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Fecal calprotectin – a valuable predictor of microscopic colitis

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Abstract. – OBJECTIVE: Microscopic colitis (MC) has been of major concern worldwide due to its relapsing and remitting nature of chronic diarrhea. Quality of life of patients suffering from this disease is quite debilitating.

PATIENTS AND METHODS: In order to understand the role and importance of fecal calprotectin (FC) we performed a statistical analysis on the patients suffering from chronic diarrhea and admitted to our hospital from 2014 to 2020, and who were prescribed Loperamide (Imodium) or Budesonide or a combination of both and had undergone FC detection test.

RESULTS: FC was found to be significantly correlated to the age, alcohol consumption and beta blocker use. A high level of the FC concentrations increases the chances of having flare-ups of diarrhea episodes making the quality of life of such patients worse.

CONCLUSIONS: FC concentrations should be monitored frequently and precautionary measures to avoid a relapse should be aimed. Measures to improve quality of life, should be of prime concern. In-depth research is required to better understand MC and to find better treatment options which can be used on a long-term basis, instead of anti-motility drugs which are able to control the acute episodes, but when discontinued result in an increased tendency to have relapses.

Key Words:
Fetal calprotectin, Watery diarrhea, Lymphocytic colitis, Collagenous colitis, Microscopic colitis, Quality of life.

Introduction

Microscopic colitis (MC) is a common cause of chronic or recurrent watery diarrhea, especially in elderly female patients[1-3]. The clinical course of MC is characterized by relapsing and remitting episodes[3]. Epidemiological studies[3,4] have shown that the annual incidence of MC is remarkably increasing, as it was estimated to be around 4.2-11.3 per 100,000 people per year. Therefore, it is crucial for both, the patients and the healthcare system, to efficiently diagnose and treat MC patients in order to improve their quality of life[3,5,6].

MC has two subtypes: lymphocytic colitis (LC) and collagenous colitis (CC), both subtypes are very similar clinically and histologically, as the chronic inflammation in the mucosa is the core of the disease. In addition, the clinical features in both subsets are similar, marked by chronic

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non-bloody diarrhea, weight loss, and abdominal pain[7-9]. However, one major difference is observed on a biopsy where CC is featured by the subepithelial collagen band, whereas the infiltrative intraepithelial lymphocytes in the mucosa, features LC. On colonoscopy, although macroscopically the colonic mucosa mostly appears normal, only sometimes edematous, the histological analysis of the biopsy is needed to establish the definitive diagnosis.

Even though the underlying etiology of MC is not established, few studies[10,11] have shown that female gender, increased age, the use of proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs) are associated with a significantly increased risk of developing MC. It is also commonly associated with celiac sprue. Furthermore, Calprotectin, a protein biomarker of the S-100 protein family is present chiefly within neutrophils, was noted to have a profound correlation between its quantitative presence in feces and the appearance of an ongoing inflammation, such as inflammatory bowel diseases (IBD)[12]. Principal role of fecal calprotectin (FC) is to help in innate immune response. The quantity varies in different body fluids and is dependent on the level of inflammation. Normal concentration of FC is found to be six times higher in the stools compared to that found in the plasma13. Therefore, it is of great importance to measure the concentration of FC in MC as a way of monitoring the course of the disease, as well as to recognize and warn patients regarding the risk of flare-ups.

A well-defined treatment for MC has not been established yet; however, some guidelines have recommended the use of budesonide as a first-line treatment for achieving remission[12,14]. A double-blinded, randomized controlled trial14 showed that the maintenance of clinical remission rate for 1 year was higher in the budesonide group (61.4%) than in the placebo group (16.7%). However, there are no randomized controlled studies that compare the efficacy of loperamide against other medications used for the treatment of microscopic colitis. Although it is efficient in subsiding the symptoms of MC and reducing the frequency of diarrhea.

Patients and Methods

We investigated the rate of relapses and the FC concentration in patients admitted to the Municipal Emergency University Hospital, Romania, during the study period that goes from 2014 to 2019. We sifted the files of the patients having diarrhea which were treated either with loperamide (Imodium) or budesonide as a monotherapy or with a combination therapy of budesonide and loperamide, depending on the clinical state, underlying cause and previous history. Based on the treatment, we divided the patients in three groups, group A consuming loperamide, Group B comprising of patients on Budesonide and group C which were on combination therapy of Imodium and Budesonide, and statistical analysis was done. Fecal calprotectin and other inflammatory parameter were analyzed. Quality of life was assessed, and underlying pathologies were noted. A total of 483 colonoscopies were performed in the four-year period (2015-2019), based on symptoms related to irritable bowel disease predominant presentation being diarrhea. Colonoscopy was performed to obtain biopsy specimens for confirming the diagnosis of microscopic colitis.

