



Sleep Disorders in Patients with Inflammatory Bowel Diseases

İltihabi Bağırsak Hastalığı Olan Hastalarda Uyku Bozuklukları

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Abstract

Objective: Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), have been associated with sleep disturbances as extra-intestinal manifestations. We aimed to evaluate sleep quality in a group of Middle Eastern IBD patients while assessing the links between disease characteristics, sleep disturbances, and related comorbidities.

Materials and Methods: Outpatient IBD cases who attended our hospital clinic from 2019 to 2021 were recruited in this prospective study. The patients filled in verified translations of the insomnia severity index, Epworth sleepiness scale, Pittsburgh sleep quality index, Berlin questionnaire for obstructive sleep apnea (OSA), and restless legs syndrome (RLS) questionnaire by means of online or phone surveys. The chi-squared test and Student's t-test were used for binary and continuous variables, respectively. The Mann-Whitney U test was used for non-normally distributed data.

Results: The sleep quality of 82 IBD patients (13 CD and 69 UC) was assessed. Low sleep quality was observed in 52 cases (63.4%), and UC patients with pancolitis were significantly more likely to have sleep disturbances compared to patients with partial colitis ($p=0.015$). Moreover, patients with elevated C-reactive protein (CRP) displayed significantly higher frequencies of OSA and RLS ($p=0.038$ and $p=0.040$, respectively).

Conclusion: Sleep impairment was identified in more than half of our IBD patient pool. Therefore, we suggest screening for sleep disturbances (particularly in UC patients with pancolitis) and related comorbidities, such as OSA and RLS (especially in patients with elevated CRP levels), in IBD patients to enhance their quality of sleep.

Keywords: Sleep, inflammatory bowel diseases, ulcerative colitis, Crohn disease

Öz

Amaç: İltihabi bağırsak hastalıkları (İBH), özellikle ülseratif kolit (ÜK) ve Crohn hastalığı (CH) ekstra-intestinal belirtiler olarak uyku bozuklukları ile ilişkilendirilmiştir. Ortadoğulu bir İBH hastası grubunda uyku kalitesini değerlendirmeyi ve hastalık özellikleri, uyku bozuklukları ve ilişkili komorbiditeler arasındaki bağlantıları değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu prospektif çalışmaya 2019-2021 yılları arasında hastanemizin kliniğine ayaktan başvuran İBH olguları dahil edilmiştir. Hastalar, çevrimiçi veya telefon anketleri aracılığıyla doğrulanmış insomnia şiddet indeksi, Epworth uyukluluk ölçeği, Pittsburgh uyku kalitesi indeksi, obstrüktif uyku apnesi (OSA) için Berlin anketi ve huzursuz bacak sendromu (RLS) anketinin tercümelerini doldurdular. İkili değişkenler için ki-kare testi ve sürekli değişkenler için Student t-testi kullanıldı. Normale uymayan dağılıma sahip veriler için Mann-Whitney U testi kullanıldı.

Bulgular: Seksen iki İBH hastasının (13 CH ve 69 ÜK) uyku kalitesi değerlendirildi. Düşük uyku kalitesi 52 olguda (%63,4) gözlemlendi. Pankolitisi ÜK hastalarında kısmi koliti olan hastalara göre uyku bozukluğu görülme olasılığı önemli ölçüde daha yüksekti ($p=0,015$). Yüksek C-reaktif protein (CRP) düzeyleri gösteren hastalarda OSA ve RLS sıklığı anlamlı olarak daha yüksekti ($p=0,038$ ve $p=0,040$, sırasıyla).

Sonuç: İBH hastalarının yarısından fazlasında uyku bozukluğu tespit edildi. Bu hastalarda uyku bozuklukları (özellikle pankolitisi ÜK hastalarında) ve OSA ve RLS gibi ilişkili komorbiditelerin (özellikle yüksek CRP düzeylerine sahip hastalarda) taranmasını öneriyoruz, böylece bu hastalardaki uyku kalitesini artırabiliriz.

