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Research Paper

# Investigating the Activity Status of Inflammatory Bowel Disease and its Related Factors: A Study Protocol

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## ABSTRACT

**Background:** While the prevalence of inflammatory bowel disease (IBD) is rising globally, there is limited knowledge regarding its activity status and associated factors, especially in Guilan Province, Iran.

**Objectives:** This protocol outlines a case-control study aiming to assess the activity status of IBD and explore its related factors in the region.

**Materials & Methods:** The study will utilize a case-control design of patients with IBD. Cases will consist of individuals with active IBD, while controls will be selected from those with inactive diseases. The selection of participants will be based on predefined criteria and matched for age and gender. A comprehensive set of variables will be examined, including demographic characteristics, nutritional status, lifestyle factors, medical history, and disease-related factors. Standardized questionnaires will gather information on disease activity, symptomatology, lifestyle behaviors, and nutritional status. Statistical analyses will be conducted to evaluate the association between disease activity status and the identified factors. Regression models will be employed to control for potential confounders and assess the independent effects of each variable.

**Conclusion:** The findings from this study are expected to provide valuable insights into the activity status of IBD and its related factors in Guilan Province, Iran. By examining a range of variables, the study aims to enhance our understanding of the disease activity and identify potential modifiable risk factors. The results may have implications for improved management strategies with IBD in this region.

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## Introduction

The prevalence of IBD has been steadily increasing worldwide, including in Iran [1, 2]. Inflammatory bowel disease (IBD) is a chronic and complex disorder that affects the gastrointestinal tract, causing inflammation and damage to the digestive system. It encompasses two main conditions: Ulcerative colitis (UC) and Crohn's disease (CD) [3]. IBD is characterized by periods of active symptoms followed by periods of remission, and it can significantly impact the quality of life for those living with this condition [4, 5].

In addition to understanding the nature of IBD as a chronic condition, it is important to assess the factors contributing to its active and inactive phases. The triggers and determinants of disease activity in IBD can vary from person to person, and identifying these factors is crucial for effective management and personalized treatment approaches [6, 7]. Factors such as genetics, environmental influences, diet, stress levels, medication adherence, and the presence of comorbidities all play a role in the activity of IBD [8-10]. By examining these factors, healthcare professionals can develop tailored strategies to minimize disease activity, optimize symptom control, and enhance the overall well-being of individuals living with IBD [11, 12].

There is limited knowledge about the activity status of IBD and its associated factors in Guilan Province, Iran. This protocol aims to outline a case-control study to assess the activity status of IBD and explore its related factors in Guilan Province, Iran. Utilizing a case-control design of patients with IBD, we aim to comprehensively understand the disease activity and its determinants in this region.

## Methods

### Aim, design and setting of the study

This present case-control study will be conducted by the Gastrointestinal and liver Disease Research Center in north of Iran (from 2022 to 2023), and the information of 306 patients (two groups of 153 patients with active IBD and inactive IBD) who are residents of Guilan Province, Iran, will be collected. Written consent will be obtained from patients to participate in the study. This study aims to assess the status of the following factors in patients with UC, CD, and intermediate IBD and their impact on the activation of the disease course, including demographic characteristics, lifestyle factors, past medical history, past surgical history, drug history, IBD related factors, and nutritional status. All patients will be from Guilan Province, and data will be collected from questionnaires. Patients using IBD-related methods will be divided into two groups: Active and inactive. The active patients will be taken from those hospitalized in Razi Hospital in Rasht, and the inactive patients will be taken from the IBD registry of the Gastrointestinal and Liver Disease Research Center. In order to identify patients with active UC, the modified Truelove and Witts severity index (MTWSI) and the Mayo index will be used. In order to evaluate CD activity, the Harvey Bradshaw severity index (HBSI) will be used. Three questionnaires, including the IBD-related variables, GAD-7, and PHQ-9 questionnaires, will be used for active and inactive patients in this study (Figure 1). The independent variable in this study will be disease activity, and the dependent variable will be the effecting factors (FFQ, IPAQ, PSQI, GAD-7 and PHQ-90).

