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PREDICTING THE RISK OF INFLAMMATORY BOWEL DISEASE IN PATIENTS WITHOUT LABORATORY SIGNS OF INFLAMMATION

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ПРОГНОЗИРОВАНИЕ РИСКА НАЛИЧИЯ ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЙ КИШЕЧНИКА У ПАЦИЕНТОВ БЕЗ ЛАБОРАТОРНЫХ ПРИЗНАКОВ ВОСПАЛЕНИЯ

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Abstract

Some patients with inflammatory bowel disease (IBD) may not have traditional criteria of inflammation: elevated CRP, ESR and leukocytosis. The aim of this study was to identify additional immunological and biochemical criteria for the risk of IBG in patients with no non-specific laboratory criteria of inflammation. The study involved 150 patients, of whom 2 groups were formed: an observation group (100 patients with a verified diagnosis of ulcerative colitis or Crohn's disease) and a control group (50 clinically healthy individuals). All subjects underwent a complete blood count, a biochemical blood test and determination of IL-1β, TNF-α, and IL-4 concentrations. Based on the results of general and biochemical blood tests, patients from the observation group were divided into two subgroups - with and without classic laboratory signs of inflammation. Three main laboratory blood parameters were assessed for diagnosing the inflammatory process: ESR, white blood cell count and CRP level. The presence of laboratory signs of inflammation was considered to be an increase in two or more of the above blood parameters. It was noted that 40% of patients with IBD had no non-specific laboratory criteria of inflammation: in ulcerative colitis in 37% of cases, in Crohn's disease in 46% of cases ($p < 0.001$). Further, a comparative analysis of the levels of cytokines and biochemical markers in the blood serum of patients from the control group and patients with IBD without laboratory signs of inflammation was carried out. Based on the obtained data, a prognostic model of the probability of the presence of IBD in patients with no non-specific laboratory criteria for inflammation, depending on biochemical and immunological blood parameters was developed. The model included such serum parameters as glucose, sodium and IL-4 concentrations. The predictive ability of the model was assessed using ROC analysis (AUC 0.970±0.018 95% CI: 0.936–1.000; $p<0.001$). An algorithm for predicting the risk of IBD in patients without non-specific laboratory criteria of inflammation was proposed. The obtained data made it possible to identify additional criteria for the risk of IBD in patients with the absence of non-specific metabolic criteria of inflammation.

Keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, laboratory criteria of inflammation, C-reactive protein, erythrocyte sedimentation rate, white blood cell count, IL-4, glucose, sodium.

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Резюме

Традиционные лабораторные критерии, указывающие на системное воспаление, такие как повышение С-реактивного белка, скорости оседания эритроцитов и лейкоцитоз, могут отсутствовать у ряда пациентов с воспалительными заболеваниями кишечника, что затрудняет постановку диагноза. Целью данного исследования являлось определение дополнительных иммунологических и биохимических критериев риска наличия воспалительных заболеваний кишечника у пациентов с отсутствием неспецифических лабораторных критериев воспаления. В работе было обследовано 150 пациентов, из которых были сформированы 2 группы – группа наблюдения (100 пациентов с верифицированным диагнозом язвенного колита или болезни Крона) и группа контроля (50 клинически здоровых лиц). Всем обследуемым проводилось исследование общего анализа крови, биохимический анализ крови с определением концентрации общего белка, белковых фракций, мочевины, креатинина, глюкозы, С-реактивного белка, активности АЛАТ, АСАТ, определение иммунологических показателей - концентрации IL-1β, TNF-α и IL-4. На основании результатов общего и биохимического анализов крови пациенты из группы наблюдения были разделены на две подгруппы – с наличием и отсутствием классических лабораторных признаков воспаления. Оценивались три основных лабораторных показателя крови для диагностики воспалительного процесса: скорость оседания эритроцитов, количество лейкоцитов, концентрация С-реактивного белка. За наличие лабораторных признаков воспаления принимали повышение двух и более вышеперечисленных параметров крови выше референтных значений. Было отмечено, что у 40% пациентов с ВЗК отсутствовали неспецифические лабораторные критерии воспаления: при язвенном колите в 37% случаев, при болезни Крона в 46% случаев ($p<0,001$). Далее был проведен сравнительный анализ уровней цитокинов и биохимических маркеров в сыворотке крови пациентов из группы контроля и пациентов с воспалительными заболеваниями кишечника с отсутствием лабораторных признаков воспаления. На основе полученных данных была разработана прогностическая модель вероятности наличия воспалительных заболеваний кишечника у пациентов с отсутствием неспецифических лабораторных критериев воспаления в зависимости от биохимических и иммунологических показателей крови. В модель были включены такие параметры сыворотки крови, как концентрация глюкозы, натрия и IL-4. Прогностическая способность модели оценена методом ROC-анализа (AUC 0,970±0,018 95% CI: 0,936–1,000; $p<0,001$). На основании полученных результатов предложен алгоритм прогнозирования риска наличия воспалительных заболеваний кишечника у пациентов с отсутствием неспецифических лабораторных критериев воспаления с учетом иммунологических и биохимических параметров сыворотки крови. Полученные данные позволили выявить дополнительные критерии риска

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наличия воспалительных заболеваний кишечника у пациентов с отсутствием неспецифических метаболических критериев воспаления.

Ключевые слова: воспалительные заболевания кишечника, язвенный колит, болезнь Крона, лабораторные критерии воспаления, С-реактивный белок, скорость оседания эритроцитов, количество лейкоцитов, IL-4, глюкоза, натрий.

