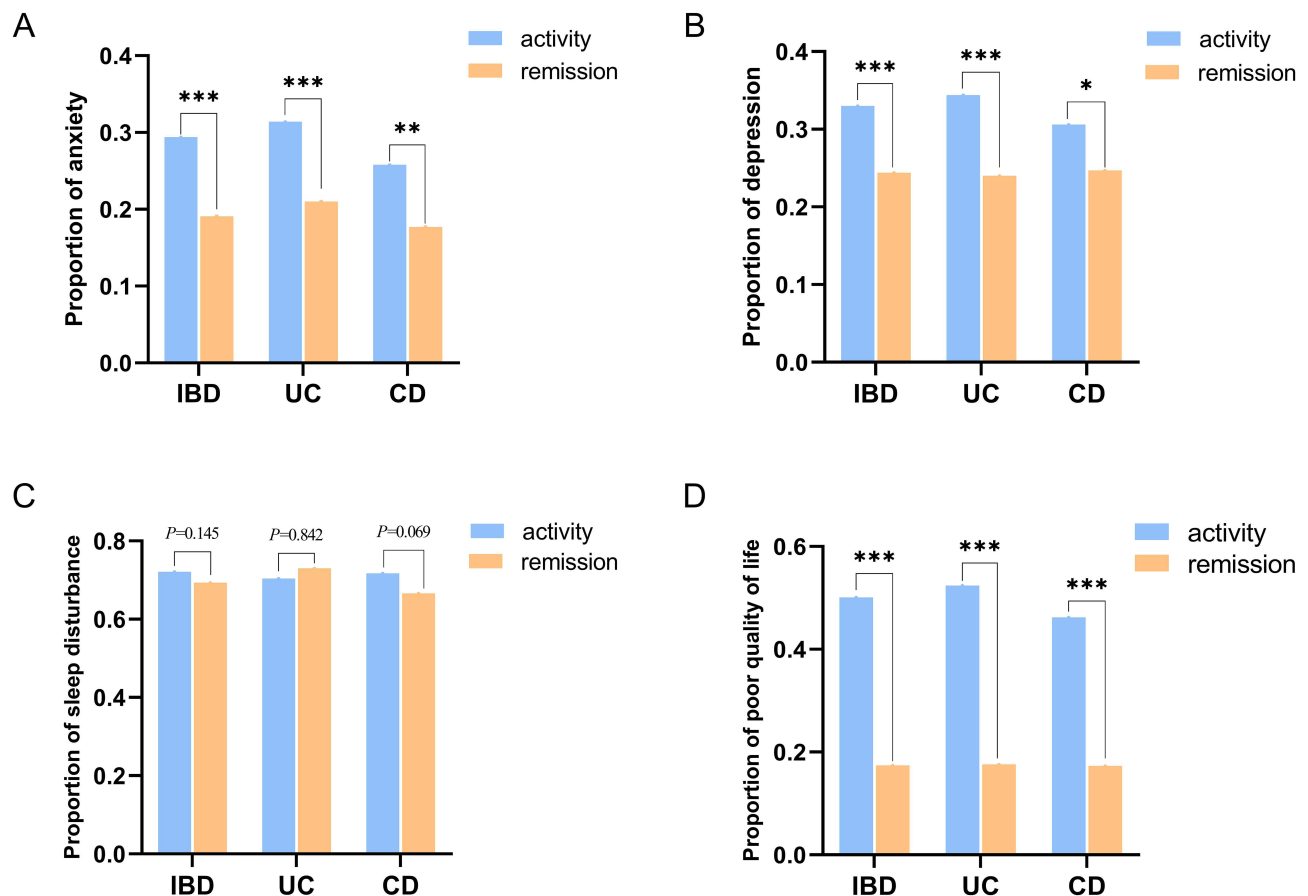


Figure 1 Proportions of anxiety (A), depression (B), sleep disturbance (C) and poor quality of life (D) in IBD patients with different disease activity (*** $P<0.001$, ** $P<0.01$, * $P<0.05$).