### Inclusion and exclusion criteria

Patients with active IBD whose diagnoses are confirmed by two expert gastroenterologists are eligible to be included in our study. The diagnosis is based on clinical symptoms, physical examination, radiological properties, endoscopy/colonoscopy findings, and pathologic features. This study will assign one patient with inactive IBD previously registered in the IBD database at the Gastrointestinal and Liver Diseases Research Center, Rasht, Iran, for each active IBD case. Also, all patients in the case group (active IBD) and control group (inactive IBD) will be matched in age and gender. A trained person will collect the information of the patients. Patients who do not consent to participate in the study will be excluded.

### Personal, social, and clinical inquiries

When meeting the patients, the personal, social, and clinical characteristics questionnaire will be completed. A trained questioner will ask the predefined items and survey patients' medical records. This questionnaire covers the following information: gender, marital status, city of birth, city of residence, race, level of education; a family history of IBD including father, mother, brother, sister, son, and daughter; infant feeding status, childhood infection history, smoking status, alcohol consumption, hookah consumption, having twins, number of deliveries including live births, abortion, stillbirth; drug history involving oral contraceptive pills (OCPs), non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and herbal medicine; and past surgical history.

This questionnaire also involves IBD characteristics including first symptoms, age at the onset of symptoms, interval between the onset of symptoms and the diagnosis, history of disease recurrence, season of the beginning of the first symptoms (spring, summer, autumn, winter), extraintestinal complications, type of drugs used for medication, duration of drug used, extent of involvement of UC (proctitis/ left sided/ pancolitis/ unspecified), CD involvement site (ileal/ colonic/ ileocolic/ upper gastrointestinal involvement alone or with other parts/ unspecified), CD behavior (only inflammation and without fistula or stricture/ penetrating or fistulizing / stricturing / unspecified), number of visits to the doctor and hospitalization in the last 12 months, duration of the disease from the onset of symptoms. In order to assess the body mass index (BMI) of patients, the height and weight of all participants will be measured, and BMI will be calculated by dividing weight (in kilograms) by the square of your height (in meters).

## Inquiries of IBD activity status

In order to identify patients with active UC, the MTWSI and Mayo index will be used. MTWSI criterion includes eight items involving diarrhea, nocturnal diarrhea, bloody stools, fecal incontinence, abdominal pain or cramping, general well-being, abdominal tenderness, and antidiarrheal or narcotics consumption. The final score ranges from 0 to 19; a score above 7 is considered active UC [13, 14]. Mayo index includes three items involving stool frequency (in the past three days), rectal bleeding (in the past three days), and physician's global assessment. The final score ranges from 0-9 and is interpreted as follows: Remission (0-1), mild disease (2-4), moderate disease (5-6), and severe disease (7-9) [15].

In order to evaluate CD activity, HBSI will be used. HBSI includes five items: General well-being, abdominal pain, number of watery stools per day, abdominal mass, and extraintestinal complications. Extraintestinal manifestations include arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous ulcers, anal fissures, new fistula, and abscesses. The final score ranges from 0 to 18. Patients with CD and a score higher than 10 according to the HBSI criteria are considered active patients [15, 16].

In this study, patients who take IBD-related medication and are under the supervision of a gastroenterologist, but do not have clinical symptoms related to the disease, are considered inactive. It should be noted that for inactive patients, the mentioned criteria will also be measured, and the patients diagnosed as active based on the questionnaire will be included in the active group and referred to the doctor for further examination.

## Nutrition questionnaire

The nutrition questionnaire will be based on the food frequency questionnaire (FFQ), showing its validity and reliability in several studies [17, 18]. This questionnaire is a 168-item food consumption frequency assessment and involves a list of everyday food items in a region. These food items are written in the first column of the questionnaire, and the unit of measurement is mentioned in front of each item, which is only specific to that item. In order to evaluate participants' consumption of each food item, the number of consumption times and the amount consumed each time will be recorded. Questioning tools, such as a picture of different containers, will be used to determine the amount of consumption each time so that the participants can report more accurately.