Out of these, a total of 76 (9.7%) patients were found to be positive for MC based on histopathologic examination results.

Further, we tried to see associations with different diseases present, socio-economic status, lifestyle, smoking and drinking habits etc. In addition to this, we also tried to see correlations in patients undergoing various treatments.

Inclusion criteria were patients suffering from chronic diarrhea, multiple hospital admissions for the same without a preset cause. Patients having gastrointestinal cancers, food poisoning, lactose intolerance cases, patients having an acute episode of gastrointestinal infection were excluded from the study. Similarly, patients undergoing bariatric surgeries being admitted for a pre-operative endoscopic evaluation were also excluded from the study lot.

Statistical Analysis

Results for targeted variables were presented using descriptive statistics (mean, standard deviation, range, median, interquartile range) for continuous data, and counts with associated percentages for categorical data. Correlations between key data were highlighted using Spearman's correlation coefficient.

Statistical analysis is based on Chi-square tests for categorical variables, with the corresponding p-values being presented in the summary tables. Pairwise comparisons are performed based on Bonferroni-adjusted significance tests, with the corresponding significance (S) ($p \leq 0.05$) or

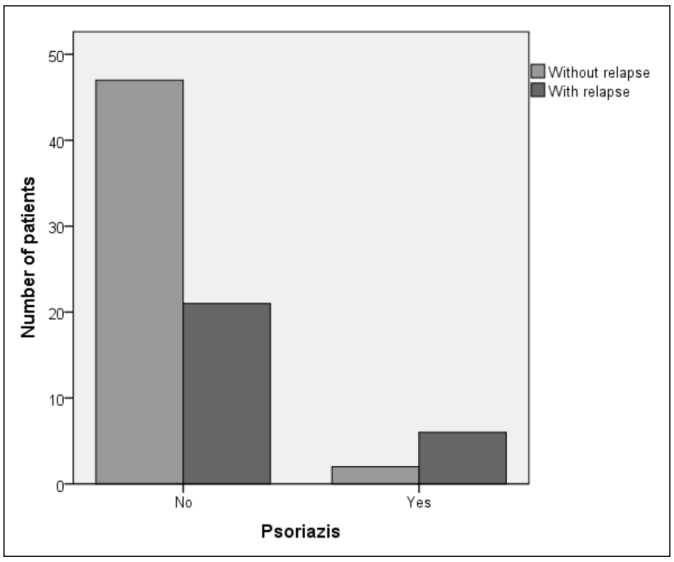

Figure 1. Bar plot of presence/absence of Psoriasis by relapse.

non-significance (NS) (p>0.05) being reported. p-values based on Bonferroni correction comparison for comparing the Imodium group with the Budesonide group of patients are flagged under p-value 1 column in the summary tables, while p-value 2 flags the comparison result of the Imodium group with the Imodium and Budesonide group, and lastly, p-value 3 flags the comparison result of the Budesonide group with the Imodium and Budesonide group.

Ethics Approval and Informed Consent Statement

Prior to the commencement of the study, ethics approval was obtained from all the relevant persons or authorities. The study was approved by the "Comisia de Etica a Cercetarii Stiintifice" (Ethics Committee for Scientific Research) of the University of Medicine and Pharmacy Victor Babes, Timisoara, (approval No. 15/03.03.2014/ rev. 2022) in accordance with the Helsinki declaration - Recommendations Guiding Medical Doctor in Biomedical Research Involving Human Subjects. All the steps of the study were conducted in accordance with the above guidelines, conforming to the standard operational procedures for clinical studies approved for Spitalul Municipal, (Municipal Emergency University Hospital, Timisoara, Romania).

This retrospective study was conducted in our university hospital and, as a part of routine procedure, informed written consent forms stating that the data can be used for future medical research purpose were signed by each patient at the time of admission in the hospital.

