# Assessing seasonal variations of biomarkers in inflammatory bowel disease

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**Objective** Inflammatory bowel diseases are chronic pathologies characterized by a complex interplay of genetic and environmental factors, as well as aberrant immune responses. This study aimed to investigate inflammation markers' seasonality and association with disease exacerbation episodes in patients with Crohn's disease and ulcerative colitis.
**Methods** 284 patients were classified based on clinical, endoscopic, and histopathological criteria. Systemic inflammation was evaluated using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and chitotriosidase, while fecal calprotectin was measured to assess intestinal inflammation. Serum vitamin D levels and the seasonality of an activity score that combines several clinical and biological parameters were also evaluated.
**Results** The peak number of patients reporting endoscopic activity occurred in autumn for Crohn's disease (82%) and spring for ulcerative colitis (95%). Regarding histological activity, spring saw the highest number of patients for both diseases (72% for Crohn's disease; 87% for ulcerative colitis). Most of the inflammatory markers exhibited lower values during winter. Systemic inflammatory markers follow a slightly different trend than fecal calprotectin and differ in the two pathologies. The maximum values of intestinal inflammation were observed in autumn for Crohn's disease (784 µg/g) and in spring for ulcerative colitis (1269 µg/g). Serum vitamin D concentrations were consistently low throughout the year. Statistical analysis revealed differences between the seasons for CRP and ESR ($P < 0.05$).
**Conclusion** The evolution of flares and inflammatory markers in Crohn's disease and ulcerative colitis displayed distinct seasonal patterns. Systemic inflammation did not consistently parallel intestinal inflammation. Eur J Gastroenterol Hepatol 36: 993–999


## Introduction

Inflammatory bowel diseases (IBD) are chronic pathologies that evolve with periods of remission alternating with periods of activity. These include Crohn's disease (CD) and ulcerative colitis (UC). Although their pathogenesis is insufficiently known, it is considered that etiology involves a complex interaction between genetic factors, environmental factors, and an aberrant immune response [1]. Because the genetic factor remains unchanged, the hypothesis was raised that modifying environmental factors could influence the immune response and the evolution of the disease [2]. The link between pathogenesis and seasonal fluctuations has been demonstrated in several diseases, including autoimmune diseases [3]. Over time, several studies have been conducted that have attempted to identify environmental factors that could influence the evolution of inflammatory bowel diseases (IBD), including seasonality. Some studies have demonstrated an association between seasons and birth month, disease onset, or exacerbations [4–9].

Different markers from blood or feces can assess inflammation in IBD. Among them are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), enzymes from the chitinases class, or fecal calprotectin [10]. It was observed that values varied depending on the season for certain markers of inflammation. Thus, CRP values are higher in cold seasons, including healthy subjects [11]. In a study that analyzed the link between birch pollen allergy symptoms and changes in the intestinal microbiota, no variability was found in the evaluated months (March–June) for fecal calprotectin [12]. Still, there are no studies that rate this link. To date, there are no studies to analyze the seasonal variability of ESR or enzymes of the chitinases class.

In an earlier investigation, we created an activity score that demonstrated excellent diagnostic capabilities. This score combines commonly utilized inflammation markers in clinical settings to identify intestinal inflammation effectively, thus potentially reducing the need for invasive procedures like colonoscopy [13]. The seasonal variability of the activity remains to be evaluated.

Among the factors incriminated in the seasonality of certain diseases is vitamin D [14]. Previous studies have shown that the incidence of vitamin D deficiency is higher in patients with IBD and is associated with the severity of the disease [15,16]. Also, some studies have demonstrated an inverse correlation between vitamin D concentration

European Journal of Gastroenterology & Hepatology 2024, 36:993–999

Keywords: Crohn's disease, inflammatory bowel disease, inflammatory markers, seasonality, ulcerative colitis

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**Received** 1 February 2024 **Accepted** 7 May 2024.

and clinical symptoms or inflammation markers [17,18]. Regarding the seasonal variability of vitamin D values in patients with IBD, a more significant deficit was observed in the winter–spring months [19].

This study aimed to assess the seasonal variation of certain inflammation markers commonly employed in clinical settings for monitoring Crohn's disease and ulcerative colitis and to investigate the correlation between the seasonality of these markers, episodes of disease exacerbation, and vitamin D levels.

