# Fatigue status quo of children and adolescents with inflammatory bowel disease and its influencing factors in China: a cross-sectional study

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# Abstract

**Background:** In recent years, the global diagnosis rate of inflammatory bowel disease of children and adolescents has been increasing. Fatigue was found to be the most exhausting symptom in inactive disease and the second most exhausting symptom in active disease. However, little is known about fatigue in pediatric inflammatory bowel disease. Hence, the aim of this study is to investigate the prevalence and status of fatigue in a cohort of pediatric inflammatory bowel disease patients in China.

**Methods:** A cross-sectional, questionnaire-based survey was conducted. The researchers recruited convenience samples of patients with inflammatory bowel disease from Department of Gastroenterology of a children's hospital located in Nanjing, China. The prevalence and status of fatigue were measured by a questionnaire, and associations potential factors were examined using multiple regression analysis.

**Results:** The total score of fatigue in children with inflammatory bowel disease was 62.22±20.55. The results of univariate analysis of fatigue degree in patients with inflammatory bowel disease showed a significant difference among regions, age, disease severity, corticosteroids and biological agents ($p< 0.05$).

**Conclusions:** Fatigue was a multidimensional symptom, and most pediatric patients with inflammatory bowel disease were distressed by fatigue symptom. The patient's region, age, disease severity, BMI and drug use were the significant predictors of fatigue. Health care providers should pay attention to the patient's fatigue symptom. After the initial assessment of the patient's fatigue, the targeted interventions should given to improve the symptom.


# 1. Introduction

Inflammatory Bowel Disease (IBD) is a chronic, non-specific intestinal inflammatory disease, mainly including ulcerative colitis (UC) and Crohn's disease (CD) [1-3]. As an incurable chronic disease, both types can cause chronic inflammatory changes in the gastrointestinal tract [4-6]. In recent years, the global diagnosis rate of children and adolescents has been increasing [7], with high-risk onset ages between 15 and 35 years. About 25% of the cases were diagnosed before the age of 18 years [1,8], and more severe intestinal infections and faster developed [4,9] in the pediatric population. IBD is a chronic intestinal disease that negatively affects in both the mental health and quality of life of the suffered children [10,11]. Although the disease may ease after treatment, fatigue and decreased physical fitness will continue to affect the patient's daily life. Fatigue was found to be the most exhausting symptom in inactive disease and the second most exhausting symptom in active disease [5]. Study [12] showed that 86% of people with moderate to severe IBD had fatigue symptoms, which was still the most exhausting symptom even in remission, and patients often paid more attention to fatigue than bowel symptoms. The IBD clinical guidelines published in 2011 proposed that the symptom of fatigue cannot be ignored because it has a serious negative impact on people's quality of life [13].

Fatigue refers to subjectively continuous tiredness, lack of energy and exhaustion, which reduces one's physical and mental activities and cannot be relieved by long sleep [14]. It is a common, independent, non-specific symptom found in many children with chronic diseases and is often reported as one of the most severe and distressing symptoms; It affects physical, emotional, cognitive and social functioning and affects quality of life [15-17]. However, fatigue is often overlooked by healthcare professionals in assessing the severity of symptoms or outcomes of many diseases. It is difficult to quantify fatigue due to the lack of consensus framework, unclear definition, and multidimensional symptom nature [18-21]. Hence, the aim of this study is to describe the prevalence and degree of fatigue in a cohort of pediatric IBD patients. In addition, we want to explore the possible associations between fatigue and/or markers of disease activity.

# 2. Methods

### 2.1 Sample and procedure

A cross-sectional, questionnaire-based design was used in this study. Patients diagnosed with IBD were recruited by using convenience sampling methods from the Department of Gastroenterology at Nanjing Children's Hospital from 1 September 2020 until 31 November 2021. The inclusion criteria were aged from 5-18 years old and diagnosed IBD over one year, able to understand and speak Chinese and to have no history of cognitive impairment. Diagnosis of IBD is based on a diagnosis of either Crohn's disease or ulcerative colitis in an individual's medical record. The exclusion criteria were associated with other serious diseases, critical condition could not complete the study and unwilling to cooperate.

The researchers explained the purpose and filling requirements of the study to the IBD children and their families by using unified guidance language. Following agreement to participate, informed written consent was obtained.  The children filled in the questionnaire by themselves. For those with poor reading ability, the researchers read the questionnaire item by item to help them fill in, avoiding the use of suggestive language. The questionnaire was filled out on the spot and returned to ensure its reliability. A total of 110 questionnaires were sent out in this study, and 105 were effectively received with effective recovery of 95.45%. This study has been approved by the Hospital Ethics Committee.