Results

Group A, B and C divided based on the treatment, were further analyzed statistically to see the relapse rate and different correlations based on various parameters and co-morbidities. Group B receiving Imodium was found to have lowest number of relapses as compared to the oth-

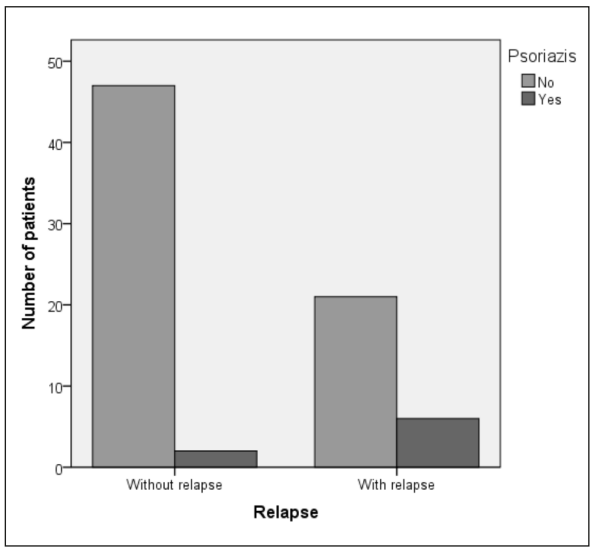

Figure 2. Bar plot of relapses in correlation to presence/ absence of Psoriasis.

Table I. Summary of the main characteristics of the treatment group for the patients included in our statistical analysis.

	Group A Imodium (N=20)	Group B Budesonide (N=24)	Group CImodium and Budesonid (N=32)	*p*-value	*p*-value 1	*p*-value 2	*p*-value 3
Relapse							
Absent	6 (30.00%)	23 (95.83%)	20 (62.50%)				
Present	14 (70.00%)	1 (4.17%)	12 (37.50%)	**<0.001**	**S**	NS	**S**

The *p*-values were obtained using the Chi-square tests. The *p*-values 1, 2, 3 are based on Bonferroni correction comparisons, indicating S for significant *p*-values, NS for non-significant *p*-values, respectively. Data are presented as counts (percentages).

er two groups (Table I). A weak positive/direct correlation between 'Relapse' and Psoriasis was revealed using Spearman's correlation coefficient (r=0.283, *p=0.013),* as shown in table I, Figure 1 and 2. A moderate positive/direct correlation between 'Relapse' and Imodium was revealed using Spearman's correlation coefficient (r=0.430, *p*<0.001) (Table II, Figure 3 and 4). A moderate negative/indirect correlation between 'Relapse' and Budesonide was revealed using Spearman's correlation coefficient (r=-0.445, *p*<0.001) (Table II, Figure 5 and 6). A weak positive/direct correlation between 'Relapse' and alcohol consumption was revealed using Spearman's correlation coefficient (r=0.280, *p*=0.014), as shown in Table II, Figure 7 and 8). A weak positive/direct correlation between 'Relapse' and, 'Fecal Calprotectin' alcohol consumption was revealed using Spearman's correlation coefficient (r=0.283, *p*=0.013) (Table II, Figure 9 and 10). When comparing the *p*-value for various basic parameters, it was found to be above 0.05 in regard to gender, smoking, depression, sleep disorders and unemployment (Table III). B-blockers in comparison to ACE inhibitors, proton pump inhibitors, SSRI, NSAIDs, statins, had *p*-value below 0.05 (Table IV). Comparing the comorbidities in different treatment group in our study lot we found diabetes mellitus with *p*-value below 0.05, in comparison to auto-

Table II. Correlation coefficient (r) and p-values of 'Relapse' with key parameters.

	Sperman's correlation coefficient (r)	*p*-value
Gender	0.065	0.574
Smoking habits	0.033	0.776
PPIs	0.023	0.841
NSAIDs	0.007	0.953
SSRI	0.168	0.146
Beta blocker	0.174	0.133
Statins	0.146	0.207
ACEI	0.181	0.118
Celiac disease	-0.197	0.088
Polyarthritis	0.068	0.558
Psoriasis	0.283	**0.013**
Autoimmune thyroiditis	-0.118	0.309
Diabetes Mellitis Type 1	0.085	0.464
CC	-0.111	0.339
LC	0.075	0.517
Imodium	0.430	**<0.001**
Budesonide	-0.445	**<0.001**
Imodium and Budesonid	0.035	0.763
Depression	0.111	0.339
Alcohol	0.280	**0.014**
Sleep disturbance	-0.027	0.814
Job loss	0.206	0.074
Fecal Calcprotectin	0.283	**0.013**

IPP – Proton Pump Inhibitors; NSAIDs – Non-Steroidal Anti-Inflammatory Drugs; SSRI – Selective Serotonin Reuptake Inhibitors; CC – collagenous colitis; LC – lymphocytic colitis.