## Materials and methods

The patients included in the study were collected from the Regional Institute of Gastroenterology and Hepatology Cluj-Napoca. All included subjects lived in Romania. Part of the included patients were collected prospectively (between 2020 and 2022), and the rest were collected retrospectively from the hospital database (between 2017 and 2020). Each patient was evaluated once, at presentation. The study was approved by the ethics committee of the University of Medicine and Pharmacy Cluj-Napoca.

Patients were included in the study based on an endoscopically and histopathologically diagnosis of Crohn's disease or ulcerative colitis after they agreed to undergo colonoscopy. The study excluded patients under 18 years of age, patients with other pathologies with an inflammatory component (neoplasia, acute or chronic infections, other autoimmune diseases, pregnant women), or patients undergoing calcium or vitamin D replacement therapy.

The date of the presentation was noted for each patient. The seasons were defined as follows: spring included March, April, and May; summer included June, July, and August; autumn included September, October, and November; winter included December, January, and February. Other relevant descriptive variables such as age at presentation, disease duration, gender, or extraintestinal manifestations were collected.

The evaluation of disease activity was based on clinical, endoscopic, and histopathological criteria through scores frequently used in clinical practice and previously validated and approved [20]. Clinical activity was assessed by the Crohn's disease activity index (CDAI) for Crohn's disease and Mayo partial for ulcerative colitis. A CDAI score <150 points and a partial Mayo score <2 points suggest the disease is in clinical remission. The simplified endoscopic score for Crohn's disease (SES-CD) and the Mayo endoscopic score for ulcerative colitis were used to evaluate the endoscopic activity. An SES-CD score <2 points and a Mayo score of 0 points were interpreted as a disease in endoscopic remission. The histopathological activity was assessed by the Naini and Cortina score for Crohn's disease and the Nancy score for ulcerative colitis. Considering the difficulty of applying these scores and the absence of validation of precise delimitation intervals between the degrees of histological activity, the statistical analysis was performed based on assessing the degree of activity or remission made by the pathologist.

For the evaluation of systemic inflammation, the monitored parameters were CRP (mg/dl), ESR (mm), and chitotriosidase (CHIT1) (nmol/ml/h). Fecal calprotectin (µg/g) was monitored to evaluate intestinal inflammation. We also calculated the activity score according to the previously mentioned formula [13]. CRP, ESR, and fecal calprotectin were performed by routine laboratory techniques carried out in the hospital. For prospective patients, venous blood was collected from the antecubital vein at the time of presentation after a 12-hour fasting period for CHIT1 activity and vitamin D dosage. Two vacutainers were collected for each patient. After homogenization, they were centrifuged for 10 min at 3000 rotations per minute. EDTA vacutainers were used to obtain plasma, and clot activator vacutainers were used to obtain serum. Plasma and serum were stored in Eppendorf tubes at –20°C until processing.

The CHIT1 activity assay was based on the method described by Hollak *et al*. [21]. Briefly, CHIT1 activity was determined by incubating 5 µl of plasma with 100 µl of the 22 mol/l fluorogenic substrate 4-methylumbelliferyl β-D-N,N′,N″-triacetylchitotrioside (Sigma M5639) in 0.1 citrate M/0.2 M buffer (pH 5.2) for 15 min at 37°C. The reaction was stopped at room temperature with 200 µl of 1 M glycine-NaOH buffer (pH 10.6). Hydrolysis of the substrate by CHIT1 produces the fluorescent molecule 4-methylumbelliferone. Its fluorescence was measured with a fluorometer at 360 nm excitation and 455 nm emission and compared to a standard calibration curve.

Serum was used for vitamin D dosing. Serum total 25-hydroxyvitamin D levels (ng/ml) were measured using the competitive ELISA technique (E-EL-0012, Elabscience, Houston, Texas, USA) according to the manufacturer's instructions.

The SPSS program (version 25; IBM Corp., Armonk, New York, USA), R program, and Microsoft Excel (2019, Redmont, Washington, USA) were used for statistical analysis. Data distribution was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests. The Z-test was used to evaluate the single proportion statistical differences between the number of patients in clinical, endoscopic, or histological activity depending on the season versus the population estimate. Comparison of the parameter values between seasons was made using the Kruskal–Wallis test. Ljung–Box test was performed to verify seasonality in R. Statistical significance was set at $P < 0.05$.

