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Clinical and laboratory markers of the pre-test probability of inflammatory bowel diseases

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ABSTRACT *AIM: to distinguish clinical and laboratory markers that could help to diagnose irritable bowel syndrome (IBS) and forms of inflammatory bowel diseases (IBD) — Crohn`s disease (CD) and ulcerative colitis (UC), before colonoscopy.*
PATIENTS AND METHODS: the retrospective study included 712 patients (CD — 39.2%, UC — 37.8%, IBS — 23%). Clinical (complaints, anamnesis) and laboratory data from medical histories of patients with confirmed flare of IBD and IBS analyzed.
RESULTS: Patients with IBS had significant direct correlations with female gender, constipation, abdominal pain, presence of concomitant functional pathology, absence of extra-intestinal (EIM) and perianal (PAM) manifestations, weight loss due to food restriction ($p < 0.001$), hemoglobin ($p < 0.001$) and total protein levels ($p = 0.002$), and inverse correlations with levels of leukocytes, fecal calprotectin (FC) and C-reactive protein (CRP) ($p < 0.0001$). Patients with IBD had significant direct correlations with night symptoms ($p = 0.045$ for CD, $p = 0.023$ for UC) and diarrhea (up to 2 times per 24 hours in CD, $p = 0.018$; ⩾ 5 times per 24 hours in UC, $p < 0.001$) and FC ($p < 0.001$). CD was categorized by the presence of PAMs and EIMs, young age, fever, surgery in anamnesis ($p < 0.001$), weight loss ($p = 0.032$), elevated CRP levels, anemia ($p < 0.001$) and hypoproteinemia ($p = 0.032$). Patients with UC had direct correlations with male gender ($p = 0.008$), stool with blood and leukocytosis ($p < 0.001$) and had inverse correlation with abdominal pain ($p < 0.001$).
CONCLUSION: the identified clinical and laboratory markers can be used as criteria to distinguish IBD from IBS in routine clinical practice. However, further prospective studies are required for validation.

KEYWORDS: *Crohn`s disease, ulcerative colitis, inflammatory bowel diseases, clinical and laboratory markers, differential diagnostic criteria*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic progressive diseases that represent two main nosologies — ulcerative colitis (UC) and Crohn's disease (CD) [1,2]. All over the world, including Russia, there is an increase in new cases and the prevalence of these diseases [3,4]. Diagnosis of IBD often takes months from the onset of the first symptoms of the disease [5–7] due to insufficient data for diagnosis verification and often long-term management of patients as irritable bowel syndrome (IBS) [8].

At the same time, patients with IBS and IBD may have a similar clinical manifestation, which creates difficulties in diagnosing these nosologies [9]. Up to 50% of patients with IBD have symptoms that are criteria for the diagnosis of IBS [9], which leads to untimely verification of the correct diagnosis.

The clinical assessment of disease activity using indices is not always objective and does not allow to distinguish between the

Table 1. *Assessed clinical and laboratory characteristics*

Clinical indicators					
Gender			Age		
Incidence of liquid stool	**The presence of constipation**	**Blood impurity in stool**	**Abdominal pain**	**Nocturnal symptoms**	**Weight loss**
Extra-intestinal manifestations (EIM)					
Arthropathy	Ankylosing spondylitis	Skin lesion	Mucosal lesion	Eyes lesion	Involvement of the gastrointestinal tract
The presence of fever	Perianal manifestations (PAM)	Strictures	Fistulas	Abscess	Abdominal mass
Surgery on the small/large intestine					
Comorbidities					
Primarysclerosingc holangitis	Primary biliary cholangitis	Autoimmune hepatitis	Rheumatoid arthritis	Other rheumatological diseases	Functional pathologies
Family history of IBD, autoimmune diseases					
Laboratory indicators					
Hemoglobin	Leukocytes	Total protein	C-reactive protein (CRP)	Fecal calprotectin (FC)	

symptoms of IBD and IBS [10]. In a study by Lahiff et al., when comparing Best's indices (Crohn's Disease Activity Index (CDAI)) in individuals with CD and IBS, 62% of patients from the group with functional diseases had a CDAI level of more than 150 points [10], which indicates the presence of activity. Moreover, serological studies in patients with typical IBS symptoms without the presence of "red flags" have low diagnostic accuracy [11]. Due to the common presence of nonspecific complaints in IBD [1,2,12] and the absence of increased markers of systemic inflammation in the mild disease [1,2] before performing colonoscopy, it is necessary to search for new clinical and laboratory markers for the differentiation of IBD and IBS.