## Physical activity questionnaire

The physical activity evaluation is based on the international physical activity questionnaires (IPAQ), and the validity and reliability are confirmed in several studies [19, 20]. This questionnaire will examine the amount of physical activity within the past seven days and contains 27 questions. Participants will be asked about the list of activities that they do at work or as part of housework, sports training, activities they do as fun in their free time, and even rest.

This questionnaire considers the four main types of physical activity as follows: Intense physical activity, which requires much physical strength and makes participants breathe harder than normal; moderate physical activity, which requires moderate strength and breathing a little faster than normal; walking, which includes walking at work, at home, going from one place to another, and any other kinds of walking that participants have done as recreation, sports, physical exercises, or in their free time; and sitting, which includes sitting at work, at home, while doing tasks, and in leisure time. For parts of intense, moderate, and walking activities, activities are recorded that have been done continuously for at least 10 minutes.

The participants will answer the intense, moderate, and walking activities in two-step questions. In the first step, the participants will report the number of days a week. In the next step, they will report the time spent on the activity in hours and minutes daily. If the person does not have one of the activities, the option "no activity"

will be selected. This questionnaire will determine the amount of physical activity according to the final score. Activities such as aerobics, high-speed cycling, mountain climbing, and basketball that require more than 6 calories per minute are considered intense physical activities. Activities such as volleyball, badminton, cleaning a room, and walking, which require 3-6 calories per minute, are considered moderate physical activity. In addition, any activity that lasts less than 10 minutes will be excluded. The total energy of the activities in the past seven days will be calculated according to the IPAQ manual, in which less than 600 met/cal/week, between 600 to 3000 met/cal/week, and more than 3000 met/cal/week will be regarded as low, moderate, and high physical activity, respectively.

## Sleep questionnaire

Our study will use the Pittsburgh sleep quality index (PSQI) questionnaire, of which validity and reliability are investigated in previous research [21-23]. This questionnaire evaluates participants sleeping quality during the last month, and it contains seven scales, including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medications consumption, and daytime dysfunction. Each of the seven scales of this questionnaire will be scored from 0-3 (0=none, 1=weak, 2=moderate, and 3=severe). The total score of the questionnaire ranges from 0 to 21, and higher scores indicate poorer sleep quality. A score greater than 5 indicates that the subject is a poor sleeper and has severe problems at least in two scales or moderate problems in more than three scales.

## Psychological questionnaire

To examine the psychological dimension of patients, three questionnaires of, patient health questionnaire-9 (PHQ-9), generalized anxiety disorder questionnaire-7 (GAD-7), and perceived stress scale-10 (PSS-10) will be used. The validity and reliability of these questionnaires have been confirmed in various studies [24-27]. The PHQ-9 is designed to measure depression based on the diagnostic and statistical manual of mental disorders (DSM-IV) and includes nine questions with a 4-point Likert response scale. This questionnaire evaluates different problems that participants may have had within the past two weeks. The scores range from 0 to 3 (0=never, 1=several days, 2=more than half of the days, and 3=nearly every day). This questionnaire has an additional question that indicates the level of disorders' interference in a person's individual, social, family, and occupational functions. The total score varies between 0 and 27; higher scores indicate more significant depression. A score of 10 is a cut-off point to diagnose individuals with depression.

The GAD-7 is designed to measure generalized anxiety disorder. This questionnaire includes seven questions with a 4-point Likert response scale from 0 to 3 (0=never, 1=several days, 2=more than half of the days, and 3=nearly every day). This questionnaire evaluates different problems that participants may have had within the past two weeks. The range of obtained scores varies from 0 to 21, and a higher score indicates more significant anxiety. A score of 10 is considered a cut-off point for diagnosing people with generalized anxiety.