## Results

Following the application of the inclusion and exclusion criteria, a number of 284 patients were included in the study. One hundred and five patients were diagnosed with Crohn's disease and the remaining 179 with ulcerative colitis. Seventy eight patients were included prospectively. Table 1 describes the general and disease characteristics of the included patients.

The majority of patients who underwent surgery had Crohn's disease. Surgical procedures were tailored based on the location and severity of the lesions, with the most common intervention being right hemicolectomy with ileocolonic anastomosis. In the case of patients with ulcerative colitis, the most frequent intervention was sigmoid resection with colostomy. Information regarding treatment is also provided in Table 1. While the majority of patients adhered to a single treatment regimen, 25% of the total cohort received combined treatment, typically involving aminosalicylates paired with azathioprine or tumor

**Table 1.** Characteristics of the included patients

| | Crohn's disease ($n$ = 105) | Ulcerative colitis ($n$ = 179) |
|---|---|---|
| Male patients $n$ (%) | 48 (45.7%) | 90 (50.3%) |
| Age at inclusion (years) (mean ± SD) | 38.4 ± 13 | 43.5 ± 16.6 |
| Disease duration (years) (mean ± SD) | 4.9 ± 5.3 | 4.8 ± 4.7 |
| Season at presentation | | |
| Spring | 30 (28.6%) | 40 (22.3%) |
| Summer | 27 (25.7%) | 42 (23.5%) |
| Autumn | 23 (21.9%) | 42 (23.5%) |
| Winter | 25 (23.8%) | 55 (30.7%) |
| Montreal classification, $n$ (%) | | |
| Age at diagnosis | | |
| <17 | 3 (2.8%) | 8 (4.4%) |
| 17–40 | 71 (66.6%) | 98 (54.7%) |
| >40 | 32 (30.4%) | 73 (40.7%) |
| Disease location | | |
| Ileum | 36 (34%) | |
| Colon | 19 (18%) | |
| Ileocolon | 50 (48%) | |
| Superior GI tract | 0 | |
| Proctitis | | 16 (9%) |
| Left-sided | | 93 (52%) |
| Extensive | | 53 (30%) |
| Disease behavior | | |
| Nonstricturing, nonpenetrating | 54 (51%) | |
| Stricturing | 31 (30%) | |
| Penetrating | 20 (19%) | |
| Perianal disease | 27 (26%) | |
| Underwent intestinal surgery for IBD in the past | 33 (31.4%) | 4 (2.2%) |
| Treatment | | |
| No treatment | 31 (29.5%) | 33 (18.4%) |
| 5-ASA | 18 (17.1%) | 55 (30.7%) |
| Azathioprine | 4 (3.8%) | 3 (1.7%) |
| Steroids | 4 (3.8%) | 13 (7.3%) |
| TNF inhibitors | 20 (19%) | 21 (11.7) |
| Interleukin inhibitors | 2 (1.9%) | 0 |
| mAb | 3 (2.9%) | 3 (1.7%) |
| Janus kinase inhibitor | 0 | 3 (1.7%) |
| Combination | 23 (21.9%) | 48 (26.8%) |

5-ASA, aminosalicylates; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

necrosis factor inhibitors along with azathioprine. There were no significant differences in age at inclusion in the study, disease duration, or presentation season between the two pathologies. In most patients with Crohn's disease, the onset of the disease was between 17–40 years, with an increased predominance of ileocolonic involvement but generally with a nonpenetrating and nonstructuring behavior of the lesions. Most of the included patients diagnosed with ulcerative colitis were in mild activity with the extension of the lesions predominantly at the level of the left colon.

In order to reduce the influence of different factors that could determine the presentation to the doctor throughout the year (e.g. summer vacations), the graphic representation of the number of patients who presented to the hospital according to the season and activity classification (from Fig. 1) was made by the ratio between the patients who presented themselves in the activity against the total number of patients who presented themselves in each season.