Anahtar Kelimeler: Uyku, iltihabi bağırsak hastalıkları, ülseratif kolit, Crohn hastalığı

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Received/Geliş Tarihi: 01.07.2023 **Accepted/Kabul Tarihi:** 07.01.2024



Introduction

Inflammatory bowel diseases (IBDs) are chronic conditions of the gastrointestinal tract comprised of two major relapsing/remitting disorders, namely Crohn's disease (CD) and ulcerative colitis (UC).¹ Even though the IBD incidence rate seems constant or decreasing in most western societies, its burden remains significant due to its prevalence exceeding 0.3% in Oceania, North America, and the majority of European countries, and even rising in Asia, South America, and Africa.² These disorders are associated with increased mortality, along with a diverse array of morbidities, such as non-alcoholic fatty liver disease, irritable bowel syndrome^{3,4}, fatigue, anxiety, depression, and a general reduction in the quality of life.⁵⁻⁸

Some studies have suggested that a considerable number of IBD patients may suffer from sleep disorders and circadian rhythm disruptions, both of which result in harmful consequences, such as increased risk of disease exacerbation, frequent relapses, hospitalization, and surgery.⁹⁻¹⁸ Sleep deprivation affects immune function through activating pro-inflammatory responses, such as increased production of tumor necrosis factor- α , interleukin (IL)-1, and IL-6 as cytokines associated with the pathogenesis of IBD.¹⁹⁻²² Impaired sleep also seems to be linked with anxiety, depression, and comorbidities, such as restless legs syndrome (RLS) and obstructive sleep apnea (OSA) in IBD patients, even though information regarding these associations is still limited.^{5,7,11,23-30}

The impact of sleep quality on IBD courses is poorly understood, and most related studies have been conducted in Western societies, leading to a paucity of data on Middle Eastern and South Asian populations. We aimed to evaluate sleep quality in IBD patients, as well as the links between disease characteristics, sleep disorders, and related comorbidities.

Materials and Methods

This cross-sectional study was approved by the Ethics Committee of Mashhad University of Medical Sciences (approval number: IR.MUMS.MEDICAL.REC.1398.447, date: 30.07.2019) and performed on adult subjects with confirmed IBD according to the "American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in IBD", whose data were registered in the registry of IBD patients in Mashhad, Iran. Informed consent was signed by all participants in this study.

The diagnosis of IBD was made by an expert gastroenterologist according to the clinical symptoms, as well as endoscopic, imaging, laboratory, and pathology investigations after ruling out other colitis etiologies.^{1,31} Patients receiving any tranquilizers or anti-anxiety medications were excluded from the study.

The Persian versions of the Pittsburgh sleep quality index (PSQI)³², insomnia severity index (ISI)³³, Epworth sleepiness scale (ESS)³⁴, Berlin questionnaire (BQ) for OSA³⁵, and RLS assessment questionnaire (RLSAQ)³⁶ were used to investigate sleep quality and the risk of sleep disorders. The ISI is comprised of seven questions. An ISI score of 0-7 means no clinically significant insomnia, while 8-14, 15-21, and 22-28 stand for subthreshold, moderate severity, and severe insomnia, respectively.

The ESS is comprised of eight questions (scoring from 0-3) and is used as a subjective measure of sleepiness and dozing off. An ESS score of 0-7 means that it is unlikely that the patient is abnormally sleepy; 8-9 stands for an average amount of daytime sleepiness; 10-15 means that the patient may be excessively sleepy depending on the situation and may want to consider seeking medical attention; and 16-24 means that the patient is excessively sleepy and should consider seeking medical attention. The BQ consists of three categories, including snoring, daytime fatigue and sleepiness, as well as medical history and anthropometric measures. The patient is considered high-risk for OSA when two or more categories are positive. The PSQI is a 19-item, self-rated questionnaire consisting of seven components, each scoring 0-3, with 3 indicating the greatest dysfunction. A PSQI score of ≥ 5 is defined as poor sleep quality. After recording the medical history [including age, gender, body mass index (BMI), disease activity, and colon involvement] and the results from the physical examination, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and hemoglobin (Hb) were checked.