The PSS-10 includes ten items which are scored on a 5-point Likert scale. The items are rated from 0 to 4 (0=never, 1=almost never, 2=sometimes, 3=fairly often, and 4=very often). This questionnaire evaluates different problems that participants may have had within the past month. The range of PSS-10 score is 0-40, and a higher score indicates more perceived stress.

## Participants and sample size

According to the result of previous studies [28-31] which compared the average scores of sleep quality, physical activity, anxiety, depression, and stress between two groups of patients with active and inactive IBD, an effect size of 0.35 was considered to calculate the sample size. Taking 17% of non-completed questionnaires into account, type I error at 0.05, and type II error at 0.2 (resulting in a power of 0.8) the final number of samples in each group is determined to be 153 participants with a final total sample size of 306.

## Statistical analysis

Data will be analysed using SPSS software, version 20. Quantitative variables will be summarized using measures such as Mean±SD. Qualitative variables will be described using numbers and percentages to depict their distribution. In order to check the normality of the data, the Kolmogorov-Smirnov test will be used, and if the data is not normal, the non-parametric equivalent of statistical analysis will be used. Hence, Independent t-test or Mann-Whitney test will be used to compare the GAD-7, PSS-10 and PHQ-9 scores between the active and inactive groups. Considering that the main goal of the present study is to determine the factors related to the activity of IBD based on individual and clinical variables, multiple logistic regression analysis will be used to analyze the data. Regression models will be used to