For each ratio, one proportion Z-test was performed between the ratio of patients in activity in each season and the general proportion of patients in activity (results shown in Fig. 1).

For both pathologies, the number of patients evaluated in clinical activity according to symptomatology was lower than those assessed in endoscopic or histological activity. In the case of Crohn's disease, the maximum number of patients included in the phase of endoscopic activity was in autumn, with a minimum in winter. From the point of view of histopathological activity, the maximum number of patients in activity was enrolled in spring, with minimum maintained in the winter period. In the case of ulcerative colitis, the endoscopic and histological activity was maximum in the spring, with a progressive decrease towards autumn.

Considering the number of patients with clinical, endoscopic, or histological activity for each season as time series we performed a Ljung–Box test with a lag of 4 in order to verify the seasonality assumption with the following results:

(1) for clinical activity for ulcerative colitis patients $P < 0.001$ and for Crohn's disease $P = 0.005$;
(2) for endoscopic activity for ulcerative colitis patients $P < 0.001$ and for Crohn's disease $P = 0.001$;
(3) and for histological activity for ulcerative colitis patients $P < 0.001$ and for Crohn's disease $P = 0.029$.

All the analyzed variables were nonnormal distributed. Tables 2 and 3 describes the observed parameters according to each season's median and 25, respectively, 75 percentiles separately for Crohn's disease and ulcerative colitis.

The seasonality of the inflammatory markers was analyzed by comparing their medians according to the seasons, using the Kruskal–Wallis test. Thus, statistically significant differences ($P < 0.05$) were obtained between seasons for CRP and ESR, both in the case of CD and UC. The differences between the diagnostic score of activity values were also significant between seasons in the case of BC. The obtained values were close to statistical significance ($P < 0.09$) for most of the other markers in the case of ulcerative colitis but not Crohn's disease. To better visualize the evolution of markers in time, we presented the graphical expression in Fig. 2.

In Crohn's disease and ulcerative colitis, the lowest values were descending towards winter for most of the markers analyzed. Systemic inflammatory markers follow a slightly different trend than intestinal markers and differ in the two pathologies. Thus, the highest values for systemic markers were recorded in spring in the case of Crohn's disease. Except for CHIT1, with maximum values in autumn, which correlates better with fecal calprotectin. In the case of ulcerative colitis, the maximum values were recorded in summer for systemic markers, unlike fecal calprotectin, with the highest values in spring. Regarding the evolution of vitamin D values and the activity evaluation score, they follow the trend of intestinal inflammation.

## Discussion

Given the relatively low prevalence of IBD (0–3%, lower in Eastern Europe [22]), the study incorporated both prospectively and retrospectively collected patient data to bolster statistical robustness.