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

there were differences in the severity of anxiety in different disease activity (IBD: $P=0.011$; UC: $P=0.051$; CD: $P=0.243$). The proportion of depression in active stage was higher than that in remission (IBD: 33.0% vs 24.4%, $P<0.001$; UC: 34.4% vs 24.0%, $P<0.001$; CD: 30.6% vs 24.7%, $P=0.032$), and there were differences in the severity of depression in different disease activity (IBD: $P=0.017$; UC: $P=0.02$; CD: $P=0.588$). There was no statistical difference in the proportion of sleep disturbances between active IBD patients and those in remission (IBD: 72.1% vs 69.3%, $P=0.145$; UC: 70.4% vs 73.0%, $P=0.842$; CD: 71.7% vs 66.6%, $P=0.069$), and the proportion of poor quality of life in active stage was higher than that in remission (IBD: 50.1% vs 17.4%, $P<0.001$; UC: 52.4% vs 17.6%, $P<0.001$; CD: 46.2% vs 17.3%, $P<0.001$).

Comorbid Anxiety, Depression, Sleep Disturbances, and Poorer Quality of Life Among IBD Patients of Different Disease Activities

In 1532 active patients, there were 11 (0.72%), 10 (0.65%), 245 (16.01%), and 242 (15.80%) patients with anxiety, depression, sleep disturbance, and poor quality of life only, respectively, and 114 (7.44%) patients with both anxiety, depression, sleep disturbance, and poor quality of life, as shown in Figure 3A. In 946 patients in remission, there were 1 (0.11%), 0 (0%), 56 (5.92%), and 251 (26.53%) patients with anxiety, depression, sleep disturbance, and poor quality of life only, respectively, and 80 (8.46%) patients with both anxiety, depression, sleep disturbance, and poor quality of life, as shown in Figure 3B. Among the 588 patients with mild activity, 54 patients (9.18%) had a combination of anxiety, depression, sleep disturbance and poor quality of life, as shown in Figure 3C. Among the 734 patients with moderate activity, 51 patients (6.95%) had a combination of anxiety, depression, sleep disturbance and poor quality of life, as