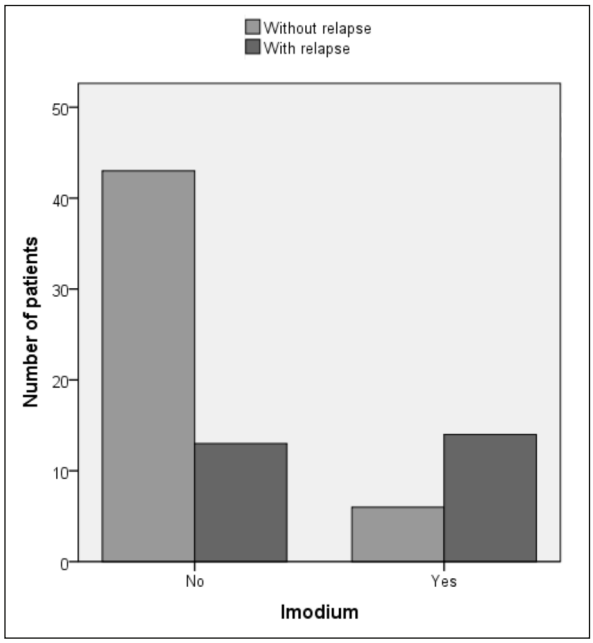

Figure 3. Bar plot of Imodium treatment by relapse.

Table III. Summary of the main characteristics of the patients included in our statistical analysis and of the treatment group of the patients included.

	All patients (N=76)	Group A Imodium (N=20)	Group B Budesonide (N=24)	Group C Imodium and Budesonid (N=32)	*p*-value	*p*-value 1	*p*-value 1	*p*-value 1
Age (years) (*) Mean (SD) Min; Max Median (Q1; Q3)	57.26 (9.775) 37; 79 58.00 (49.50; 65.00)	66.60 (6.700) 55; 79 67.50 (60.50; 71.00)	46.83 (6.077) 37; 57 47.50 (42.50; 52.00)	59.25 (5.634) 47; 69 59.00 (57.00; 63.50)	**<0.001**	**S**	**S**	**S**
Gender Female Male	51 (67.11%) 25 (32.89%)	17 (85.00%) 3 (15.00%)	17 (70.83%) 7 (29.17%)	17 (53.13%) 15 (46.87%)	0.053	NS	NS	NS
Smoking No Yes	55 (72.37%) 21 (27.63%)	18 (90.00%) 2 (10.00%)	15 (62.50%) 9 (37.50%)	22 (68.75%) 10 (31.25%)	0.106	NS	NS	NS
Relapse Absent Present	49 (64.47%) 27 (35.53%)	6 (30.00%) 14 (70.00%)	23 (95.83%) 1 (4.17%)	20 (62.50%) 12 (37.50%)	**0.001**	**S**	NS	**S**
Depression No Yes	45 (59.21%) 31 (40.79%)	10 (50.00%) 10 (50.00%)	16 (66.67%) 8 (33.33%)	19 (59.38%) 13 (40.62%)	0.534	NS	NS	NS
Alcoholism No Yes	66 (86.84%) 10 (13.16%)	20 (100%) 0 (0%)	22 (91.67%) 2 (8.33%)	24 (75.00%) 8 (25.00%)	**0.024**	NOP	NOP	NS
Sleep disorders No Yes	38 (50.00%) 38 (50.00%)	8 (40.00%) 12 (60.00%)	13 (54.17%) 11 (45.83%)	17 (53.13%) 15 (46.87%)	0.579	NS	NS	NS
Job loss No Yes	64 (84.21%) 12 (15.79%)	19 (95.00%) 1 (5.00%)	20 (83.33%) 4 (16.67%)	25 (78.13%) 7 (21.87%)	0.265	NS	NS	NS

NoP=Comparison not performed because one of its column proportions is equal to zero or one. The *p*-values are obtained with ANOVA one-way tests (*) and with Chi-square tests. *p*-values 1, 2, 3 are based on Bonferroni correction comparisons, indicating S for significant *p*-values, NS for non-significant *p*-values, respectively. Continuous data (*) are summarized as mean (standard deviation); minimum and maximum value; median and associated quartiles (Q1-25 percentage quartile; Q3-75 percentage quartile). Quartiles were obtained with Tukey's method. Categorical data are presented as counts (percentages).