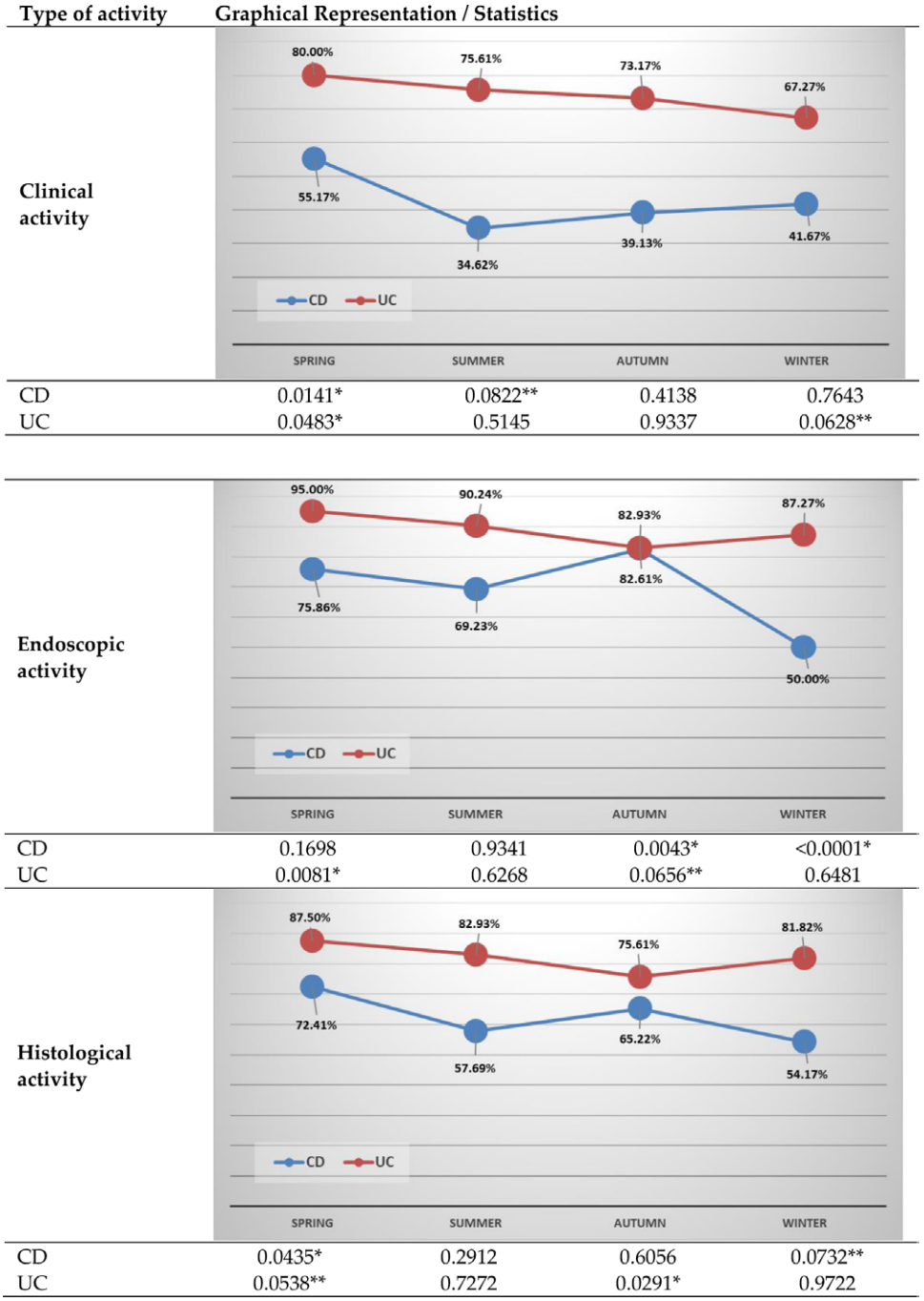


**Fig. 1.** The proportion of active patients from the total of those presented in each season separately, 1-sample *z*-test for a proportion. CD, Crohn disease; UC, ulcerative colitis. *Statistically significant; **tendency in obtaining a statistical significance.

Environmental factors play a pivotal role in both the etiology and exacerbation of IBD, although research on the correlation between disease exacerbations and seasonality has yielded conflicting outcomes. Some investigations suggest a higher incidence of IBD activity during spring [23,24], whereas others indicate heightened activity during autumn or winter [4,25,26]. Contrariwise, other studies did not find a link between periods of activity and seasonality [8,27]. These discordant results indicate a nuanced relationship influenced by geographical and climatic variances. Thus, different countries might have their specific pattern of onset and recurrence of IBD.

In the present study, IBD exacerbation tends to be more frequent in the warmer seasons (spring/summer), with fewer visits to the doctor in autumn and winter. This pattern might be attributed to seasonal fluctuations in immune responses, where decreased synthesis of proinflammatory cytokines during colder months [28] contrasts with heightened inflammatory mediator secretion and leukocyte activity in warmer weather [29]. Additionally, the secretion of corticoids, responsible for decreasing inflammation and immune response, is lower in the warmer seasons [30]. The increased frequency of exacerbation episodes in the spring could be explained by the seasonal