### 2.2 Measures

#### 2.2.1 General information questionnaire

A self-designed questionnaire was applied, including gender, age, location, education status, source of medical expenses, duration of illness (/year), disease types, severity of disease, complications and medication use, etc.

#### 2.2.2 Multidimensional Fatigue Scale (MFS)

Multidimensional Fatigue Scale (MFS) was developed by Varni et al [22] and later Chinesization by Bu Xiuqing et al [23]. It mainly measures the fatigue feelings of children with chronic diseases in the past one

month, including three versions of 5-7 years old, 8-12 years old and 13-18 years old, which are composed of three dimensions of general fatigue, sleep fatigue and cognitive fatigue, with a total of 18 items. It was reversely scored with Likert level 5 scoring method, 0=100 points (never happened), 1=75 points (almost never happened), 2=50 points (sometimes happened), 3=25 points (often happened), 4=0 points (always happens). Dimension score = total score of this dimension/number of items of this dimension, total score = total score of items/total number of items. The lower the score, the higher the fatigue level. The Cronbach's α coefficients of the three versions of scales in this study were 0.835, 0.842 and 0.924, respectively.

### 2.3 Data analysis

Data were entered by EpiData3.1 double check to ensure its accuracy. SPSS 23.0 statistical software was used to analyze the data. The measurement data with normal distribution is described by , and the counting data is represented by frequency, constituent ratio and rate. T test, ANOVA and multiple linear regression were used to analyze the influencing factors of fatigue in children with IBD, and $p < 0.05$ was considered to be statistically significant.

# 3. Results

All of the 105（100%） distributed questionnaires were valid. Thus, the study included 105 respondents, of whom 71 (67.62%) were male and 34 (32.38%) were female. And 95 (90.48%) of them were Crohn's disease, other 10 (9.52%) were ulcerative colitis. The age of the respondents ranged from 6 to 18, with a median (Me) of 16 years (interquartile ranges 14-18). Regarding severity of disease, there were 40 (38.10%) with mild, 49 (46.67%) with moderate and 16 (15.24%) with severe. And 89(84.76%) cases with complications and 16 (15.24%) cases without. Table 1 shows the demographics of the study sample.

The total score of fatigue in children with inflammatory bowel disease was 62.22±20.55, with the lowest score of 11 and the highest of 100. Of the three dimensions of the questionnaire, the highest average score was 65.16±28.75 and this was achieved for the dimensions of “cognitive fatigue”, while the “sleep/rest fatigue” dimensions received the lowest average score (60.63±20.07). As for “general fatigue”, it is 60.87±24.68.(Table 2)

The results of univariate analysis of fatigue degree in patients with IBD showed a significant difference among regions, age, disease severity, corticosteroids and biological agents ($p< 0.05$). While no significant differences were found in gender, source of medical expenses, course of disease, type of disease, immunosuppressants, the use of enteral nutrition, per capita annual household income (p 0.05) (Table 1).

Taking total fatigue as dependent variables, the area, education level, disease severity and glucocorticoid application, biologic application which were showed significant differences in univariate analysis and body mass index which has clinical significance were incorporated into multivariate analysis. Dummy

Table 1 demographic data of cases

| Characteristic | Children with IBD N(%) | | Statistics | *p*-values |
|---|---|---|---|---|
| **Gender** | | | t=-0.354 | 0.724 |
| **Boys** | 71(67.62) | 62.72±20.57 | | |
| **Girls** | 34(32.38) | 61.19±20.76 | | |
| **Location** | | | t=2.261 | 0.026 |
| **Rural** | 20(19.05) | 53.06±23.55 | | |
| **Urban** | 85(80.95) | 64.38±19.30 | | |
| **Education status** | | | F=3.241 | 0.043 |
| **Primary and below** | 16(15.24) | 67.71±21.05 | | |
| **Junior high school** | 46(43.81) | 65.88±19.72 | | |
| **High school and above** | 43(40.95) | 56.27±20.20 | | |
| **Source of medical expenses** | | | t=1.148 | 0.254 |
| **Self-paying** | 45(42.86) | 59.57±20.42 | | |
| **Medical insurance** | 60(57.14) | 64.21±20.59 | | |
| **Duration of illness (/year)** | | | F=0.808 | 0.449 |
| **1~3** | 59(56.19) | 64.31±20.08 | | |
| **3~5** | 42(40.00) | 59.99±21.56 | | |
| **5** | 4(3.81 ) | 54.86±15.94 | | |
| **Disease types** | | | t=0.179 | 0.858 |
| **CD** | 95(90.48) | 62.11±21.41 | | |
| **UC** | 10(9.52) | 63.33±9.33 | | |
| **Severity of disease** | | | F=6.211 | 0.003 |
| **Mild** | 40(38.10) | 69.17±18.27 | | |
| **Moderate** | 49(46.67) | 60.83±19.78 | | |
| **Severe** | 16(15.24) | 49.13±22.10 | | |
| **Complications** | | | t=-1.793 | 0.076 |
| **Existence** | 89(84.76) | 66.67±15.49 | | |
| **Inexistence** | 16(15.24) | 59.38±22.88 | | |