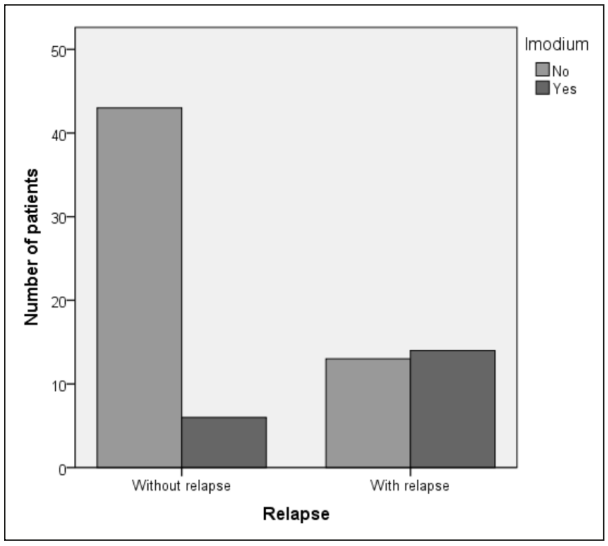

Figure 4. Bar plot of relapse by Imodium treatment administration.

Table IV. Summary of the medications prescribed to the patients included in our statistical analysis and of the treatment group of the patients included.

	All patients (N=76)	Group A Imodium (N=20)	Group B Budesonide (N=24)	Group C Imodium and Budesonid (N=32)	*p*-value	*p*-value 1	*p*-value 2	*p*-values 3
PPI								
No	49 (64.47%)	10 (50.00%)	15 (62.50%)	24 (75.00%)	0.181	NS	NS	NS
Yes	27 (35.53%)	10 (50.00%)	9 (37.50%)	8 (25.00%)				
NSAIDs								
No	51 (67.11%)	10 (50.00%)	19 (79.17%)	22 (68.75%)	0.118	NS	NS	NS
Yes	25 (32.89%)	10 (50.00%)	5 (20.83%)	10 (31.25%)				
SSRI								
No	58 (76.32%)	13 (65.00%)	18 (75.00%)	27 (84.38%)	0.274	NS	NS	NS
Yes	18 (23.68%)	7 (35.00%)	6 (25.00%)	5 (15.62%)				
Beta blocker	48 (63.16%)	12 (60.00%)	22 (91.67%)	14 (43.75%)	0.001	S	NS	S
No	28 (36.84%)	8 (40.00%)	2 (8.33%)	18 (56.25%)				
Yes								
Statins								
No	52 (68.42%)	13 (65.00%)	18 (75.00%)	21 (65.63%)	0.703	NS	NS	NS
Yes	24 (31.58%)	7 (35.00%)	6 (25.00%)	11 (34.37%)				
ACEI								
No	56 (73.68%)	13 (65.00%)	20 (83.33%)	23 (71.88%)	0.371	NS	NS	NS
Yes	20 (26.32%)	7 (35.00%)	4 (16.67%)	9 (28.12%)				

p-values are obtained with Chi-square tests. *p*-values 1, 2, 3 are based on Bonferroni correction comparisons, indicating S for significant *p*-values, NS for non-significant *p*-values, respectively. Data are presented as counts (percentages). IPP – Proton Pump Inhibitors; NSAIDs – Non-Steroidal Anti-Inflammatory Drugs; SSRI – Selective Serotonin Reuptake Inhibitors.

Table V. Summary of comorbidities of the patients included in our statistical analysis and of treatment group for the patients included.

	All patients (N=76)	Group A Imodium (N=20)	Group B Budesonide (N=24)	Group C Imodium and Budesonid (N=32)	*p*-value	*p*-value 1	*p*-value 2	*p*-value 3
Celiac Disease								
No	71 (93.42%)	20 (100%)	19 (79.17%)	32 (100%)	0.003	NoP	NoP	NoP
Yes	5 (6.58%)	0 (0%)	5 (20.83%)	0 (0%)				
Polyarthritis								
No	67 (88.16%)	16 (80.00%)	23 (95.83%)	28 (87.50%)	0.267	NS	NS	NS
Yes	9 (11.84%)	4 (20.00%)	1 (4.17%)	4 (12.50%)				
Psoriasis								
No	68 (89.47%)	18 (90.00%)	23 (95.83%)	27 (84.38%)	0.383	NS	NS	NS
Yes	8 (10.53%)	2 (10.00%)	1 (4.17%)	5 (15.62%)				
Tiroidita Autoimuna	63 (82.89%)	17 (85.00%)	21 (87.50%)	25 (78.13%)				
No	13 (17.11%)	3 (15.00%)	3 (12.50%)	7 (21.87%)	0.627	NS	NS	NS
Yes								
Diabetes Mellitus type 1	65 (85.53%)	14 (70.00%)	23 (95.83%)	28 (87.50%)	0.048	NS	NS	NS
No	11 (14.47%)	6 (30.00%)	1 (4.17%)	4 (12.50%)				
Yes								