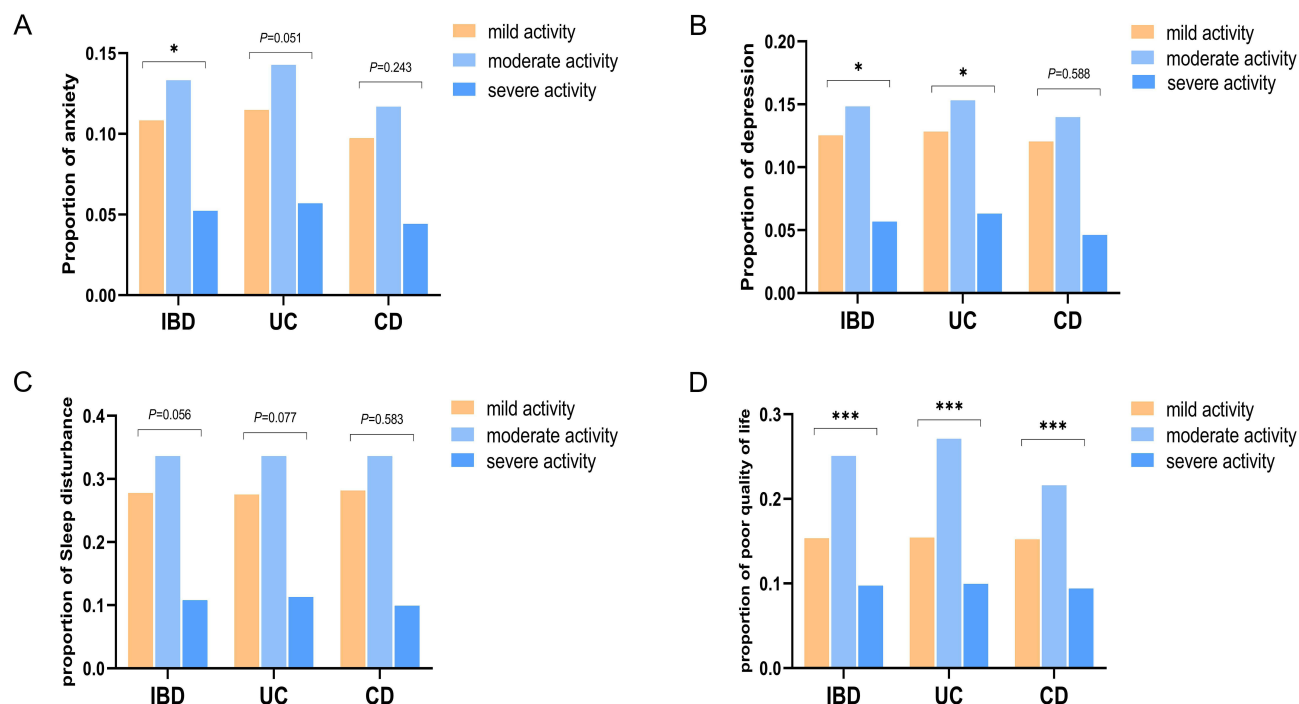


Figure 2 Proportions of anxiety (A), depression (B), sleep disturbance (C) and poor quality of life (D) in patients with mild, moderate and moderately active IBD (** $P < 0.001$, * $P < 0.05$).

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

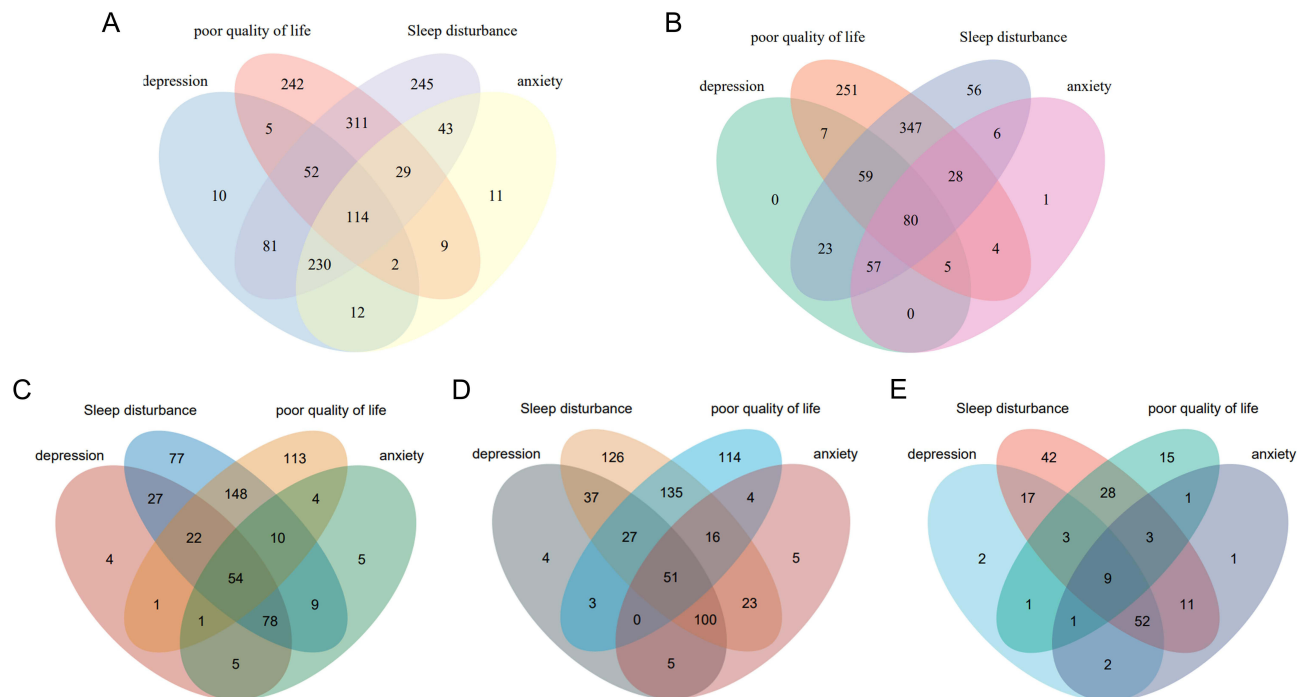


Figure 3 Venn diagram of comorbid anxiety, depression, sleep disturbance and poor quality of life in IBD patients with different disease activity (A): active stage, (B): remission stage, (C): mild activity, (D): moderate activity, (E): severe activity.

