**DOI:** 10.14744/cm.2022.89266
Comprehensive Medicine 2023;15(3):268-72

RESEARCH ARTICLE

# Serum Macrophage Migration Inhibitory Factor Levels in the Patients with Active Ulcerative Colitis

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## ABSTRACT

**Objective:** Macrophage migration inhibitory factor (MIF) is a cytokine that plays a critical role in immunity and inflammation. We compared serum MIF levels in patients diagnosed with active ulcerative colitis (UC) for the 1 time with those in healthy controls and attempted to determine whether serum MIF levels were different in the patients with active UC.

**Materials and Methods:** A total of 38 naive patients who were admitted to our hospital between 2019 and 2020 and diagnosed with active UC by colonoscopy were included in the study as the case group, and 37 patients without acute or chronic diseases whose colonoscopy was normal were included as the control group.

**Results:** There was no statistically significant difference in MIF levels between the patients with UC and the control group ($p>0.05$). Serum MIF levels were analyzed by comparing the patients with UC and the control group in terms of disease localization and severity. The serum MIF levels of the patients with UC were grouped according to the Montreal classification ($p>0.05$) and the Truelove and Witts criteria. There was no statistically significant difference in serum MIF levels between the patient groups or between them and the control group ($p>0.05$).

**Conclusion:** Serum MIF levels were not higher in the patients with naive active US than in healthy control subjects. There are not many previous clinical studies on this topic. Further clinical studies are needed to investigate serum MIF levels in UC.

**Keywords:** Inflammatory bowel diseases, macrophage migration inhibitory factor, ulcerative colitis

**How to cite this article**: Akbaş E, Ülfer G. Serum Macrophage Migration Inhibitory Factor Levels in the Patients with Active Ulcerative Colitis. CM 2023;15(3):268-72

## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of unknown cause, with periods of remission and activation, resulting from an exaggerated immune response to various antigens or environmental factors in a genetically susceptible individual. UC constitutes one of the most common health problems worldwide.[1] Increased intestinal permeability in the pathogenesis of UC is a common result of a complex set of pathophysiological processes created by genetic structure or environmental triggers. In UC, an impaired CD4 T helper type 1 (Th1) cell-mediated immune response of the intestinal mucosa leads to the overproduction of a number of pro-inflammatory cytokines, in particular interferon-gamma (IFNγ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNFα).[2] In addition, another cytokine, macrophage migration inhibitory factor (MIF), is thought to play a critical role in immunity and inflammation. MIF is secreted by a variety of immune cells, including macrophages, dendritic cells, lymphocytes, neutrophils, and pituitary cells.[3,4] When secreted, MIF regulates a variety of immune and inflammatory activities, including the induction of inflammatory cytokines such as TNFα, IFNγ, IL-1β, IL-12, IL-6, and IL-8.[5] However, when the MIF gene is mutated, it upsets the immune balance in the microenvironment. It has been shown that MIF gene mutation is associated with many autoimmune diseases such as rheumatoid arthritis, glomerulonephritis, and IBD.[6–10] While Donn et al. reported that the MIF-173 polymorphism is a risk factor for juvenile idiopathic arthritis, Baugh

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**Received date:** 10.01.2021
**Revised date:** 17.08.2022
**Accepted date:** 14.09.2022
**Online date:** 17.07.2023

et al.[11,12] reported that there was a correlation between the MIF-794 CATT microsatellite and disease severity in patients with rheumatoid arthritis. It has also been reported that MIF gene polymorphism is a risk factor for other immune diseases such as atrophy, asthma, and sarcoidosis in patients with erythema nodosum.[13] Therefore, it is an important issue to investigate whether both serum MIF levels and MIF gene polymorphisms are associated with IBD. In our study, we attempted to determine whether MIF levels are increased in patients with active UC by comparing serum MIF levels with those of healthy normal controls.

## MATERIALS and METHODS

Ethical approval for this study was granted by the Ethics Committee of our institution before the start of the research. The study was conducted in case and control groups. A total of 38 patients, 14 females and 24 males, who were diagnosed with naive active UC by colonoscopy, biopsy, and laboratory findings from the patients consecutively admitted to our clinic between 2019 and 2020 constituted the case group. A total of 37 patients, 12 females and 25 males, who were found to have normal colonic mucosa after colonoscopy, no chronic inflammatory disease, and normal laboratory values were included as a control group. All participants were enrolled on a voluntary basis, and each patient signed an informed consent form before participation. Blood samples were collected from patients whose diagnosis of UC was confirmed before the start of treatment and from the control group in the same manner and stored at –80 °C. At the end of the study, serum MIF levels of these samples were determined using the "Macrophage MIF ELISA Kit" and studied using the "double-antibody sandwich" method.