NoP=Comparison not performed because one of its column proportions is equal to zero or one. *p*-values are obtained with Chi-square tests. *p*-values 1, 2, 3 are based on Bonferroni correction comparisons, indicating S for significant *p*-values, NS for non-significant *p*-values, respectively. Data are presented as counts (percentages).

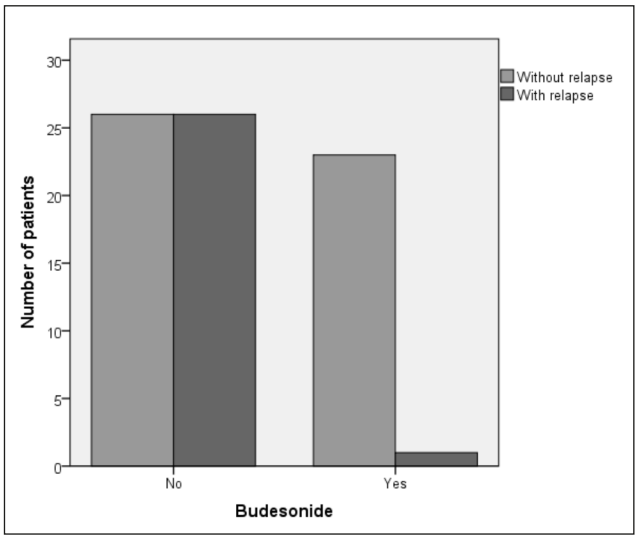

Figure 5. Bar plot of Budesonide treatment by relapse.

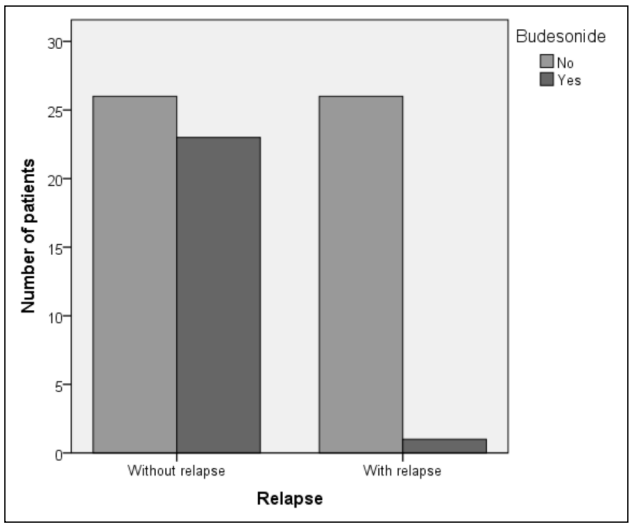

Figure 6. Bar plot of relapse by Budesonide treatment administration.

Table VI. Summary of laboratory test results of the patients included in our statistical analysis and of the treatment group for the patients included.

	All patients (N=76)	Imodium (N=20)	Budesonide (N=24)	Imodium and Budesonid (N=32)	*p*-value	*p*-value 1	*p*-value 2	*p*-value 3
Fecal Calprotectin								
Normal	37 (48.68%)	5 (25.00%)	13 (54.17%)	19 (59.38%)				
High	39 (51.32%)	15 (75.00%)	11 (45.83%)	13 (40.62%)	0.044	NS	S	NS
CC								
No	31 (40.79%)	9 (45.00%)	9 (37.50%)	13 (40.63%)	0.880	NS	NS	NS
Yes	45 (59.21%)	11 (55.00%)	15 (62.50%)	19 (59.37%)				
LC								
No	46 (60.53%)	11 (55.00%)	15 (62.50%)	20 (62.50%)	[0].841	NS	NS	NS
Yes	30 (39.47%)	9 (45.00%)	9 (37.50%)	12 (37.50%)				

p-values are obtained with Chi-square tests. *p*-values 1, 2, 3 are based on Bonferroni correction comparisons, indicating S for significant *p*-values, NS for non-significant *p*-values, respectively. Data are presented as counts (percentages). CC – collagenous colitis; LC – lymphocytic colitis.