| | | | | |
|---|---|---|---|---|
| **Glucocorticoid** | | | t=3.001 | 0.003 |
| **Use** | 27(25.71) | 65.63±20.05 | | |
| **Nonuse** | 78(74.29) | 52.37±19.04 | | |
| **Immunosuppressant** | | | t=0.811 | 0.419 |
| **Use** | 52(49.52) | 60.58±20.75 | | |
| **Nonuse** | 53(50.48) | 63.84±20.41 | | |
| **Biological agents** | | | t=0.070 | 0.006 |
| **Use** | 76(72.38) | 66.29±19.23 | | |
| **Nonuse** | 29(27.62) | 55.04±21.07 | | |
| **Enteral nutrition** | | | t=0.939 | 0.350 |
| **Use** | 66(62.86) | 60.77±19.81 | | |
| **Nonuse** | 39(37.14) | 64.67±21.77 | | |
| **Per capita annual household income (/thound) (RMB)** | | | F=1.650 | 0.197 |
| **30** | 36(34.29) | 58.26±21.85 | | |
| **30~50** | 27(25.71) | 67.70±19.39 | | |
| **50** | 42(40.00) | 62.10±19.77 | | |
| **Bmi** | | | F=0.888 | 0.415 |
| **18.5** | 49(46.67) | 59.41±21.54 | | |
| **≥18.5,24** | 48(45.71) | 64.41±20.17 | | |
| **≥24** | 8(7.62) | 66.32±15.81 | | |

**Table 2 scores of total and each dimension for fatigue**

| **Categories** | Items | Full marks | Lowest mark | Highest mark | |
|---|---|---|---|---|---|
| **General fatigue** | 6 | 100 | 0 | 100 | 60.87±24.68 |
| **Sleep/rest fatigue** | 6 | 100 | 0 | 100 | 60.63±20.07 |
| **Cognitive fatigue** | 6 | 100 | 0 | 100 | 65.16±28.75 |
| **Total score** | 18 | 100 | 11 | 100 | 62.22±20.55 |

variables were set for education level, disease severity and body weight, with education status as primary school, disease severity as mild and body weight as reference variables (Table 3). The results showed that urban residence, non-use of glucocorticoids and use of biological agents were the

protective factors for fatigue (P < 0.05), while malnutrition, severe disease severity and high school education or above were the risk factors for fatigue (P < 0.05) (Table 4).

**Table 3 independent variable assignment methods**

| **Independent variable** | Methods |
|---|---|
| **Gender** | boys=1，girls=2 |
| **Location** | rural=1，urban=2 |
| **Source of medical expenses** | self-paying=1，medical insurance=2 |
| **Duration of illness (/year)** | 1~3=1，3~5=2，>5=3 |
| **Disease types** | cd=1，uc=2 |
| **Severity of disease** | mild=1，moderate=2，severe=3 |
| **Complications** | existence=1，inexistence=2 |
| **Glucocorticoid** | use=0，nonuse=1 |
| **Immunosuppressant** | use=0，nonuse=1 |
| **Biological agents** | use=0，nonuse=1 |
| **Enteral nutrition** | use=0，nonuse=1 |
| **Per capita annual household income(/thound) (rmb)** | <30=1，30~50=2，>50=3 |
| **BMI** | BMI<18.5=1，18.5≤BMI<24=2，BMI≥24=3 |