### Data Analysis

Statistical analyses were performed using Number Cruncher Statistical System 2007 software (Kaysville, Utah, USA). Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) and comparative statistical methods were used to evaluate the study data. Kolmogorov–Smirnov and Shapiro–Wilk tests and graphical evaluations were used to determine whether the quantitative data were normally distributed or not. Normally distributed quantitative data of the two groups were compared using Student's t-tests, and non-normally distributed data were compared using Mann–Whitney U-tests. Data from three or more groups that were not normally distributed were compared using Kruskal–Wallis tests. Qualitative data were compared using Pearson chi-square tests. Significance was considered at least at the level of $p<0.05$.

## RESULTS

The study was performed on a total of 75 cases, 65.3% (n=49) male and 34.7% (n=26) female. The age of the cases ranged from 19.6 to 78.4 years, with a mean of 37.61±12.66 years. The demographic characteristics of the case and control patients included in the study are shown in Table 1.

The cases in the control group were randomly included in the study regardless of their demographic characteristics and age. The values of age, height, and body mass index of the case group and the values of the control group showed statistically significant differences ($p<0.05$). There was no significant difference in other demographic parameters between the case and control groups ($p>0.05$).

After comparing the UC patients with the control group, the UC patients were also compared with the control group separately according to disease involvement area and disease severity. Disease spread was evaluated according to the Montreal classification, and disease severity was evaluated according to the Truelove and Witts criteria. Relevant MIF data and demographics are shown in Table 2.

While the mean serum MIF level of the cases in the case group was 3.75±2.95 ng/mL, the mean serum MIF level of the subjects in the control group was 4.21±3.72 ng/mL. There was no statistically significant difference in MIF levels between patients and controls ($p>0.05$). Regarding the site of involvement, 26.3% (n=10) of cases with UC had ulcerative proctitis, 34.2% (n=13) had left colitis, and 39.4% (n=15) had pancolitis. Serum MIF levels of cases classified according to the Montreal classification were not statistically different between classes/groups ($p>0.05$). According to disease severity, 28.9% (n=11) of the cases were classified as mild, 39.4% (n=15) as moderate, and 31.5% (n=12) as severe colitis. The serum MIF levels of patients with UC classified according to the Truelove and Witts criteria did not show a statistically significant difference among themselves and between them and the control group ($p>0.05$). A graphical representation of serum MIF levels according to site and severity of involvement in patients with UC is shown in Figure 1 (Montreal classification; $p=0.375$, Truelove and Witts criteria; $p=0.796$).

## DISCUSSION

UC is a chronic and recurrent colitis, the etiology of which remains unclear. MIF is a key pro-inflammatory mediator. MIF has been shown to be an important regulator in the regulation of the immune response and the development of inflammation in gastritis and colitis.[14] Ohkawara et al.[15] showed that serum MIF levels were increased in mice with

**Table 1. Distribution of demographic characteristics of case and control patients (n=75)**

| | Total (n=75) | | Control group (n=37; 49.3%) | | Case group (n=38; 50.7%) | | p |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Age (years) | | | | | | | |
| Min-max (median) | 19.6–78.4 (35.7) | | 20.5–64.3 (40.4) | | 19.6–78.4 (31.2) | | 0.014 |
| Mean±SD | 37.61±12.66 | | 41.23±11.83 | | 34.09±12.58 | | |
| Sex | | | | | | | |
| Male | 49 | 65.3 | 25 | 67.6 | 24 | 63.2 | 0.688 |
| Female | 26 | 34.7 | 12 | 32.4 | 14 | 36.8 | |
| Height (cm) | | | | | | | |
| Min-max (median) | 152–190 (170) | | 152–181 (168) | | 155–190 (172.5) | | 0.043 |
| Mean±SD | 170.41±8.65 | | 168.22±8.06 | | 172.47±8.66 | | |
| Weight (kg) | | | | | | | |
| Min-max (median) | 45–120 (74) | | 49–120 (75) | | 45–103 (72) | | 0.184 |
| Mean±SD | 74.59±15.43 | | 76.92±16.54 | | 71.87±14.21 | | |
| BMI (kg/m$^2$) | | | | | | | |
| Min-max (median) | 17.1–44.1 (25) | | 19.1–44.1 (26.2) | | 17.1–35.4 (24.5) | | 0.017 |
| Mean±SD | 25.55±5.22 | | 27.00±5.59 | | 24.15±4.48 | | |