Abbreviation: IBD, inflammatory bowel disease.

shown in Figure 3D. Among 210 patients with severe activity, there were 9 patients (4.49%) with combined anxiety, depression, sleep disturbance and poor quality of life, as shown in Figure 3E.

Scores of GAD-7, PHQ-9, PSQI, and IBD-Q in IBD Patients of Different Disease Activity

IBD patients with different degrees of disease activity differed in GAD-7 scores, PHQ-9 scores, PSQI scores, and IBD-Q scores (all $P < 0.001$). GAD-7 scores, PHQ-9 scores, and PSQI scores were higher in the active stage of IBD (including UC and CD) than in remission ($P < 0.001$), and total IBD-Q scores were higher in IBD patients in remission ($P < 0.001$), see Table 4 and Figure 4. Scores of GAD-7, PHQ-9, PSQI, and IBD-Q were significantly different in IBD patients with mild and moderately severe activity ($P < 0.001$) (Table 5). When anxiety, depression, and sleep disturbance were present together, the three interact with each other to further aggravate disease activity (Table 6).

Discussion

IBD is a chronic disabling disease that affects mental health and overall quality of life, and its prevalence is gradually increasing worldwide.^{19–22} In this study of 2478 Chinese patients with IBD, it was found that 25.5% and 29.7% of IBD patients were eligible for moderate-to-severe anxiety and depression, and that different levels of anxiety/depression were closely related to different levels of disease activity. It was found that patients with IBD are mostly in the active phase of the disease when there are psychosomatic problems of anxiety, depression, and sleep disturbance. The results of this study are related to the recurrent nature of the IBD disease course, lifelong medication monitoring, adverse drug reactions, and financial burden, which will lead to significant psychological stress in these patients, which was verified by several clinical trials.^{23–27} In this study, with 38.1% and 41.4% of IBD patients with combined anxiety/depression and at severe activity, respectively. In a study by Lewis et al²⁸ of 242 patients with IBD, it was found that 30.6% and 40.1% of patients met the diagnostic criteria for anxiety and depression, respectively, but about 1/3 and 2/3 were undiagnosed. In this study, the active patients with anxiety and depression accounted for 29.4% and 33.0%, respectively, and none of them was given corresponding psychological treatment. In addition, above an animal experimental study of IBD activity, it was found that a mouse model of colitis in a depressed state reactivated intestinal inflammation,²⁹ and its activity remitted after active psychotherapy.³⁰ Clinical studies have further confirmed that immunotherapy can decrease the PHQ-9 score of IBD patients and significantly improve the risk of moderate and severe depression in IBD patients,³¹ mainly because there is a bidirectional nature between mental health status and IBD, and the two affect each other.^{32,33} Patients with IBD with psychological disorders have increased sympathetic autonomic activity and catecholamine secretion from the adrenal medulla, which exacerbates the inflammatory response by stimulating mast cells and macrophages, which in turn leads to increased disease activity.^{33,34} The bidirectional role of the brain-gut axis plays an important role in the development of disease activity, and the anxiety/depression can increase the activity of IBD disease by reactivating inflammation through multiple pathways,^{4,35–38} as well as leading to poor patient compliance with treatment and further