Statistical Analysis

The IBM SPSS Statistics (version 21; IBM Inc., Armonk, New York) software package was used for data analysis. Data are presented as mean \pm standard deviation for continuous variables and as frequency for categorical variables. Intergroup comparisons were investigated by the chi-squared test for binary variables and the Student's t-test for continuous variables. The Mann-Whitney U test was employed for the data that was not distributed normally. A p-value of <0.05 was considered statistically significant.

Results

A total of 82 IBD patients, including 13 patients with CD and 69 with UC (a mean age of 38.9 ± 11.5 years, 32% male), were consecutively included in this study. The demographic data of patient participants in this study is shown in Figure 1.

The frequencies of different disease conditions are shown in Figure 2. Almost 80% ($n=65$) of the participants were in the remission phase of the disease, while only 20.7% ($n=17$) were in the active phase. In total, 50.7% ($n=35$) of patients with left-colon involvement or less and 49.3% ($n=34$) of those with pancolitis had poor sleep quality.

Poor sleep quality (according to PSQI scores) was reported in 52 patients (63.4%) overall. In addition, RLS was reported in 51 IBD cases (62.2%), and the high risk of sleep apnea was evident in 18 individuals (Figure 3).

No statistically significant relationship was found between the extent of involvement and ISI scores, OSA, and RLS. Furthermore, we could not provide any statistically significant comparisons in CD patients due to the insufficient number of CD cases.

Almost 72% ($n=52$) of IBD patients were suffering from impaired sleep quality based on PSQI. Although 61.5% ($n=40$) and 70.5% ($n=12$) of patients in remission and active phases, respectively, had impaired sleep quality based on PSQI, no

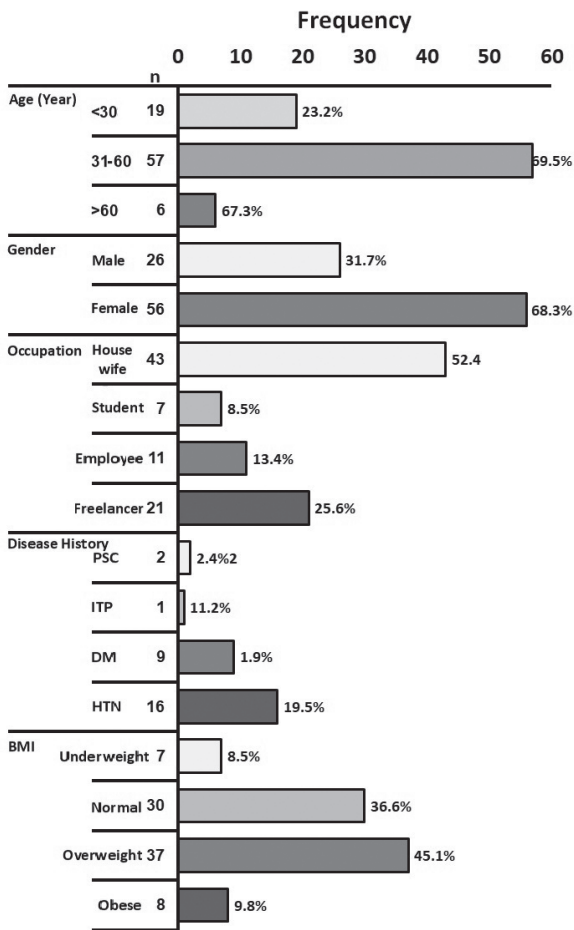


Figure 1. Demographic data of patient participants
BMI: Body mass index, PSC: Primary Sclerosing Cholangitis, ITP: Idiopathic Thrombocytopenic Purpura, DM: Diabetes Mellitus, HTN: Hypertension