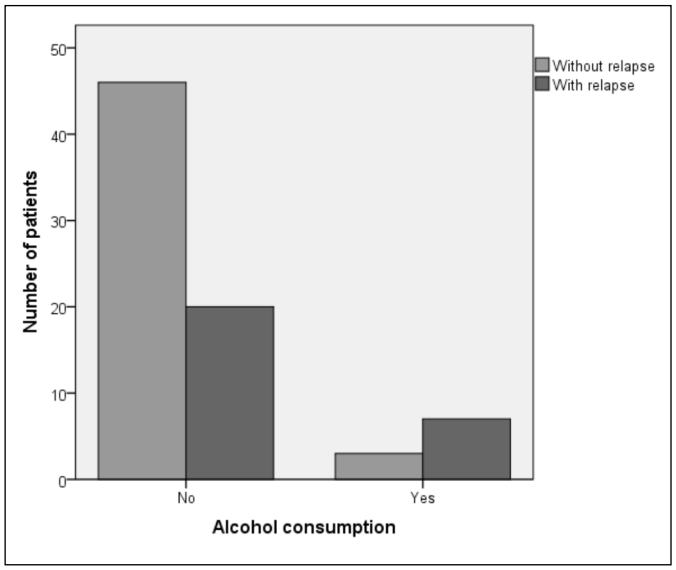

Figure 7. Bar plot of alcohol consumption by relapse.

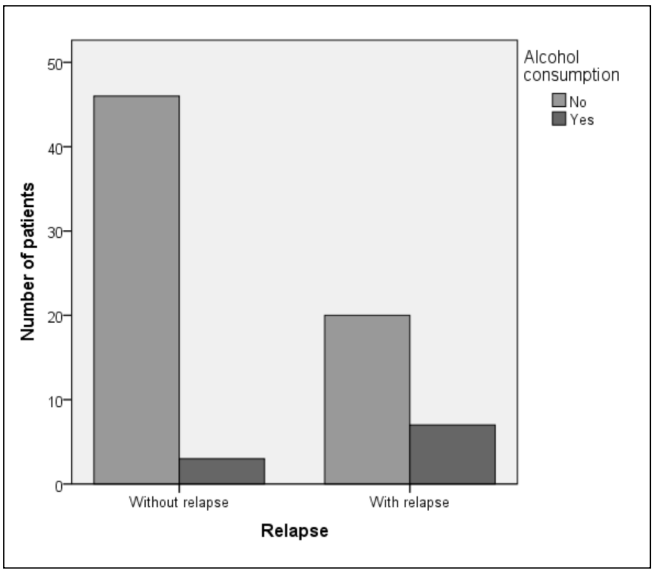

Figure 8. Bar plot of relapse by alcohol consumption.

immune thyroiditis, psoriasis and polyarthritis where it was above this value. Unfortunately, for celiac disease it was not possible to compare due to statistical reasons, as any value being "0", does not allow to run the statistical test (Table V). Fecal calprotectin was found to be high in above 50% of the entire study lot of 76 patients, also the *p*-value was 0.44. In detail analysis in the 3 groups divided as per their treatment plan are shown in table VI, including the analysis of patients diagnosed with collagenous colitis and lymphocytic colitis where the *p*-value was 0.880 and 0.841 respectively.

Discussion

Fecal calprotectin indicates the ongoing gastrointestinal inflammation and was considered to be a marker to evaluate the recurrence or relapse rate of chronic diarrhea. A study conducted by Kim et al[15] to demonstrate the association of PPI to in-

testinal inflammation *via* assessing the levels of FC revealed no significant correlation. Similar results were seen in our study in the patients undergoing PPI therapy, in all three groups. In regard to beta blocker users from our study, there was a significant correlation seen in FC presence and disease process. Excessive alcohol consumption often leads to excessive damage to the intestines, and causes an increased inflammatory response, which in turn leads to flooding of white blood cells. FC, which is a protein found in granulocytes (neutrophils) cytoplasm, concentration of which was found to be unaffected in alcoholics16. While in our study we found a weak correlation between the FC presence and chances of relapse in alcoholic patients. FC and CRP are used by physicians to exclude the presence of inflammatory bowel disease. But more extensive studies are required to set the precise diagnostic criteria, and to quantify the values of FC concentrations in regard to the disease severity. The quality of life should be assessed in patients suffering from such type of diseases, as in many cases (especially in cardiac pathologies) it can further lead to constant psychological stress and might affect the daily routine chores adding to anxiety and stress[6,17,18].