**Table 2.** Description of the inflammatory markers in Crohn's disease

| | Spring ($n$ = 30) | Summer ($n$ = 27) | Autumn ($n$ = 23) | Winter ($n$ = 25) |
|---|---|---|---|---|
| | Median (25–75 percentile) | Median (25–75 percentile) | Median (25–75 percentile) | Median (25–75 percentile) |
| CRP[a] | 3.76 (0.78–6.83) | 0.51 (0.42–2.01) | 1.25 (0.42–7.97) | 0.61 (0.41–1.68) |
| ESR[a] | 54 (24–72) | 16 (10–40) | 34 (20–46) | 42 (18–50) |
| CHIT1 | 200 (100–245) | 160 (95–270) | 325 (270–380) | 120 (60–170) |
| FC | 700 (180–1510) | 450 (12–1920) | 784 (316–1732) | 270 (150–1046) |
| Vit D | 20.02 (11.08–25.49) | 14.01 (8.18–22.46) | 15.74 (15.74–15.74) | 15.79 (13.53–23.89) |
| Score[a] | 6.21 (1.39–10.13) | 2.15 (0.68–4.80) | 3.91 (1.74–11.41) | 1.36 (0.86–3.88) |

CHIT1, chitotriosidase (nmol/ml/h); CRP, C-reactive protein (mg/dl); ESR, erythrocyte sedimentation rate (h); FC, fecal calprotectin (μg/g); n, number of patients; vit D, vitamin D.
[a]Kruskal–Wallis test $P < 0.05$.

**Table 3.** Description of the inflammatory markers in ulcerative colitis

| | Spring ($n$ = 40) | Summer ($n$ = 42) | Autumn ($n$ = 42) | Winter ($n$ = 55) |
|---|---|---|---|---|
| | Median (25–75 percentile) | Median (25–75 percentile) | Median (25–75 percentile) | Median (25–75 percentile) |
| CRP[a] | 0.53 (0.39–1.71) | 1.74 (0.43–6.47) | 0.44 (0.38–1.10) | 0.47 (0.39–2.86) |
| ESR[a] | 29 (16–64) | 38 (24–60) | 17 (10–44) | 24 (10–52) |
| CHIT1[b] | 215 (170–270) | 225 (200–330) | 190 (50–240) | 110 (60–200) |
| FC[b] | 1269 (380–2100) | 970 (300–1890) | 547 (90–1900) | 628 (126–1950) |
| Vit D[b] | 22.46 (13.53–25.49) | 17.88 (14.01–33.84) | 10.82 (6.73–15.74) | 14.54 (10.02–17.20) |
| Score[b] | 14.55 (4.63–22.51) | 11.64 (4.41–20.08) | 7.84 (2.46–21.33) | 7.51 (2.34–21.30) |

CHIT1, chitotriosidase (nmol/ml/h); CRP, C-reactive protein (mg/dl); ESR, erythrocyte sedimentation rate (h); FC, fecal calprotectin (μg/g); n, number of patients; vit D, vitamin D.
[a]Kruskal–Wallis test $P < 0.05$.
[b]Kruskal–Wallis test $P < 0.10$.

exposure to certain infectious agents that could modulate the immune response and contribute to the reactivation of the disease. The association between respiratory infections and exacerbation episodes in IBD has also been suggested by other studies [31,32]. While seasonal variability appears to influence the frequency of activity flares, however, this study did not find significant statistical differences for all seasons. Notably, spring exhibited statistically significant differences in the frequency of clinical and histological activity detection for both diseases. When considering activity detected endoscopically, statistically significant differences were observed in autumn and winter for Crohn's disease but in spring for ulcerative colitis. So, the comparison of frequencies using the Z-test against the study population's average reveals a predominance of activation in the spring. Seasons without statistically significant variation exhibit effects very similar to the average.

Interestingly, while clinical criteria tend to follow the trends observed in endoscopic and histopathological evaluations of disease activity, clinical scores alone may not be sufficiently accurate to classify patients into remission or activity phases. As corroborated by previous research, mucosal healing emerges as a critical criterion for accurate disease classification [33].

Seasonal variability in specific biomarker values and the secretion of proinflammatory cytokines has been noted in other studies [34,35], although the impact of climate change on inflammatory marker values in IBD remains unexplored. This study observed seasonal fluctuations in inflammatory markers, although they were not perfectly aligned with variations in disease flares assessed by clinical, endoscopic, or histological scores. Moreover, while systemic inflammatory markers exhibited more pronounced fluctuations than intestinal inflammatory markers, discrepancies were observed between disease types. In Crohn's disease, intestinal inflammatory markers peak in fall with minimal systemic inflammation, except for CHIT1, which correlates best with fecal calprotectin. Winter sees reduced activity levels, indicated by decreased intestinal and systemic inflammation markers values, followed by a significant increase in systemic markers in spring. This may be due to increased respiratory infections in spring. Things are slightly different in the case of ulcerative colitis, where intestinal inflammation assessed by fecal calprotectin seems to increase as changes are detected by activity scores (spring). Systemic inflammation, however, is more pronounced after the acute episode (summer). This suggests that initial inflammation occurs at the intestinal level before manifesting systemically.