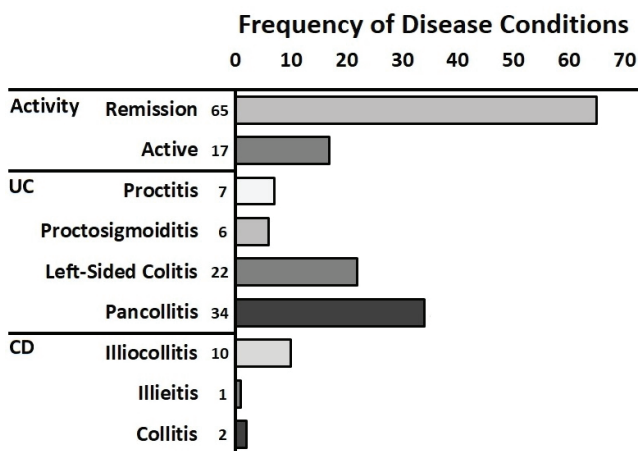


Figure 2. Frequency of different disease conditions among study participants
UC: Ulcerative colitis, CD: Crohn's disease

statistically significant difference was found in the distribution of good or bad sleep quality between these two groups of patients ($p=0.49$) (Figure 4 G). Patients with elevated CRP demonstrated a significantly higher frequency of OSA (38.1%) than patients with normal CRP levels (16.4%) ($p=0.038$). Additionally, there was a higher likelihood that patients with elevated CRP levels suffered from RLS (81%) ($p=0.040$). However, no significant correlation was seen between elevated CRP and sleep quality ($p=0.72$), as well as insomnia severity ($p=0.82$). Other factors such as age ($p=0.771$, $p=0.469$, $p=0.202$, and $p=0.111$), gender ($p=0.22$, $p=0.568$, $p=0.459$, and $p=0.121$), BMI ($p=0.116$, $p=0.62$, $p=0.149$, and $p=0.778$), anemia, ESR ($p=0.543$, $p=0.566$, $p=0.104$, and $p=0.674$), and disease activity ($p=0.49$, $p=0.33$, $p=0.86$, and $p=0.423$) did not show any statistically significant relations with PSQI, ISI, OSA, or RLS scores (Figure 4).

Discussion

The association between IBD and sleep quality has not yet been clearly elucidated. In this study, sleep disturbances were evaluated in patients with IBD. According to the findings, sleep impairment was evident in more than half of our IBD patient pool (63.4%). The frequency of poor sleep quality increased in UC patients with worse disease phenotypes (the extent of involvement). Patients with pancolitis were significantly more likely to have sleep disturbances than those with partial colitis. Additionally, IBD patients with elevated CRP displayed higher frequencies of OSA and RLS than cases with normal CRP levels. Our study could have benefited from a healthy control group for comparison. Furthermore, our patients were initially intended to undergo a polysomnography test; however, due to several

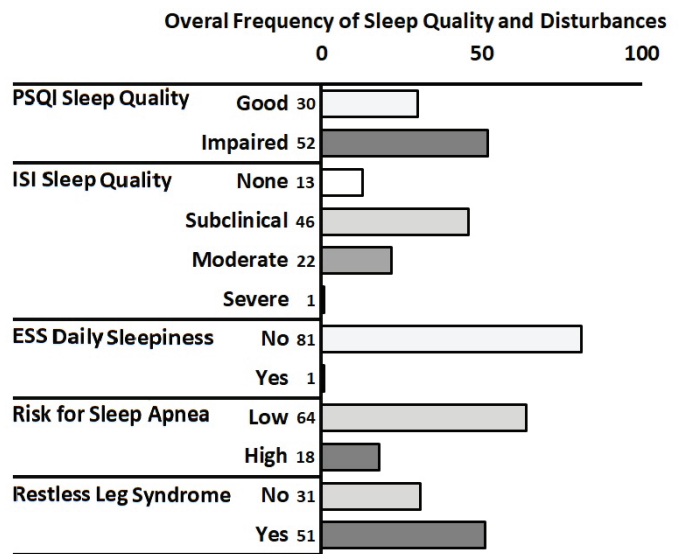


Figure 3. Overall frequency of sleep quality and sleep disturbances
PSQI: Pittsburgh sleep quality index, ISI: Insomnia severity index, ESS: Epworth sleepiness scale