THE AIM OF THE STUDY

Determination of the clinical and laboratory symptoms that will allow to differentiate IBS and nosological forms of IBD before the videocolonoscopy is performed.

PATIENTS AND METHODS

We retrospectively analyzed the medical histories of 840 patients with UC, CD and IBS. The study included patients over 18 years of age with clinical exacerbation: 2 or more points on the Mayo index without evaluation of the endoscopic part for UC and more than 150 points on the Best index (CDAI) for CD [8,13], as well as patients with typical IBS complaints (abdominal pain associated with defecation, frequency change and/or forms of stool ⩾ 1 time per week for the last 3 months with a total duration of symptoms of more than six months) [14]. The study excluded patients with identified intestinal infections, comorbidities that could lead to gastrointestinal complaints (diverticular disease, adhesive disease), as well as in the presence of endoscopic remission in IBD.

The analysis evaluated patient complaints, anamnesis data and laboratory parameters (Table 1). The presence of strictures, fistulas, inflammatory infiltrates and abscesses was assessed both at the initial visit and in the anamnesis. Stool disorders (⩾ 25% of type 1–2 defecations

Table 2. *Characteristics of patients included in the study*

Characteristic	CD (*n* = 278)	UC (*n* = 270)	IBS (*n* = 164)	
Male gender — number (%)	124 (44.6%)	137 (50.7%)	53 (32.3%)	
Age — years				
Median	33	36	43	
IQR	26–44	29–49	33–60	
Hemoglobin — g/l				
Median	125 (*n* = 273)	126 (*n* = 255)	**Arithmetic mean**	133.42 ± 13.618 (*n* = 121)
IQR	112–134	109.5–140	**95% CI**	130.96–135.88
Leukocytes — 109/l				
Median	6.9 (*n* = 271)	7.3 (*n* = 255)	5.4 (*n* = 120)	
IQR	5.25–9.35	5.7–10.2	4.7–6.7	
Total protein — g/l				
Median	70 (*n* = 208)	72 (*n* = 194)	75 (*n* = 86)	
IQR	67–76	67–76	69–77	
C-reactive protein — mg/l				
Median, (min, max)	5.93 (*n* = 250)	3.4 (*n* = 237)	1 (*n* = 110)	
IQR	2.16–16.5	1.38–9.43	0.5–2.4	
Fecal calprotectin — mcg/g				
Median	600 (*n* = 158)	800 (*n* = 109)	26.18 (*n* = 77)	
IQR	221–1000	362–1800	25.0–64.16	

IQR — Interquartile range; CI — coincidence interval.

according to the Bristol Scale (BS) for constipation and ⩾ 25% of type 6–7 defecations according to BS for diarrhea), the presence of blood impurities, abdominal pain syndrome, weight loss (⩾ 5% of the original body weight), the presence of a temperature increase of more than 37.0°C were evaluated for 3 months prior to seeking medical help. Body weight loss was assessed in two variants: unintentional and against the background of compliance with dietary restrictions by the patient.

All patients subsequently underwent a video colonoscopy and other studies, if necessary, to confirm the main diagnosis.

The study was approved by the local Ethics Committee and was a part of a PhD thesis on the development of a program for the diagnosis and differential diagnosis of IBD using artificial intelligence.

Statistical processing was carried out with the StatSoft Statistica 12 program. Spearman's rank correlation coefficient was used as a measure to assess the relationship between variables. The choice of the criterion was determined by the fact that the analyzed data array contained both quantitative and categorical variables.

