EVALUATING PREDICTIVE FACTORS FOR DISEASE ACTIVITY AMONG PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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EVALUATING PREDICTIVE FACTORS FOR DISEASE ACTIVITY AMONG PATIENTS WITH INFLAMMATORY BOWEL DISEASE (Abstract) Aim: this study focused on evaluating several potential predictive factors for an increase in disease activity at 6 months for patients with inflammatory bowel disease (IBD). Material and methods: We performed a prospective cohort study, including patients who were evaluated at baseline and at 6 months. We assessed disease activity, clinical and biochemical parameters, anxiety and depression using Hospital Anxiety and Depression Scale (HADS) and sleep disorders using Pittsburgh Sleep Quality Index (PSQI) both at baseline and at 6 months. Results: Among the 59 patients who completed the follow-up, there was a statistically significant correlation between the presence of hyposideremia (p=0.023), hypercholesterolemia (p= 0.015) and altered psychological state (p=0.006) at baseline with an increase in disease activity at 6 months. Moreover, among the studied parameters, hypercholesterolemia (OR 5.18; 95% CI, 1.25-21.44), the neutrophil to lymphocyte ratio (OR 3.83; 95% CI, 1.87-7.83) and the depression score (OR 1.56; 95% CI, 1.22-2.01) were predictors for increase in disease activity at 6 months. Conclusions: Beyond usual inflammatory markers, neutrophil to lymphocyte ratio could have potential predictive value for systemic inflammation in IBD patients and could be easily assessed at routine evaluations. An integrative management, addressing several comorbidities, such as dyslipidemia and alteration of psychological distress could contribute to diminishing the risk for future disease flares in this patient category. Keywords: INFLAMMATORY BOWEL DISEASE, PREDICTIVE FACTORS, HADS.

Inflammatory bowel disease (IBD) represent chronic inflammatory disorders which evolve with a relapsing-remitting pattern and include two main subtypes, namely ulcerative colitis (UC) and Crohn’s disease (CD). Although with increasing prevalence in the past decades, there is still no curative treatment and relatively few information on the factors which could predict disease evolution. After diagnosis, disease monitoring is essential via clinical, biological and endoscopic criteria but also through evaluation of disease activity scores, the most commonly used being Mayo score for UC and Crohn’s disease activity index (CDAI) for CD.

Although non-invasive disease monitoring following various biological parameters
reflecting inflammation such as C reactive protein (CRP), fibrinogen, fecal calprotectin is available (1) less information is available on noninvasive parameters predictive for future disease activity. Identifying predictors of unfavorable clinical course are useful, since they could facilitate treatment decisions, indicate requirement for tight monitoring and avoid overtreatment (2). Our aim was to identify potential predictive factors for increased disease activity at 6 months evaluation among several accessible parameters in the clinical practice.

MATERIAL AND METHODS
This prospective study assessed the prediction value of several parameters for disease activity at 6 months and included IBD patients from the Institute of Gastroenterology and Hepatology from “Sf. Spiridon” County Clinical Emergency Hospital, Iași, Romania between September 2019 and February 2020, who were evaluated at baseline and at 6 months.

Inclusion criteria were age above 18, written informed consent, diagnosis of IBD based on clinical, endoscopic and histological criteria. The exclusion criteria included refusal to participate in the study, active infections and various aspects which might influence psychological status and sleep quality (9): pregnancy, history of neoplasia, previously diagnosed psychiatric disorders, history of alcohol or drug use, sleep apnea, BMI > 35, significant major associated illness (active malignancy, significant cardiac or pneumological comorbidities), night shift workers, and associated medications (analgesics, muscle relaxants, antineoplastic agents, thyroid medication).

For the enrolled patients, clinical and anamnestic data were collected during patients’ evaluations, including information related to extraintestinal manifestations, current and previous medication, IBD-related surgery. For the evaluation of disease activity, Crohn’s Disease Activity Index (CDAI) was used for patients with CD and Mayo score for UC. The biochemical evaluation included not only markers of systemic inflammation, namely C reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fibrinogen, but also evaluation of the complete blood count (CBC) with calculation of neutrophil-to-lymphocyte ratio (NLR), iron level, ferritin, albumin, cholesterol, triglycerides. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and psychological distress was evaluated through the Hospital Anxiety and Depression Scale (HADS). Impaired sleep was defined as a PSQI ≥5 (3), while altered psychological status was considered when either of the 2 HADS sub scores, namely HADS-depression (HADS-D) and HADS-Anxiety (HADS-A) were ≥8 (4). All these parameters have been evaluated at baseline, while at 6 months clinical and anamnestic data, CBC, inflammatory markers (CRP, fibrinogen) were recorded and disease activity scores (CDAI, MAYO) calculated.