**Table 4 Multi-factor analysis of factors affecting fatigue**

| | **Regression coefficient** | **Standardized regression coefficient** | **t** | ***p*** |
|---|---|---|---|---|
| **Age** | -2.831 | -.345 | -3.655 | **.000** |
| **Location** | 9.040 | .174 | 2.086 | **.040** |
| **Glucocorticoid** | 11.580 | .248 | 2.894 | **.005** |
| **Biological agents** | -9.022 | -.212 | -2.474 | **.015** |
| **BMI≥24** | .330 | .004 | .050 | .960 |
| **BMI<18.5** | -10.706 | -.261 | -2.684 | **.009** |
| **Moderate** | -9.047 | -.221 | -2.419 | **.017** |
| **Severe** | -15.321 | -.269 | -2.967 | **.004** |
| $R^2$=35.8，Adjustment $R^2$=30.4 | | | | |

# 4. Discussion

## 4.1 Fatigue in children with IBD

The results of this study showed that the total fatigue score of children with IBD was 27.20±14.79, which was different from the results of Lucia [24], which might be related to racial differences. According to the study of Grossman [25], children with Crohn's disease of different races reported different levels of anxiety and fatigue.

In this study, the scores of various dimensions were compared, sleep/rest fatigue and general fatigue were at a higher level, while cognitive fatigue was at a lower level, which was the same as Marcus [21], possibly related to the fact that patients were more sensitive to physical symptoms than psychological symptoms. Found in the study of adult patients with IBD, fatigue is closely related to anxiety, depression and other emotional [26]. However, relevant studies in children are insufficient [27], so they are easily ignored. It suggests that we should not only pay attention to physical fatigue, but also psychological fatigue when managing fatigue symptoms in children with IBD.

## 4.2 Analysis of influencing factors of fatigue in children with IBD

### 4.2.1 Fatigue and region

The study suggests that the fatigue degree of children living in cities is lower than that in rural areas. The reason is that the income of urban population is higher than that of rural population [28], and the per capita income will affect the investment in health [29]. Moreover, the health literacy level of urban residents is generally higher than that of rural residents. In addition, high-quality medical resources are mostly concentrated in big cities, while rural medical and health resources are insufficient to form reasonable medical guidance, leading to lagging development of medical. In addition, in the construction of equal access to basic medical and health services in urban and rural areas, there are problems such as insufficient total supply and unbalanced supply structure, so rural residents have relatively limited access to public health resources compared with urban residents [30]. Therefore, children living in cities are more timely in disease diagnosis and treatment. In addition, parents of children in cities have more support from communities and schools than parents living in rural areas. There are more ways to acquire disease-related health knowledge and it is easier to understand these knowledge. Moreover, they can better master the methods of drug application and management for children, and also guide children to symptom management according to the relevant content of health education. They pay more attention to insist on regular follow-up and long-term control treatment, so fatigue symptom management of children is more scientific.

It is suggested that in addition to improving access to medical treatment in rural areas, targeted health education should be carried out for children in different areas, with special emphasis on disease

management and fatigue symptom relief in rural children. Furthermore, More attention should be paid to the regular follow-up of children in rural areas to promote scientific symptom management and relieve fatigue symptoms of children.

### 4.2.2 Fatigue and age:

Our study shows that age is positively correlated with the degree of fatigue in children, which is the same as the Tomlinson's study of cancer-related fatigue in children with hematopoietic stem transplantation [31]. From the perspective of social psychology, children gradually enter puberty from school age, which is a critical period of growth and development. They are facing great changes in body and mind, and are more sensitive to changes in all aspects of body and mind [32]. As the child grows, the understanding of the disease and the perception of symptoms increases. Furthermore, IBD negatively impacts on school attendance due to hospital attendance, disease burden and then causes school difficulties [33], as a consequence, cause greater psychological stress to children. In addition, disease symptoms such as abdominal pain and diarrhea cause great inconvenience in life, making children feel confused about their future, leading to irritability, low self-esteem, anxiety, depression and other emotions in children, affecting the disease management of children and aggravating children's fatigue. Needs of children with IBD must be addressed by ensuring effective partnership between education and health and targeting those with risk factors for poor attendance with preventative measures. This reminds us focus on the emotional and mental state of adolescent children, using strategies to minimize healthcare burden and provide more integrated care can directly impact service provision.

### 4.2.3 Fatigue and drug use:

This study showed that children treated with biologics had less fatigue than those not treated with biologics. This is similar to the results of Borren [34]. Borren studied the longitudinal trajectory of fatigue in patients who started biotherapy for more than one year, and the results showed that fatigue improved with the start of biotherapy and relief of clinical symptoms. At present, the only biological agent approved for clinical use in China is infliximab [35], which mainly targets soluble and transmembrane tumor necrosis factor (TNF)-α, which is a powerful pro-inflammatory cytokine and plays a role in the dysregulation of mucosal immune response in IBD [36]. Thus, infliximab may alleviate fatigue through cytokine action and may also alleviate fatigue by improving clinical symptoms in children.