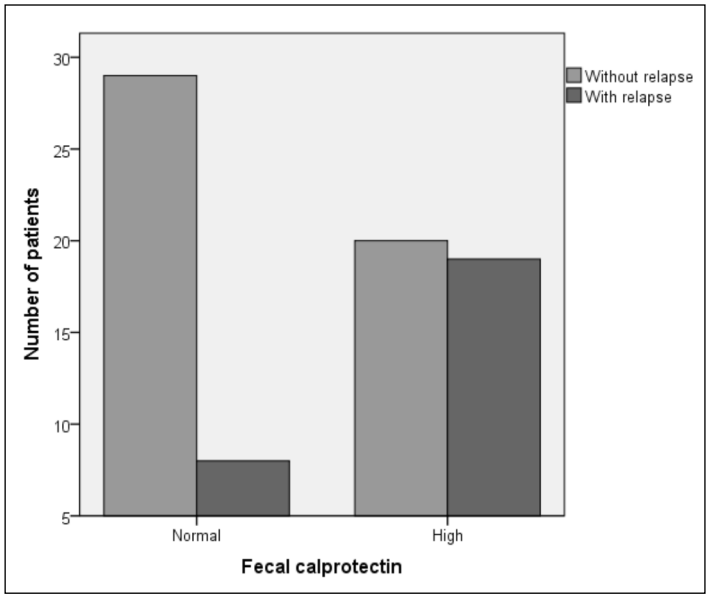

Figure 9. Bar plot of fecal calprotectin by relapse.

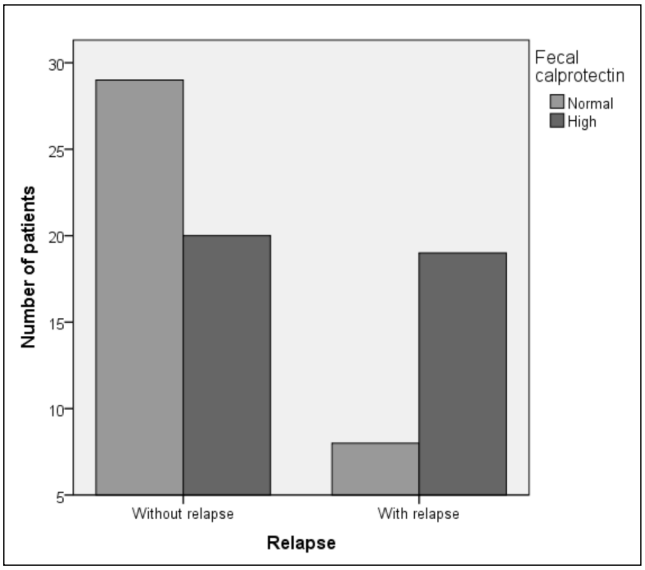

Figure 10. Bar plot of relapse by fecal calprotectin.

Conclusions

Based on the statistical analysis, it can be stated that fecal calprotectin can be considered as a valuable predictor for flare-up risks in microscopic colitis patients. Evaluation of fecal calprotectin should be done to assess the severity of the disease and its tendency in future to lead to relapse. Imodium seems to be more promising as compared to budesonide, yet combination of two can give far better results in severe cases. Keeping in mind the approach based on the principle that "a stitch in time saves nine", to reduce the financial burden on the state insurance companies and above all to improve the quality of life of patients suffering from microscopic colitis new guidelines should be implemented in regard to diagnosis and treatment of MC. Anti-motility drugs, when discontinued, result in relapse; hence there is a dire need for new drugs which can be c

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

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Acknowledgments

Not applicable.

Ethics Approval

The study was approved by the "Comisia de Etica a Cercetarii Stiintifice" (Ethics Committee for Scientific Research) of the University of Medicine and Pharmacy Victor Babes, Timisoara, (approval No. 15/03.03.2014/rev. 2022) in accordance with the Helsinki declaration - Recommendations Guiding Medical Doctor in Biomedical Research Involving Human Subjects.

Informed Consent

Informed written consent were obtained from all the patients/individuals.

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