RESULTS

At the initial screening, the study included 840 patients, out of whom 128 patients were excluded due to the detection of comorbidities leading to similar clinical and laboratory picture, and endoscopic remission in patients with IBD. The characteristics of 712 patients included in the study are presented in Table 2.

Table 3. *Correlation analysis of clinical and laboratory parameters*

Indicators	Number of patients	Crohn's disease			Ulcerative colitis			Irritable bowel syndrome		
		Spearman's Coefficient	t(N-2)	*p*-level	Spearman's Coefficient	t(N-2)	*p*-level	Spearman's Coefficient	t(N-2)	*p*-level
Gender	712	–0.010099	–0.2691	0.787928	–0.099975	–2.6773	0.00759*	0.12683	3.407	< 0.001*
Age	712	–0.197422	–5.36608	< 0.001*	0.021571	0.57491	0.56554	0.204052	5.554	< 0.001*
Constipation	712	–0.143552	–3.86509	< 0.001*	–0.237563	–6.5166	< 0.001*	0.439989	13.0555	< 0.001*
Liquid stool 1–2 times/24hr	712	0.088808	2.37576	0.017777*	–0.125662	–3.3751	< 0.001*	0.041736	1.1131	0.266063
Liquid stool3-4ts/24hr	712	0.071478	1.90947	0.056604	0.001176	0.03132	0.97502	–0.08423	–2.2523	0.024611*
Liquid stool ⩾ 5 ts/24hr	712	–0.022625	–0.60302	0.546691	0.250339	6.88987	< 0.001*	–0.26204	–7.2349	< 0.001*
Blood impurity in stool	712	–0.152077	–4.09991	< 0.001*	0.560594	18.0385	< 0.001*	–0.46921	–14.1576	< 0.001*
Abdominal pain	711	0.007158	0.19061	0.848886	–0.200639	–5.4533	< 0.001*	0.22252	6.0774	< 0.001*
Nocturnal symptoms	711	0.0752	2.00804	0.045018*	0.085475	2.28431	0.02265*	–0.18551	–5.0269	< 0.001*
Weight loss	712	0.091214	2.44064	0.014905*	0.029321	0.78161	0.43471	–0.13952	–3.7542	< 0.001*
Weight loss on a diet background	712	–0.110161	–2.95331	0.003248*	–0.091083	–2.4371	0.01505*	0.232604	6.3727	< 0.001*
Absence of EIM	712	–0.272905	–7.5587	< 0.001*	0.020189	0.53806	0.5907	0.293158	8.17042	< 0.001*
Fever	712	0.156293	4.2164	< 0.001*	0.01085	0.28911	0.77258	–0.1937	–5.26093	< 0.001*
Absence of PAM	712	–0.403901	–11.7646	< 0.001*	0.280978	7.80116	< 0.001*	0.144737	3.89767	< 0.001*
Surgical treatment	712	0.328751	9.2754	< 0.001*	–0.199131	–5.4144	< 0.001*	–0.15185	–4.09376	< 0.001*
Functional pathology	712	–0.131001	–3.52097	< 0.001*	–0.103511	–2.773	0.0057*	0.271076	7.50402	< 0.001*
Family history of autoimmune diseases	710	0,015435	0.41075	0.681378	0.062023	1.65351	0.09867	–0.08925	–2.38437	0.017371*
Hemoglobin	649	–0.149972	–3.85834	< 0.001*	–0.022671	–0.5768	0.56427	0.219322	5.7179	< 0.001*
Leukocytes	646	0.035479	0.90092	0.367965	0.188648	4.87489	< 0.001*	–0.28198	–7.4584	< 0.001*
Total protein	488	–0.097088	–2.15051	0.032007*	–0.009991	–0.2203	0.82576	0.138778	3.0893	0.002121*
CRP	597	0.275101	6.97974	< 0.001*	0.007887	0.19238	0.84751	–0.3615	–9.4576	< 0.001*
FC	344	0.217022	4.11143	< 0.001*	0.337025	6.61999	< 0.001*	–0.63566	–15.2279	< 0.001*

** Changes in indicators are statistically significant ($p < 0.05$)*

IBS revealed a significant direct correlation with female sex, constipation, abdominal pain syndrome, the presence of concomitant functional pathology, absence of extra-intestinal and perianal manifestations, family history of autoimmune diseases ($p < 0.001$), and this category of patients tended to lose weight against the background of dietary restriction ($p < 0.001$) (Table 3). When analyzing laboratory parameters, there was an inverse correlation with the level of leukocytes, FC and CRP ($p < 0.001$), and a positive correlation with the level of hemoglobin ($p < 0.001$) and total protein ($p = 0.002$).