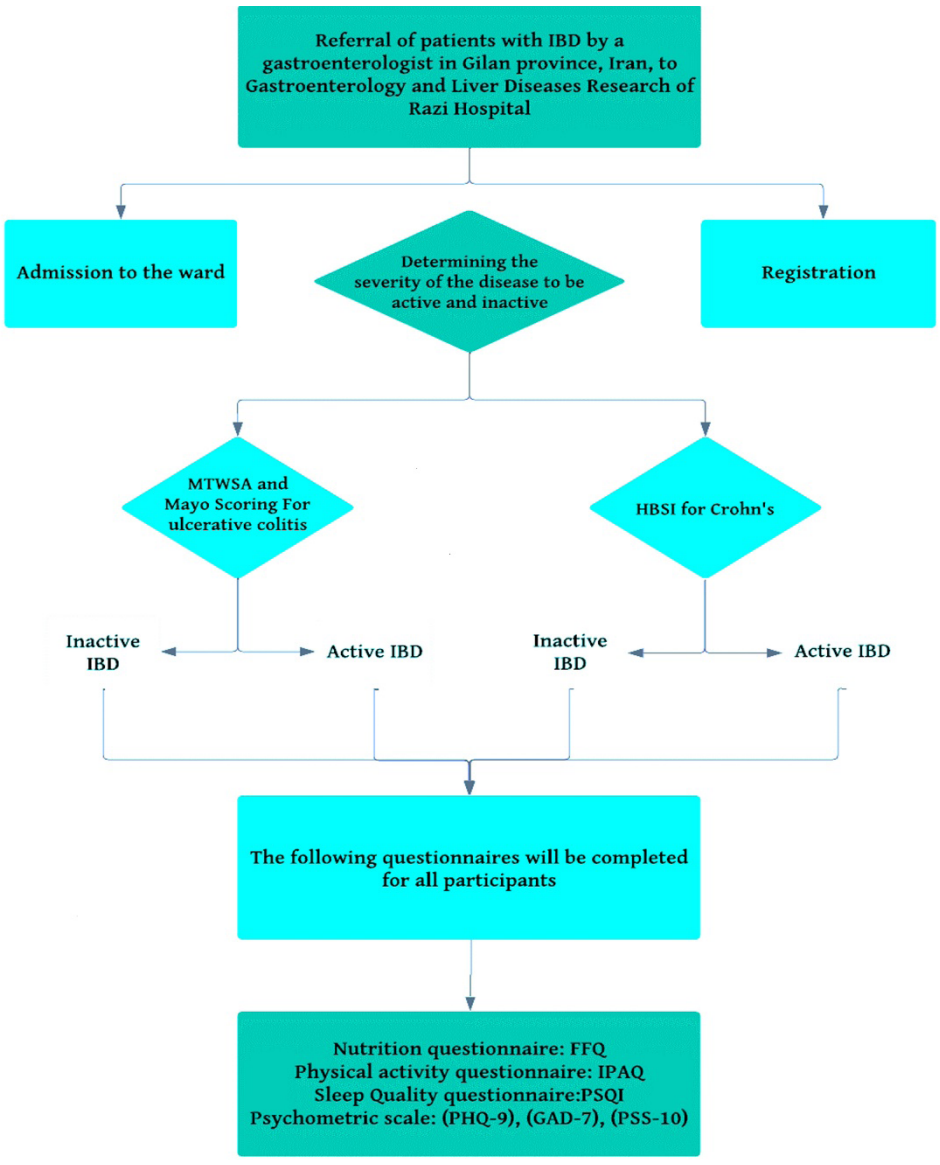


**Figure 1.** Study process flow chart

control possible confounding variables. According to the case-control study type, odds ratio (OR) with 95% confidence interval will be estimated for each variable. The significance level for all tests is considered to be <0.05.

## Discussion

Since IBD is a chronic and debilitating condition with a rising global incidence, despite extensive research on IBD, it is necessary to investigate its activity status and related factors in specific geographic regions to understand the disease burden better and optimize patient care [32, 33].

Conducting this study is crucial for determining the activity status of IBD in Guilan Province, Iran. In addition, identifying the related factors contributing to IBD's activity status in Guilan Province, Iran, is of paramount importance. These factors may include genetic predispositions, environmental triggers, lifestyle choices, dietary habits, and socioeconomic factors [34]. By understanding the unique factors at play in Guilan Province, Iran, tailored interventions can be designed to address the specific needs of the local population.

Moreover, the case-control study design chosen for this investigation offers several advantages. Firstly, it allows for efficient data collection as it leverages existing data from individuals with and without IBD. This retrospective approach minimizes the time and resources required for recruitment, thereby increasing the feasibility of the study. Additionally, the case-control design is

particularly suitable for investigating rare diseases or outcomes, making it an ideal choice for studying IBD in Guilan Province, Iran, where the prevalence might be lower compared to other regions [35]. Furthermore, the case-control design enables the examination of multiple risk factors simultaneously, providing a comprehensive understanding of the disease. Researchers can assess the association between various factors and IBD's activity status by comparing cases (individuals with active IBD) to carefully selected controls (individuals with inactive IBD). This methodology enhances the study's internal validity, enabling more robust conclusions to be drawn.

One of the study limitation will be the use of self-reported measures that may introduce recall bias in assessing symptoms. In order to prevent recall bias, the questions should be checked at the beginning so that they are understandable for the patients and give the patients enough time to recall long-term memories.

The findings of this study may contribute to the existing body of literature on IBD, especially in the context of the Middle East and Iran. Research specific to the region helps fill gaps in knowledge and contributes to a more comprehensive understanding of IBD worldwide. The results can also be compared with similar studies conducted in other regions, facilitating cross-cultural comparisons and promoting a global perspective on IBD research.

## Ethical Considerations

### Compliance with ethical guidelines

The study was approved by the Medical Ethics Committee of the Guilan University of Medical Sciences (Code: IR.GUMS.REC.1400.625). All subjects will give their informed consent to participate in the study. All methods will be carried out in accordance with relevant guidelines and regulations that is Declaration of Helsinki.

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### Authors' contributions

Conceptualization and study design: Mehrnaz Asgharnezhad, Soheil Hassanipour, Farahnaz Joukar, Saman Maroufizadeh, Adele Isanazar, Marjan Mahdavi-Roshan, and Fariborz Mansour-Ghanaei; Writing the original draft: Ehsan Amini-Salehi, Niloofar Faraji, Mehrnaz Asgharnezhad and Zahra Hedayatzadeh; Final approval: All Authors.

### Conflict of interest

The authors declared no conflict of interest.

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