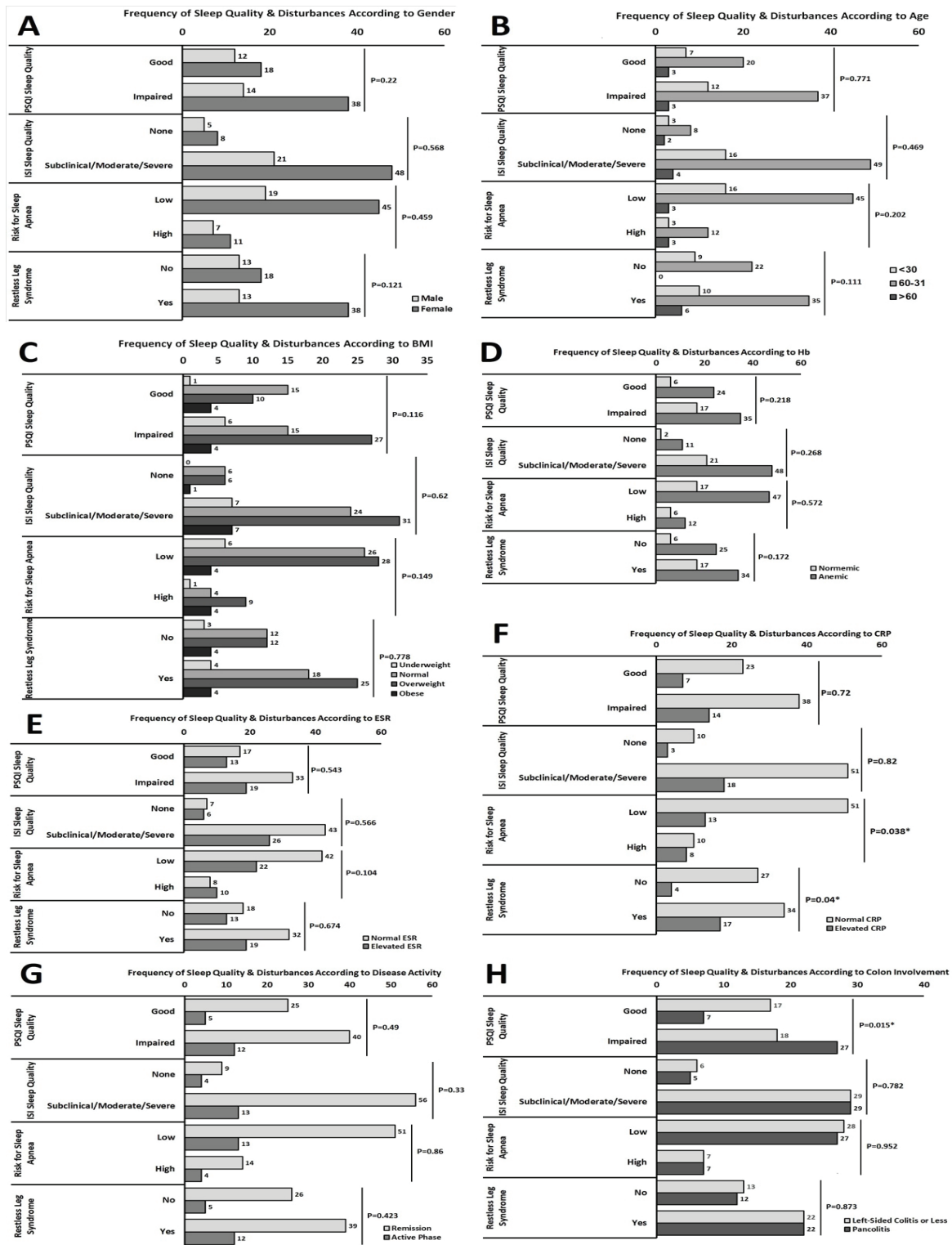


Figure 4. Frequencies of sleep disturbances according to (A) gender, (B) age, (C) BMI, (D) Hb, (E) ESR, (F) CRP, (G) disease activity, and (H) colon involvement
PSQI: Pittsburgh sleep quality index, ISI: Insomnia severity index, BMI: Body mass index, Hb: Hemoglobin, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

constraints during the coronavirus disease-2019 pandemic, we were neither able to perform this test on our cases nor recruit a healthy control group willing to participate in our study.