The study found that the fatigue degree of children who used glucocorticoids was higher than that of those who did not, which was the same as the results of vanLangenberg et al. [37]. It was considered that the reason might be related to the serious side effects of corticosteroids. Studies have shown that corticosteroid treatment can lead to adrenal insufficiency in IBD patients, affect the healing of peptic ulcer, and increase the risk of respiratory tract infection and sepsis [38,39]. Therefore, in the future management of fatigue symptoms in children and adolescents, attention should be paid to drug use in children and timely treatment of drug side effects.

### 4.2.4 fatigue and BMI:

BMI are reliable indicators of protein energy malnutrition, and are simple and feasible methods for screening malnutrition. According to the diagnosis of BMI grade, this study showed that 46.67% of the children with IBD were malnourished. It is reported in foreign literature that the incidence of malnutrition in IBD is 16%, 85%, 85%, 100% in children with CD, who have a history of malnutrition [40,41]. This study shows that the fatigue symptoms of malnourished children are more serious than other children, which is the same as that of Whelan et al [42]. Inflammatory bowel disease is associated with anorexia. Typical symptoms include abdominal pain, diarrhea and vomiting. These symptoms further lead to discomfort and loss of appetite [43]. IBD children often lead to changes in dietary behavior due to hospitalization and dietary restrictions in order to control gastrointestinal symptoms. Further hinder dietary intake [44], which in turn aggravates the symptoms of fatigue. In addition, there are many micronutrient deficiencies in children with IBD, such as iron [45] and vitamin B12 [46]. These trace elements are closely related to fatigue symptoms. Therefore, a number of guidelines emphasize attention to the nutritional status of children with inflammatory bowel disease, and recommend enteral nutrition therapy as a first-line dietary source of CD-induced remission in mild to moderate children, emphasizing regular detection and timely correction of micronutrient levels [35,40,42]. However, in this study, there is no significant correlation between the use of enteral nutrition and the symptoms of fatigue in children. The reason may be related to the time and preparation of enteral nutrition, or to the size of the sample. A large sample study is needed to determine the relationship between the use or time of enteral nutrition and the symptoms of fatigue in children.

### 4.2.5 Fatigue and disease severity

Our study shows that children with moderate to severe disease severity are more fatigued than children with mild disease, which is the same as that of Pellino [47], but different from that of Chavarría [48]. Research tool to assess fatigue and disease activity. In addition, the sample size of the study and the type of study have an impact on the results of the study. Children with severe disease are often accompanied by severe clinical symptoms, such as abdominal pain and diarrhea, and the severity of the disease is closely related to children's anxiety, depression, and loneliness [49], while mental factors can directly affect the symptoms of fatigue [50]. Therefore, the severity of illness affects children's fatigue symptoms both physically and psychologically.

There are some limitations in this study. First of all, a cross-sectional survey was adopted in the study. Due to the limitations of the survey method, the causal relationship cannot be determined. In addition, due to the small sample size, the study results may be affected by confounding factors. Future studies with larger sample sizes are needed to confirm relevant conclusions. However, this study directly evaluated fatigue and related variables from the perspective of children, and identified multiple related factors of fatigue in children with IBD, providing a reference for further research and eventual clinical application. This study suggests that in addition to actively treating diseases and managing concurrent mental disorders, attention should also be paid to children's nutritional status and cognition of diseases, and personalized management methods should be provided.

# 5. Conclusions

Fatigue is common in IBD patients, and there are several factors that contribute to fatigue in addition to the disease mentioned in our study. To date, the mechanism of fatigue is not clear, and there is no scientific and effective systematic management mode. Therefore, after a comprehensive understanding of fatigue symptoms and their influencing factors in patients with different types of IBD, systematic, comprehensive and targeted interventions should be developed to help patients maximize the improvement of fatigue symptoms, help patients return to society and improve their quality of life.

# Abbreviations

IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; MFS: Multidimensional Fatigue Scale; BMI: Body Mass Index.

# Declarations


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### Authors contributions

JJC, YH and ML contributed to the study conception and design. Data collection was performed by JJC and LR and analysis were performed by YYW. The first draft of the manuscript was written by JJC and YYW and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.


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### Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. The ethics committee of Nanjing Childrens' Hospital affiliated to Nanjing Medical University has approved the study protocol. Written informed consent was obtained from participants and parents or legal guardians of participants .

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interest.

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