The data was statistically analyzed using SPSS version 25. Variables were reported as mean values and standard deviation, or as median with 25th-75th percentiles, after testing for normality of the distribution using Kolmogorov-Smirnov test. To evaluate the homogeneity of variance, Levene test was used. The comparisons between the analyzed groups were performed using Student’s t-test for normally distributed continuous variables.

The qualitative variables were presented as absolute (n) and relative (%) frequencies and the comparison among the groups was based on the results of Chi-square tests. The
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Bivariate correlation analysis was completed based on Pearson Correlation test. Predictive value for several parameters was evaluated using logistic regression and variables with significant results were afterwards included in the multivariate analysis. ROC curve analysis was used to evaluate the prediction power of some variables. For all tests applied, the calculated significance level (p-value) was considered for p <0.05.

The study protocol was in accordance with the ethical standards of the institutions’ Ethical Review Boards and with the 1964 Helsinki declaration and its later amendments and the study was performed after obtaining approval from the institutions involved.

RESULTS
Among the 82 eligible patients with IBD, 59 completed the study; 6 did not consent for participation in the study, 14 could not complete the follow-up, 2 had active infection, 1 had history of neoplasia. For the 59 patients included in the study several characteristics were evaluated, with no statistically significant differences between these parameters depending the disease subtypes (Crohn’s disease and ulcerative colitis) (tab. I).

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Descriptive statistics of the evaluated parameters</th>
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<tbody>
<tr>
<td>Patient characteristics</td>
<td>Study Group n=59 (100%)</td>
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<tr>
<td></td>
<td>Ulcerative colitis n=41 (69.5%)</td>
</tr>
<tr>
<td>Active disease, n (%)</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>19 (32.2%)</td>
</tr>
<tr>
<td>Disease activity scores median (Q25;Q75)</td>
<td>Mayo score 3 (1.7)</td>
</tr>
<tr>
<td>Hemoglobin, median (Q25;Q75)</td>
<td>12.6 (11.7; 14.25)</td>
</tr>
<tr>
<td>Seric iron level median (Q25;Q75)</td>
<td>59 (23; 86)</td>
</tr>
<tr>
<td>Ferritin median (Q25;Q75)</td>
<td>75 (36; 174)</td>
</tr>
<tr>
<td>CRP median (Q25;Q75)</td>
<td>0.82 (0.24; 2.09)</td>
</tr>
<tr>
<td>Albumin (mean ± SD)</td>
<td>4 ± 0.55</td>
</tr>
<tr>
<td>Fibrinogen (mean ± SD)</td>
<td>412.41 ± 59.62</td>
</tr>
<tr>
<td>ESR median (Q25;Q75)</td>
<td>5 (3; 10)</td>
</tr>
<tr>
<td>Cholesterol (mean ± SD)</td>
<td>179.71 ± 47.21</td>
</tr>
</tbody>
</table>
In order to identify potential predictive value for increased disease activity at 6 months, reflected by increased values of CRP and fibrinogen, we evaluated potential correlations with parameters such as anemia (defined as Hb<12 g/dL for female patients and <13 g/dL for male patients), hyposideremia (seric iron level <50 mg/dL), hypercholesterolemia (Cholesterol level>200 mg/dL), extraintestinal manifestations, impaired sleep (PSQI ≥ 5), altered psychological status (HADS-A and/or HADS-D ≥ 8). Pearson test revealed a statistically significant correlation between the presence of hypercholesterolemia (p=0.015) and altered psychological status (p=0.06) at baseline with increased values of CRP at 6 month evaluation; moreover, hyposideremia (p=0.023), hypercholesterolemia (p=0.01) and impaired sleep (p=0.039) at baseline were correlated with increased fibrinogen value at 6 month evaluation IBD patients (tab. II).

### TABLE II
**Correlations between various parameters at baseline and increased inflammatory markers (CRP, fibrinogen) at 6 months**

<table>
<thead>
<tr>
<th>Parameters evaluated at baseline</th>
<th>Increased CRP value at 6-month evaluation IBD patients (p value)</th>
<th>Increased fibrinogen value at 6-month evaluation IBD patients (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>0.118</td>
<td>0.852</td>
</tr>
<tr>
<td>Hyposideremia</td>
<td>0.054</td>
<td>0.023*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.015*</td>
<td>0.01*</td>
</tr>
<tr>
<td>Extraintestinal Manifestations</td>
<td>0.198</td>
<td>0.274</td>
</tr>
<tr>
<td>Impaired sleep</td>
<td>0.960</td>
<td>0.039*</td>
</tr>
<tr>
<td>Altered psychological status</td>
<td>0.006*</td>
<td>0.256</td>
</tr>
</tbody>
</table>