Table 4 Scores of GAD-7, PHQ-9, PSQI, and IBD-Q in IBD Patients in Activity Compared with in Remission (Scores, $\bar{X} \pm S$)

| Projects | IBD | | | UC | | | CD | | |
|-------------------|---------------|---------------|--------|---------------|---------------|--------|---------------|---------------|--------|
| | Remission | Activity | P | Remission | Activity | P | Remission | Activity | P |
| GAD-7 score | 5.92±4.643 | 7.05±5.459 | <0.001 | 6.21±4.940 | 7.12±5.582 | 0.012 | 5.71±4.402 | 6.93±5.245 | <0.001 |
| PHQ-9 score | 6.25±5.405 | 7.51±6.402 | <0.001 | 6.22±5.563 | 7.38±6.452 | 0.011 | 6.27±5.290 | 7.72±6.317 | 0.001 |
| PSQI score | 6.46±3.448 | 7.17±3.922 | <0.001 | 6.65±3.491 | 7.15±3.924 | 0.045 | 6.32±3.412 | 7.21±3.923 | 0.002 |
| IBD-Q score | 189.84±23.513 | 167.16±31.898 | <0.001 | 189.50±24.175 | 165.32±32.992 | <0.001 | 190.09±23.027 | 170.32±29.687 | <0.001 |
| Bowel symptoms | 62.49±7.353 | 54.55±10.531 | <0.001 | 62.24±7.749 | 53.28±10.843 | <0.001 | 62.67±7.004 | 56.72±9.603 | <0.001 |
| Systemic symptoms | 29.10±4.416 | 25.75±5.574 | <0.001 | 29.18±4.427 | 25.67±5.710 | <0.001 | 29.04±4.411 | 25.90±5.334 | <0.001 |
| Emotional ability | 71.34±10.248 | 62.73±13.066 | <0.001 | 71.01±10.549 | 62.23±13.243 | <0.001 | 71.54±10.022 | 63.59±12.723 | <0.001 |
| Social ability | 26.91±4.111 | 24.13±5.234 | <0.001 | 27.01±4.028 | 24.14±5.418 | <0.001 | 26.84±4.174 | 24.11±4.935 | <0.001 |

Abbreviations: GAD-7, Generalized Anxiety Disorder 7-item Scale; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; IBD-Q, Inflammatory Bowel Disease Quality-of-Life Questionnaire; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; P, P value.