Although the prevalence of IBD is known to be only slightly dominant in females, the significantly higher frequency of IBD in our study population can be attributed to the fact that our participants were recruited consecutively, and females are usually more cooperative in these sorts of studies.

Previous studies have recorded a wide range of prevalence rates for sleep disturbance in IBD patients, from 32% to 77%, and our patients fell on the more severe side of that spectrum.^{25,26,37-40}

To the best of our knowledge, the relationship between disease phenotype (the extent of involvement) and sleep quality has not been previously studied. We identified a significant inverse relationship among these factors, meaning that the frequency of poor sleep quality in patients with pancolitis was significantly higher than patients with left-colon involvement or less.

A systematic review and meta-analysis has reported a significant association between disease activity and subjective sleep quality (pooled odds ratio: 3.52, 95% confidence interval: 1.82-6.83, $p < 0.001$).⁴¹ However, no association was found between disease activity and sleep quality in our patient pool. We have to point out that only 20.7% of our cases ($n=17$) with active disease and 40 out of 65 patients in remission (61.5%) reported poor sleep quality. Other studies have also highlighted that poor sleep quality was not only common in patients with active IBD but was also a serious concern in inactive disease cases.^{26,42-44}

Several studies have reported that patients with high CRP values (high inflammatory activity) were more likely to suffer from poor sleep quality^{30,37,45}, whereas CRP levels were not associated with poor sleep quality, according to our findings. The aforementioned studies explained that they could not investigate the correlation between sleep quality and CRP values independent of disease activity as the majority of their patients with elevated CRP levels also suffered from clinically active disease. However, the number of patients who had active disease in our study was limited, and poor sleep quality was evident even in patients in remission, which might justify the absence of an association between CRP and sleep disturbance among our patients.

Our results for the first time showed that high CRP was associated with OSA and RLS. A recent study has shown that patients with active disease were more likely to be at a high risk for OSA⁴⁶; however, no link was found between OSA and disease activity in our patient population. We recommend screening for OSA and RLS in patients with increased inflammatory activity, such as high CRP, regardless of the disease activity status.

According to our results, the management of subsequent comorbidities, such as sleep disturbances, should be dependent on the disease phenotype and the extent of involvement. Even though clinicians should pay close attention to sleep disturbances in all UC patients, we suggest paying more attention to patients with pancolitis and providing more serious management strategies for improving their sleep quality.

Future studies should further investigate this relationship. We also recommend recruiting and comparing patients newly diagnosed with chronic IBD so that the long-term effects of the ailment and treatments can also be taken into account.

Conclusion

According to our findings, sleep impairment was evident in more than half of our IBD patient pool. Therefore, we suggest screening for sleep disturbances (particularly in UC patients with pancolitis) and their related comorbidities, such as OSA and RLS (especially in patients with elevated CRP levels), in IBD patients in order to enhance their quality of sleep.

Acknowledgements

The authors would like to appreciate the help from the Clinical Research Development Unit, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the Ethics Committee of Mashhad University of Medical Sciences (approval number: IR.MUMS.MEDICAL.REC.1398.447, date: 30.07.2019)

Informed Consent: Informed consent was signed by all participants in this study.

Authorship Contributions

Concept: M.A., H.V., M.A., Design: A.M., M.A., H.V., H.M-M., M.A., Data Collection or Processing: R.N., H.M-M., S.A., M.R., A.T., Analysis or Interpretation: A.M., S.A., M.R., A.T., K.M., M.A., Literature Search: A.M., Writing: A.M., M.A., K.M., M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The current study was financially supported by Mashhad University of Medical Sciences (#980304).

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