The scoring system [13] used to evaluate the activity of diseases closely mirrors the seasonality of intestinal inflammation and the evolution of endoscopic or histopathological activity, indicating its potential utility in assessing intestinal changes and avoiding invasive procedures like colonoscopy. While marker variability is apparent graphically, statistical tests only found significant seasonal variation for CRP and ESR, likely due to small sample sizes per season subcategory.

Recent studies have highlighted vitamin D as a predictor of IBD activity. Low concentrations correlate with systemic or intestinal inflammation and increased hospitalizations or exacerbations necessitating steroid therapy or treatment escalation [36]. Vitamin D exhibits seasonal variability, with lower levels observed in winter and spring among patients with active disease but not those in remission. This suggests greater susceptibility to deficiency in activity flares [18]. Values considered suggestive of vitamin D deficiency are still controversial in the current literature; however, values <20 ng/ml are characteristic of deficiency [37,38]. Given the fact that vitamin D values are influenced by sun exposure, we mention that the

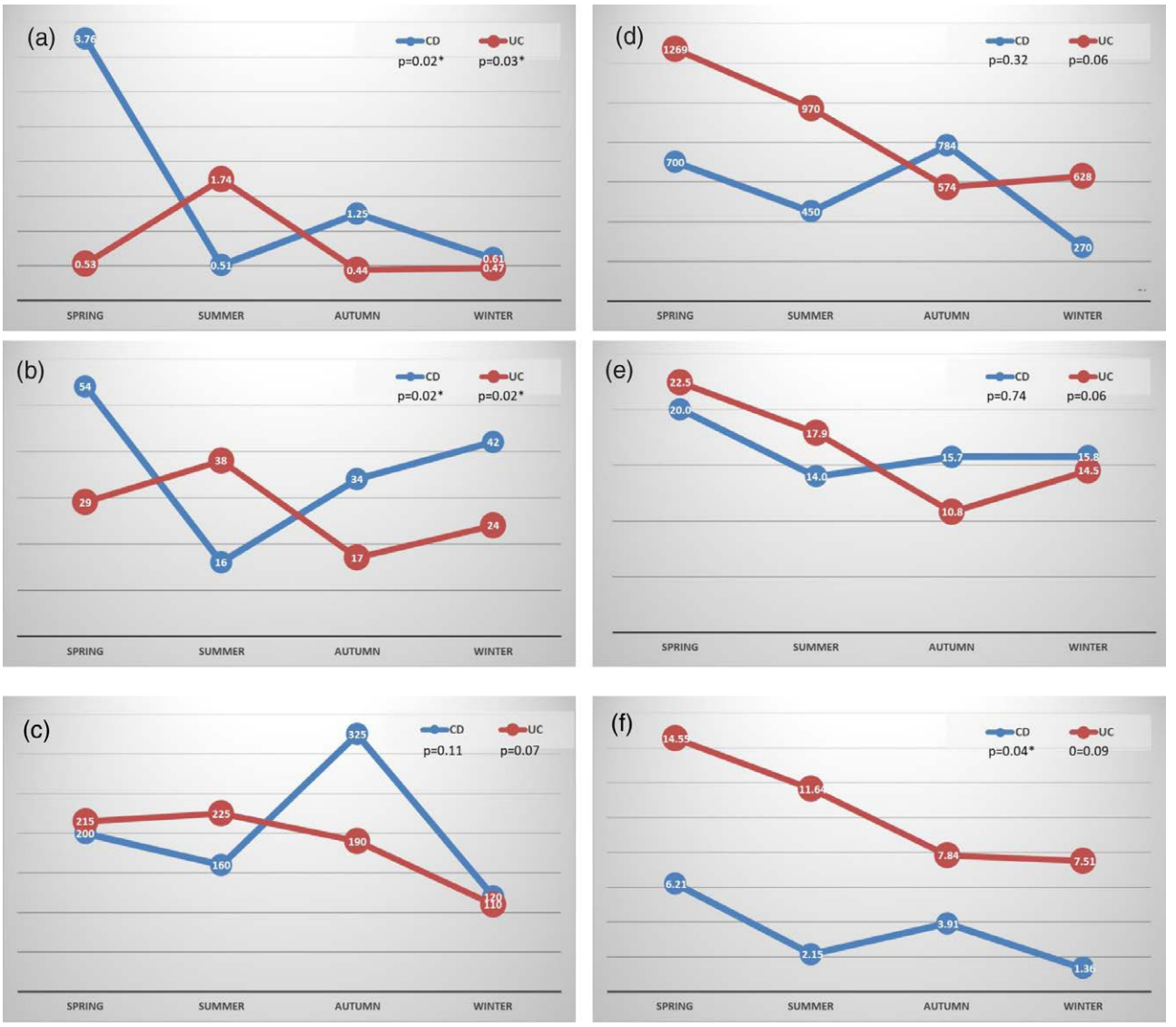


**Fig. 2.** Variability of the inflammatory marker values according to season. (a) C-reactive protein (mg/dl); (b) erythrocyte sedimentation rate (h); (c) chitotriosidase (nmol/ml/h); (d) fecal calprotectin (μg/g); (e) vitamin D (ng/ml); (f) score; *Kruskal–Wallis test $P < 0.05$.

study was performed in Romania, which lies between latitudes 43° and 49° N and longitudes 20° and 30° E [39]. Contrary to findings in other studies where the lowest values were noted in winter and spring, in the present study we observed consistently lower vitamin D concentrations throughout the year, with minimum values in summer for Crohn's disease and autumn for ulcerative colitis. This discrepancy may be attributed to COVID-19-related restrictions impacting sun exposure and endogenous vitamin D synthesis among prospectively enrolled patients.

The study's limitations include its single-center design, retrospective data collection for some patients, and relatively small sample sizes for subcategories based on presentation season. Given that environmental factors are different between different geographical areas, multicenter studies, including a larger group of patients, are needed to interpret the results of this paper. Moreover, the