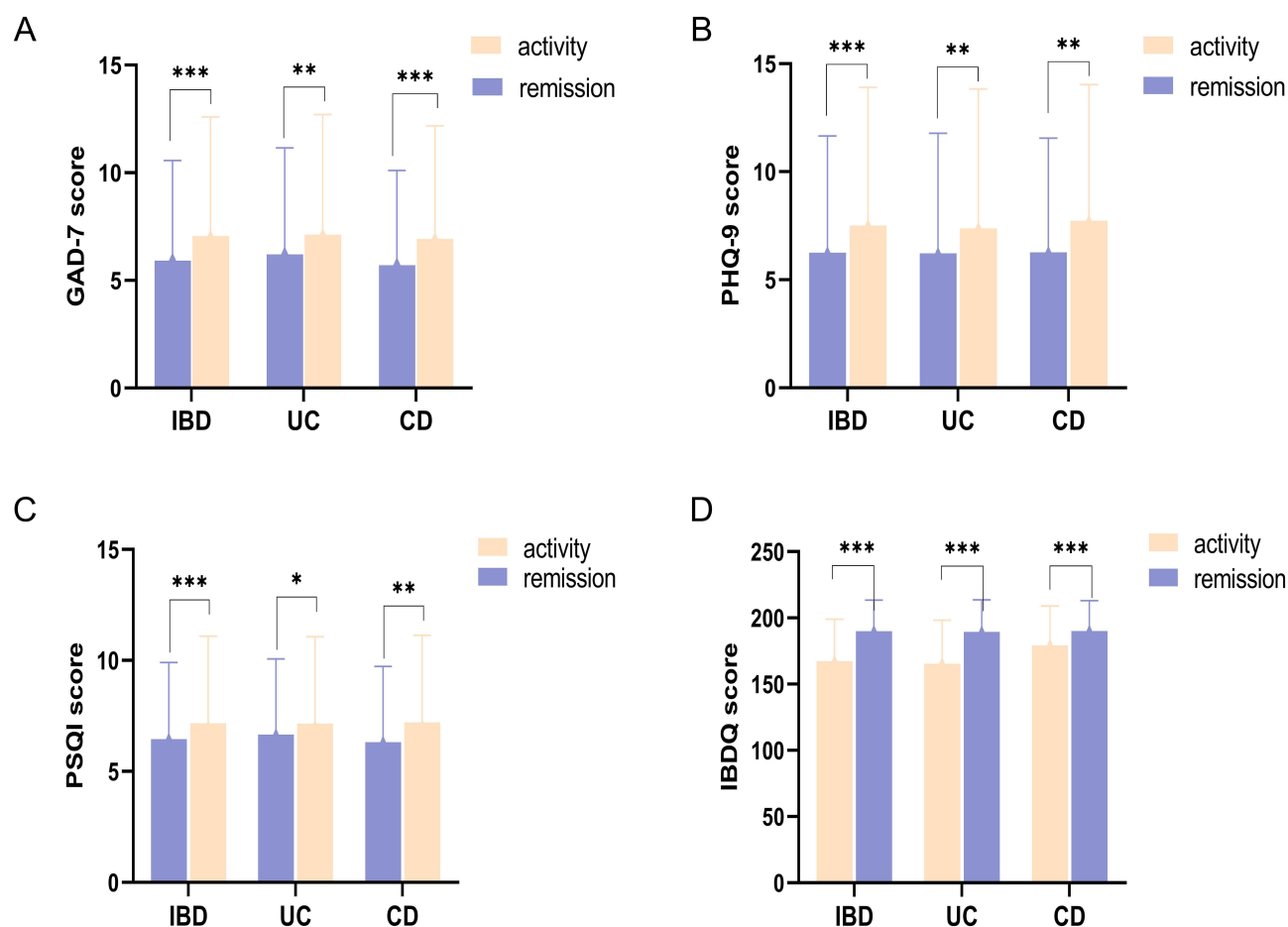


Figure 4 GAD-7 score (A), PHQ-9 score (B), PSQI score (C), and IBD-Q score (D) in IBD patients with different disease activity (*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$). **Abbreviations:** IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; GAD-7, Generalized Anxiety Disorder 7-item Scale; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; IBD-Q, Inflammatory Bowel Disease Quality-of-Life Questionnaire.

morbidity and mortality.^{39–41} In addition, patients with mild anxiety were also in the majority in this study. Therefore, routine psychological assessment is important in the assessment of disease activity to effectively identify patients at higher risk of disease activity at an early stage.⁴² Improving the distress of psychosocial factors and alleviating anxiety/depression in patients with IBD through psychological state regulation can not only improve disease activity but also optimize quality of life.

Table 5 Scores of GAD-7, PHQ-9, PSQI, and IBD-Q in IBD Patients in Mild, Moderate, Severe Activity (Scores, $\bar{X} \pm S$)

| Projects | IBD | | | UC | | | CD | | |
|-------------------|--------------|---------------------|--------|--------------|---------------------|--------|--------------|---------------------|--------|
| | Mild | Moderate and Severe | P | Mild | Moderate and Severe | P | Mild | Moderate and Severe | P |
| GAD-7 score | 6.90±5.38 | 8.00±5.81 | 0.012 | 7.27±5.33 | 7.03±5.72 | 0.995 | 7.07±5.22 | 6.85±5.26 | 0.528 |
| PHQ-9 score | 7.29±6.32 | 8.85±6.75 | 0.001 | 7.38±6.31 | 7.38±6.54 | 0.365 | 7.72±6.52 | 7.72±6.19 | 0.710 |
| PSQI score | 6.98±3.83 | 8.35±4.28 | <0.001 | 6.93±3.717 | 7.28±4.04 | 0.25 | 7.16±3.86 | 7.24±3.96 | 0.328 |
| IBD-Q score | 170.03±30.29 | 149.09±35.66 | <0.001 | 173.57±29.10 | 160.22±34.22 | <0.001 | 176.50±25.64 | 166.40±31.40 | <0.001 |
| Bowel symptoms | 55.38±10.01 | 49.32±12.11 | <0.001 | 56.13±9.46 | 51.52±11.26 | <0.001 | 58.42±8.31 | 55.65±10.20 | <0.001 |
| Systemic symptoms | 26.27±5.24 | 22.47±6.43 | <0.001 | 27.00±4.83 | 24.84±6.04 | <0.001 | 27.10±4.54 | 25.14±5.65 | <0.001 |
| Emotional ability | 63.76±12.53 | 56.27±14.49 | <0.001 | 64.99±12.12 | 60.53±13.62 | <0.001 | 65.93±11.17 | 62.10±13.41 | <0.001 |
| Social ability | 24.62±4.97 | 21.02±5.79 | <0.001 | 25.45±4.91 | 23.33±5.56 | <0.001 | 25.06±4.77 | 23.51±4.94 | <0.001 |