SD: Standard deviation; BMI: Body mass index

**Table 2. Distribution of MIF data by Montreal classification and Truelove and Witts criteria (n=75)**

| | Control group (n=37) | Case group (n=38) | | | p |
|---|---|---|---|---|---|
| | | Montreal classification | | | |
| | | Ulcerative proctitis (n=10) | Left colitis (n=13) | Pancolitis (n=15) | |
| MIF (ng/mL) | | | | | |
| Min–max (median) | 0.1–13 (3) | 0.3–10.6 (2.3) | 0.2–8.3 (2.5) | 0.3–9.5 (3.7) | 0.571 |
| Mean±SD | 4.21±3.72 | 3.36±3.60 | 3.27±2.62 | 4.46±2.85 | |
| | | Truelove and Witts criteria | | | |
| | | Mild (n=11) | Moderate (n=15) | Severe (n=12) | |
| MIF (ng/mL) | | | | | |
| Min–max (median) | 0.1–13 (3) | 0.3–8.3 (2.2) | 0.2–10.6 (5.5) | 0.3–6.1 (2.6) | 0.213 |
| Mean±SD | 4.21±3.72 | 2.70±2.44 | 5.27±3.40 | 2.67±1.78 | |

MIF: Migration inhibitory factor; SD: Standard deviation

artificially induced active UC. There are not enough clinical studies investigating serum MIF levels in patients with active UC. In our study, there was no significant difference in serum MIF levels between the patients with naive active UC and the control group. Moreover, when the patients with UC were classified according to the site of involvement and disease

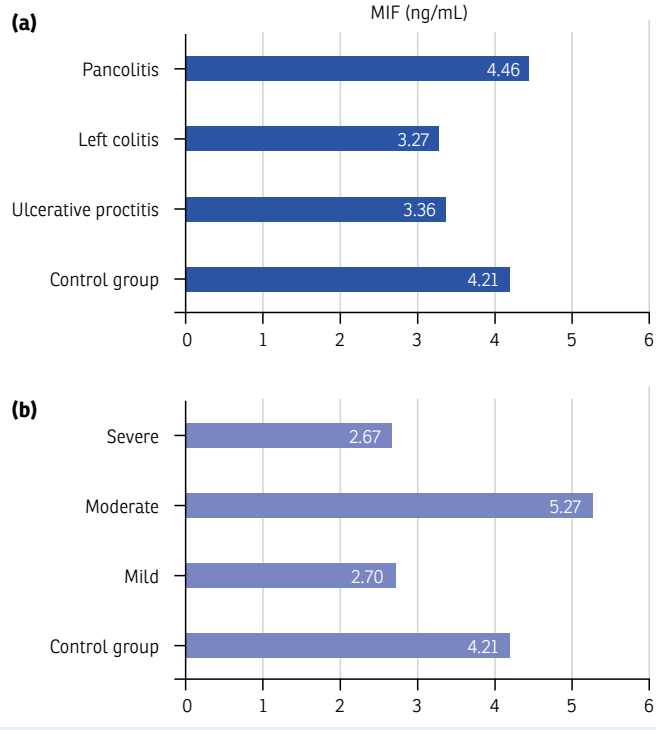


**Figure 1.** Serum MIF levels by **(a)** Montreal classification and **(b)** Truelove and Witts criteria

*MIF: Migration inhibitory factor*

severity, no significant difference was found between them, and no significant difference could be detected between them and the control group. Our results suggest that serum MIF levels may not be a diagnostic or prognostic parameter in active UC. However, it must be taken into account that we are highly dependent on the sensitivity of commercially available diagnostic kits for the determination of this marker in serum. In our study, we believe that the statistically significant difference in age between the US case group and the healthy control group will not affect the evaluation, as this was not a prevalence or risk analysis study by age.

Furthermore, there are some clinical studies on MIF gene polymorphism to demonstrate the importance of MIF in the etiopathogenesis of UC. However, not all studies on this topic have yielded the same results. Griga et al.[16] found that there was no significant difference between patients with IBD and control groups regarding the MIF gene type. In a few other studies, the MIF gene was found to be a risk factor for IBD.[17,18] The role of serum MIF levels and MIF gene polymorphism in UC and other inflammatory bowel diseases is poorly understood. Further clinical studies, especially on serum MIF levels, will shed light on the role of this pro-inflammatory parameter in UC.

## CONCLUSION

MIF is a key pro-inflammatory mediator. Researchers have shown that MIF is increased in case of active UC in experimental animal models. However, there is no clinical study investigating serum MIF levels in patients with active UC. In our study, serum MIF levels in patients with active UC were found to be similar in the case and control groups.

### Disclosures

**Ethics Committee Approval:** The study was approved by the Medipol University Non-interventional Clinical Research Ethics Committee (No: 692, Date: 30/11/2018).

**Informed Consent:** Written informed consent was obtained from all patients.

**Peer-review:** Externally peer reviewed.

**Authorship Contributions:** Concept: E.A.; Design: E.A., G.Ü.; Supervision: E.A.; Funding: E.A.; Materials: G.Ü.; Data Collection or Processing: E.A., G.Ü.; Analysis or Interpretation: E.A., G.Ü.; Literature Search: E.A.; Writing: E.A.; Critical review: E.A.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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