Pearson correlations, (*) marked effects are significant for p < 0.05

Considering the previously mentioned findings, logistic regression was used to identify predictors of sleep quality and examine the effect of various parameters at baseline for increase in disease activity at 6 months. In the study group, the univariate analysis showed that the presence of hyposideremia (OR: 13.09; 95% CI: 1.57-109.11), hypercholesterolemia (OR: 5.18; 95% CI: 1.25-21.44), the values for NLR (OR 3.835; 95% CI, 1.87-7.83) and HADS-D (OR 1.56; 95% CI, 1.22-2.01) at baseline were predictors for an increase of disease activity at 6 months. In the multivariate analysis, however only hyposideremia was identified as a predictive factor (tab. III).
Increased disease activity was defined as an increase in MAYO and respectively CDAI score at 6 months compared to baseline since NLR and HADS-D might have predictive value on the increase of the inflammatory parameters, we used ROC curve analysis in order identify a cut-off value for these parameters, which could predict active disease at 6 months. Consequently, we identified a cut-off value of 2.7 for NLR and a cut-off value of 8.5 for HADS-D at baseline to be predictive for an increase in disease activity at 6 months (fig. 1).

![ROC Curve](image)

**Fig. 1.** ROC curve evaluating the prediction power of (a) NLR and (b) HADS-D at baseline on disease activity at 6 months.
DISCUSSION

Considering that IBD represent diseases with a relapsing-remitting pattern, with high disease burden, but also with significant socio-economic impact (5), there are efforts in identifying potential predictors of disease severity and disease flares. In the current study, we searched for parameters which could be easily used in the clinical practice to predict future disease flare and consequently to identify patients who require tight monitoring, for better disease control.

We have identified several factors that could contribute to predicting disease activity at 6 months in IBD patients, among parameters that are or could be routinely evaluated. Among the biochemical parameters we identified increased NLR, low seric iron level and hypercholesterolemia as predictors for active disease at 6 months. An interesting finding was that the presence of hyposideremia, but not necessarily the presence of anemia constituted predictive factors for disease activity, which highlights once more the importance of diagnosing and correcting the low iron levels in patients with IBD, as this influences disease-related outcome (6). This could be due to the coexistence of inflammation (either clinical or subclinical) with histologic changes, which play a role in iron deficiency, probably mediated by the hepcidin-ferroportin axis (7).

As far as the other biochemical markers are concerned, NLR has been investigated as marker of subclinical inflammation and it can be easily available from the CBC. A study performed by Acaturk G et al., investigated the utility of NLR in evaluating disease activity in IBD patients and identified an NLR cut-off point for active CD and UC was 3.2 and 3.1. In our study, a cut-off NLR of 2.7 was a predictor for disease activity at 6 months (8).

Regarding other parameters identified as potential predictors for active disease at 6 months, we identified that psychological distress correlated with the presence of inflammatory syndrome at 6 months. Our findings also included that increased depression, but not anxiety score is predictive for active disease at 6 months. Psychological comorbidity is important in the evolution of IBD, as it can promote inflammation and it can be associated with sleep impairment which could enhance the effects of psychological distress on the proinflammatory status (9). Moreover, there is a potential bidirectional relationship between psychological status and IBD activity, with inflammation driving depression and vice versa (10). Considering that several studies have highlighted that the presence of depression and anxiety generates a subsequent worse course of disease compared to IBD patients without psychiatric comorbidity (11-14), early identifying and targeting the associated psychological impairment could contribute to improving disease control (10). Considering that, we evaluated a potential cut-off value for HADS-D of 8.5 as predictive for disease activity at 6 months. This aspects could support the role of screening for depression among IBD patients, so that the psychological comorbidity could be addressed and consequently to improve disease outcome.

Although the univariate analysis highlighted significance for all the above-mentioned parameters, when using multivariate analysis to study the parameters, we did not obtain significant results; however, this is most probably due to low sample size and is the main limitation of our study. Therefore, prospective cohort studies with large number of patients should be per-
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formed in order to further evaluate easily available markers with predictive value for disease activity and lead to improving IBD patients’ management.

**CONCLUSIONS**

There is an increased need for identifying predictive factors for disease activity in IBD patients in order to optimally tailor the disease monitoring and adjust treatment. Among commonly assessed parameters, hyposideremia, hypercholesterolemia, increased NLR and the presence of depression symptoms show promising value as predictive factors and could be easily followed in the daily clinical practice.

**REFERENCES**