Abbreviations: GAD-7, Generalized Anxiety Disorder 7-item Scale; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; IBD-Q, Inflammatory Bowel Disease Quality-of-Life Questionnaire; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; P, P value.

Table 6 Scores of Patients with IBD in Active versus Remission When Combined with One (Anxiety, Depression or Sleep Disturbance), Two (Anxiety + Depression, Anxiety + Sleep Disturbance, Depression + Sleep Disturbance) or Three (Anxiety + Depression + Sleep Disturbance) (Scores, $\bar{X} \pm S$)

| Projects | IBD | | | UC | | | CD | | |
|-------------|-------------|-------------|--------|-------------|-------------|-------|-------------|-------------|--------|
| | Remission | Activity | P | Remission | Activity | P | Remission | Activity | P |
| GAD-7 score | | | | | | | | | |
| A | 6.68±2.508 | 7.01±2.271 | 0.39 | 6.55±1.549 | 7.15±2.426 | 0.225 | 6.80±3.199 | 6.76±1.964 | 0.068 |
| A+B | 8.13±2.513 | 8.95±3.113 | 0.007 | 8.62±2.767 | 9.23±3.109 | 0.18 | 7.78±2.266 | 8.43±3.072 | 0.124 |
| A+C | 6.08±1.230 | 7.10±2.744 | 0.079 | 6.08±1.311 | 7.52±3.203 | 0.147 | 6.07±1.207 | 6.53±1.908 | 0.443 |
| A+B+C | 10.23±3.894 | 11.62±4.362 | <0.001 | 10.91±4.239 | 11.91±4.327 | 0.025 | 9.74±3.555 | 11.16±4.387 | <0.001 |
| PHQ-9 score | | | | | | | | | |
| B | 6.28±1.350 | 6.84±2.872 | 0.304 | 6.00±0.943 | 7.26±3.737 | 0.303 | 6.41±1.501 | 6.45±1.703 | 0.932 |
| B+A | 8.29±2.954 | 8.79±3.150 | 0.122 | 8.35±3.293 | 8.97±3.314 | 0.211 | 8.25±2.705 | 8.45±2.806 | 0.639 |
| B+C | 6.75±1.867 | 7.19±2.271 | 0.36 | 6.80±1.935 | 7.17±2.379 | 0.608 | 6.71±1.863 | 7.22±2.173 | 0.44 |
| B+A+C | 11.56±4.858 | 13.18±5.534 | <0.001 | 11.80±5.022 | 13.28±5.373 | 0.007 | 11.38±4.743 | 13.03±5.789 | 0.002 |
| PSQI score | | | | | | | | | |
| C | 7.97±1.154 | 8.53±1.953 | 0.035 | 8.0±1.145 | 8.62±2.052 | 0.129 | 7.95±1.176 | 8.34±1.753 | 0.259 |
| C+A | 7.81±1.059 | 8.40±1.482 | 0.082 | 7.75±0.965 | 8.35±1.465 | 0.212 | 7.86±1.167 | 8.47±1.546 | 0.231 |
| C+B | 9.66±2.835 | 9.83±2.400 | 0.763 | 10.07±3.035 | 9.93±2.348 | 0.872 | 9.29±2.687 | 9.7±2.512 | 0.63 |
| C+A+B | 9.89±2.674 | 10.70±2.962 | <0.001 | 10.13±2.871 | 10.80±2.906 | 0.025 | 9.72±2.516 | 10.55±3.048 | 0.004 |

Abbreviations: A, Anxiety; B, depression; C, sleep disturbance; GAD-7, Generalized Anxiety Disorder 7-item Scale; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; IBD-Q, Inflammatory Bowel Disease Quality-of-Life Questionnaire; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; P, P value.