For the group of patients with IBD, significant positive correlations were found with nocturnal symptoms ($p = 0.045$ in CD, $p = 0.023$ in UC), FC ($p < 0.001$), as well as diarrheal syndrome (up to 2 times/24-hrwithCD, $p = 0.018$; ⩾ 5 times/24-hr with UC, $p < 0.001$). CD was characterized by: young age, the presence of perianal and extra-intestinal manifestations, fever, a history of surgery ($p < 0.001$), weight loss ($p = 0.015$), increased CRP, anemia ($p < 0.001$), and hypoproteinemia ($p = 0.032$). UC is characterized by: male sex ($p = 0.008$), the presence of blood in the stool ($p < 0.001$) and leukocytosis ($p < 0.001$), as well as an inverse correlation with abdominal pain ($p < 0.001$).

DISCUSSION

According to global statistics, IBS symptoms are detected in almost 50% of patients seeking help from a gastroenterologist [15]. Even if there are clear diagnostic criteria for IBS [14], some patients do not have a typical clinical picture, and functional disorders are regarded as unclassified IBS [16]. At the same time, the increasing incidence of IBD [5–7] requires careful identification of "red flags" in all patients with symptoms of intestinal dyspepsia.

Due to the fact that IBD can manifest itself with various clinical symptoms, we tried to include in the assessed signs the most frequent and characteristic complaints of patients according to clinical guidelines [1,2,14].

According to the results of our study, significant correlations with clinical and laboratory indicators were revealed, which, after further studies, can be used in routine clinical practice for effective differential diagnosis between UC, CD and IBS until the endoscopic examination. So, to distinguish between functional and organic pathology, there were significant correlations with such indicators as female sex, constipation, abdominal pain syndrome, weight loss against the background of predominant dietary restriction, concomitant functional pathology, absence of autoimmune diseases in relatives of the 1st line for IBS, and increased FC, nocturnal symptoms, diarrheal syndrome for IBD. Abdominal pain was predominantly a characteristic symptom for IBS, more likely due to the fact that this sign is a mandatory diagnostic criterion [14].

In turn, for further differentiation between types of IBD, age, the presence of perianal and extra-intestinal manifestations, fever, surgical treatment, weight loss, anemia, increased CRP and a decrease in total protein characteristic of CD, and blood impurities in the stool, male sex and the presence of a more pronounced diarrheal syndrome for UC should be taken into account.

The search for simple and affordable markers has been going on for a long time all over the world. Thus, Danese et al. developed and validated a questionnaire of the pre-test probability of Crohn's Disease (Red flag score), including 21 questions, for its differential diagnosis with IBS [17]. By multivariate analysis, 8 independent signs were identified that significantly correlate with CD and were included in this questionnaire: non-healing or complex perianal fistula, abscess or perianal lesions; a 1st-line relative with confirmed IBD; weight loss over the last 3 months (5% of body weight); chronic abdominal pain (for over 3 months); nocturnal diarrhea; subfebrility for 3 months; absence of abdominal pain for 30–45 minutes after eating, especially vegetables; absence of imperative urges [17]. Patients who scored 8 or more points as per the questionnaire had the highest probability of detecting CD compared to the population (OR 290, 95% CI 77–1086), sensitivity and specificity were 0.94 (95% CI 0.88–0.99) and 0.94 (95% CI 0.90–0.97), respectively [17]. The data obtained by us are similar to the results by Danese et al. However, according to the results of our study, there was no correlation with the presence of a burdened hereditary history for CD and abdominal pain syndrome.