classification of patients in remission based on histological evaluation relies on subjective assessments by pathologists, highlighting the need for validated and easily performed histological scores for objective differentiation between remission and activity phases. Furthermore, certain drugs, such as non-steroidal anti-inflammatory drugs, antibiotics, or certain contraceptives, as well as smoking could influence the frequency of flares or the seasonality of certain inflammation markers, which could be a factor of error and were not studied in the present work.

## Conclusion

In conclusion, while Crohn's disease and ulcerative colitis share a relatively similar pathogenesis, this study reveals distinct seasonal patterns in the evolution of flares and inflammatory markers. Notably, Crohn's disease exhibits a higher frequency of flares during transitional seasons (spring/autumn), whereas ulcerative colitis flares are more prevalent in warmer seasons (spring/summer). The seasonality of inflammatory markers exhibits nuanced differences compared to flare episodes, indicating that systemic inflammation may not always align with intestinal inflammation.

The observed influence of seasonal changes on patient habits and the environment, including work environments, underscores the importance of recognizing and addressing these factors in disease management. This study's findings emphasize the need for tailored approaches to account for the impact of seasonal variations on disease activity. Furthermore, understanding the nuanced interplay between seasonal factors and disease exacerbation paves the way for developing targeted strategies to prevent disease reactivation. This insight holds promise for enhancing disease management and treatment outcomes in individuals with Crohn's disease and ulcerative colitis.

## Acknowledgements

Neamti Lidia is acting as the submission's guarantor and takes responsibility for the integrity of the work as a whole. All authors approved the final version of the manuscript.

This research was funded by 'Iuliu Hatieganu' University of Medicine and Pharmacy PCD grant number 2461/49/17.01.2020.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of 'Iuliu Hatieganu' University of Medicine and Pharmacy Cluj-Napoca (protocol code no. 93 : 9 March 2020).

Data presented in this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy regulations.

### *Conflicts of interest*

There are no conflicts of interest.

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