In this study, 28.4% and 21.9% of UC and CD patients had a moderate anxiety state, respectively, and 31.4% and 27.7% of patients had a moderate depressive state, respectively, and the severity of anxiety/depression also influenced the activity of IBD, and when anxiety was co-morbid with UC or CD, it was more closely associated with disease activity as the level of anxiety increased, which is consistent with the results of previous studies.^{39,43,44} The main reason may be that the development of depression/anxiety complicates the clinical management of IBD and can increase the frequency of disease activity.^{26,44} It has also been found that even in disease remission, about 1/3 of IBD patients develop irritable bowel syndrome-like symptoms in response to the brain-gut axis,⁴⁵ making psychological disturbances more severe and more likely in patients with CD.^{46,47} In recent years, the incidence of depression in patients with IBD has also increased year by year, with a significant impact on the severity of the disease, both in terms of exacerbating disease activity and increasing the risk of surgery for CD.^{36,48,49} The earliest prospective studies also confirmed that depressive symptoms are an independent predictor of CD activity.^{4,42} Therefore, psychosocial status should not be neglected in the treatment of IBD patients, and some patients can control the disease activity by improving their emotions and lifestyle, which is very important for the development of IBD disease and disease prognosis, as well as reducing the economic burden of patients and avoiding the adverse effects caused by medication, improving the quality of life of patients, and relieving the medical burden.

Sleep quality was also strongly associated with disease activity in this study, and impaired sleep may influence the pathogenesis and course of IBD by decreasing systemic immunity.⁵⁰ This was confirmed by several studies in which patients with sleep-impaired CD had a twofold increased risk of disease activity within a 6-month period.^{51,52} In this study, the sleep quality of IBD patients was mostly moderate (43.3%) and mostly in remission, when the sleep quality was poor or very poor the disease was mostly in active phase, which may be related to the increase in the number and degree of diarrhea and abdominal pain in active patients, in addition, the proportion of glucocorticoids used in active patients is large, and the side effects of this drug also affect sleep, therefore, sleep disorders can further aggravate the disease activity of the disease. In addition, this study also found that sleep has a greater impact on active CD, and patients with moderate sleep quality are already in the active phase of the disease, which is mainly related to more pronounced systemic symptoms in patients with CD, and prolonged mild sleep disturbance in patients in remission may cause a recurrence of intestinal symptoms. Patients in remission with poor sleep quality were reported to have a higher risk of

active disease at 6-month follow-up than those without sleep problems.⁵³ Therefore, sleep quality problems in IBD should be attended to and treated. Studies have shown that although patients with IBD in remission (both UC and CD) have a better quality of life than those in active disease, they still have a lower quality of life compared to healthy individuals,^{54,55} which requires extensive attention.

In conclusion, anxiety, depression, sleep disturbance and quality of life were strongly associated with disease activity in Chinese patients with IBD, and IBD with varying degrees of psychological disturbance was more often in the active phase of the disease and had a low quality of life. The issue of mental health status of patients with active IBD should receive more attention.

One of the limitations of this study, which was a cross-sectional study, is that it does not provide a causal relationship between psychosomatic mental status and disease activity, and further validation by prospective studies is more needed in the future. Another limitation is that patients' psychological symptoms were assessed in a retrospective survey, and we did not assess lifetime risk, 12-month risk or changes in psychological status over time, which would be subject to recall bias, and future prospective observational and treatment studies are needed to determine the responsiveness of psychosomatic status in the assessment of changes over time.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The study complies with the Declaration of Helsinki. The study was approved by the Institutional Review Board of Renmin Hospital of Wuhan University, and informed consent was obtained from all patients. The clinical research Ethics Review approval number of Renmin Hospital of Wuhan University was WDRY2022-K150.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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