Serological markers also have their place in the differentiation between functional disorders of the gastrointestinal tract and IBD. The CRP and erythrocyte sedimentation rate (ESR) used in routine practice are indicators of the presence and severity of systemic inflammation, but they are not specific to IBD and in many cases do not reflect histological inflammation [18]. Fecal calprotectin (FC) is an accurate marker of inflammation of the intestinal mucosal layer and one of the most convenient due to its noninvasiveness [19].

The FC level, which should be used to distinguish functional and organic pathology of the gastrointestinal tract, is still being discussed: many studies indicate that its values characteristic of IBS can range from 45 [20] to 188 mcg/g [21]. However, there are studies that reveal a range of FC in IBS of 16–294 mcg/g [22], which once again indicates the need for a comprehensive assessment of the clinical and laboratory parameters of the patient. The international consensus on standardization of FC measurements has not come to a consensus on the threshold value of FC, but at the same time it is emphasized that its level correlates with endoscopic and histological activity in IBD [19]. In our study, an increase in the FC level was considered to be a reference laboratory value of more than 50 mcg/g, and its increase had

a positive correlation with the presence of CD or UC in the patient.

When conducting a correlation analysis between laboratory parameters, data were obtained on a negative correlation for the levels of hemoglobin and total protein in CD, and on a positive correlation with the levels of CRP and FC. At the same time, the highest correlation values were noted for CRP and FC (0.275 and 0.217, respectively). In UC, a significant correlation was found only for leukocytes and FC (correlation coefficient 0.189 and 0.337, respectively, $p < 0.001$). The values of hemoglobin and total protein had an inverse correlation at values $p > 0.05$, which shows the lack of reliability of the results obtained. The increase in the level of CRP also showed no significant correlation ($p = 0.84$).

It should be noted that the diagnosis of IBD requires a lot of experience and knowledge of a number of details when collecting and evaluating the patient's anamnesis and laboratory parameters. A doctor who has had little experience in the management of patients with IBD may not focus on mucosal lesions or joint syndrome, which, in our opinion, should be attributed to differential diagnostic tools when verifying IBD. However, despite this, at the same time there is a tendency to increase the number of "falsely" diagnosed IBD, which increases the burden on the healthcare system due to increased visits to various specialists and repeated endoscopic interventions.

All of the above shows that it is necessary to develop questionnaires or programs that will already contain targeted questions and will help doctors identify a focus group of patients for further examination, which will allow timely diagnosis of these diseases.

Our research has a number of features and limitations that should be taken into account when using the results in practical work. Firstly, patients' complaints were evaluated retrospectively, and the quality of anamnesis collection depended on the qualifications and communication skills of the doctor. Secondly, there are difficulties in calculating the sample of patients. Thus, the estimated number of patients in St. Petersburg for UC is 293 people, for CD — 126 people [3,23,24]. However, it is not possible to calculate the IBS sample for St. Petersburg, given the limited data on morbidity, which makes it possible to use only a "global" sample. Thirdly, we did not conduct correlation studies depending on the extent of the pathological process (in UC and CD), the nature of the disease course in CD (stricturing, penetrating, inflammatory) and IBS (with a predominance of constipation, diarrheal syndrome and a mixed variant), as well as the severity of exacerbation of IBD. Fourth, a prospective study is required to validate the data obtained.

CONCLUSION

The identification of IBD among gastroenterological patients is a difficult task for many doctors due to the low prevalence and polymorphism of their manifestations, which leads to the diagnosis at a late stage against the background of the development of extra-intestinal manifestations and complications.

In the course of the study, clinical and laboratory indicators were identified that were more characteristic of IBD and IBS, which can help clinicians to pay attention to such patients in a timely manner and send them for a deep check-up. In our opinion, it is advisable to create and introduce questionnaires into the practice of primary care physicians to identify focus groups of patients suspicious of IBD, which will allow them to further conduct targeted follow-up tests and ensure the diagnosis of IBD at early stages.

It seems that the creation of questionnaires for early diagnosis of IBD will be possible during a prospective study.

AUTHORS CONTRIBUTION

Concept and design of the study: *Irina A. Rasmagina, Igor G. Bakulin*

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