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1 Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory processes of the gastrointestinal tract, characterized by a relapsing and remitting course. These nosological forms are similar to some extent, have common symptoms and lead to digestive disorders [5]. The diagnosis of IBD is based on a combination of clinical symptoms with features detected during endoscopic and radiological studies, which play an important role in diagnosis and severity assessment [3]. However, the invasiveness of the procedure is associated with significant risk and does not allow to assess condition of the entire gastrointestinal tract. Alternative non-invasive biomarkers are being studied as tools for predicting IBD and managing the course of the disease [4]. The search for biomarkers that would reflect the actual development of the disease and thus play an important role in the therapy of IBD is currently relevant. To date the search for biomarkers that would reflect the actual development of the disease and thus play an important role in the treatment of IBD is relevant. Therefore, correct diagnosis and accurate monitoring play an important role in the treatment of patients with IBD. Traditionally used laboratory markers of systemic inflammation, such as C-reactive protein or white blood cell count, are not sensitive and specific enough to diagnose IBD or determine the treatment strategy. Endoscopy and biopsy remain the gold standard methods. However, these procedures are invasive, expensive, and associated with a risk of complications. In addition, in clinical practice, there may be cases where patients with IBD may not have classic laboratory signs of inflammation (increased erythrocyte sedimentation rate, C-reactive protein and leukocytosis). This group of patients is of particular interest from the point of view of differential diagnosis of IBD, since the atypical clinical and laboratory manifestations can lead to underdiagnosis of this pathology and, as a consequence, a decrease in the quality of life of such patients due to untimely diagnosis and lack of treatment.

The aim of this study was to identify additional immunological and biochemical criteria for the risk of inflammatory bowel disease in patients with no non-specific laboratory criteria of inflammation.

2 Materials and methods

The study was approved by the Committee on Ethics and Evidence of Medical Scientific Research of the Federal State Budgetary Educational Institution of Higher Education «Samara State Medical University» of the Ministry of Healthcare of the Russian Federation (protocol dated November 23, 2019). The study involved 150 patients, of whom 2 groups were formed: an observation group (100 patients with IBD) and a control group (50 clinically healthy individuals). The following inclusion criteria were used to select patients for the observation group: a verified diagnosis of UC or CD, confirmed by laboratory and clinical diagnostic methods, including histological examination of biopsy specimens; absence of concomitant diseases that prevent the examination; patient age from 16 to 80 years; signed informed consent to participate in the study.

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The exclusion criteria were: unconfirmed diagnosis of IBD; concomitant diseases of the cardiovascular, respiratory, endocrine and urinary systems; pregnancy; presence of malignant tumors of any localization at present; chemoradiotherapy; patients taking selective immunosuppressants; a history of mental pathology that prevents the patient from participating in the study; refusal to participate in the study.

All subjects underwent a complete blood count using a SYSMEX XT 2000i hematology analyzer (Japan). Biochemical blood test to determine the concentration of total protein, protein fractions, urea, creatinine, glucose, C-reactive protein, ALT and AST activity was performed using a Hitachi 902 automatic biochemical analyzer, Japan [1, 2]. Immunological parameters - IL-1β, TNF-α and IL-4 concentrations in blood serum - were determined by enzyme immunoassay using commercial test systems (BioChemMack, Russia).

Statistical data processing was performed using StatTech v. 4.4.1 (developer - StatTech LLC, Russia). Data distribution was assessed using the Shapiro-Wilk test. Intergroup comparisons were performed using the Mann-Whitney test with Bonferroni correction. Pearson's chi-square test was used to analyze nominal features. The development of a prognostic model of the probability of an outcome was performed using the logistic regression method. ROC analysis was used to assess the diagnostic significance of quantitative features in predicting a specific outcome.

3 **Results and discussion**

Based on the results of general and biochemical blood tests, patients from the observation group were divided into two subgroups - with and without classic laboratory signs of inflammation. Three main laboratory blood parameters were assessed for diagnosing the inflammatory process: erythrocyte sedimentation rate, white blood cell count and C-reactive protein level. The presence of laboratory signs of inflammation was considered to be an increase in two or more of the above blood parameters. It is noted that 40% of patients with IBD do not have non-specific laboratory criteria of inflammation: in UC in 37% of cases, in CD in 46% of cases ($p < 0.001$).

Further, a comparative analysis of the levels of cytokines and biochemical markers in the blood serum of patients from the control group and patients with IBD with no laboratory signs of inflammation was carried out (Table).

Based on the obtained data, a prognostic model was developed using the logistic regression method to determine the probability of the risk of IBD in patients without laboratory signs of inflammation based on immunological and biochemical blood parameters. The number of observations was 93. The observed dependence is described by the equation:

$$P = 1 / (1 + e^{-z}) \times 100\%$$

$$z = -5.6 - 1.863 \times Glu - 3.775 \times IL4 + 0.128 \times Na$$

where P – probability of absence of the risk of IBD; Glu – Glucose, mmol/L; IL4 – IL4; ng/ml; Na – Sodium, mmol/L; e – exponent (e = 2.7182 – constant); z –

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dependent binary variable (presence and absence of IBD); -5.083 – constant; -5.6; -1.863; -3.775; -0.128 – coefficients obtained experimentally.

When assessing the dependence of the probability of no risk of IBD in patients with the absence of non-specific laboratory criteria of inflammation on the value of the logistic function P using the ROC analysis, the curve in Figure 1 was obtained.

The area under the ROC curve comprised 0.970 ± 0.018 with 95% CI: 0.936 – 1.000. The resulting model was statistically significant ($p < 0.001$).

The cut-off value of logistic function P is 0.534. The absence of IBD risk in patients with no non-specific metabolic criteria of inflammation was predicted when logistic function P value was greater than or equal to this value. The sensitivity and specificity of the model were 98.0% and 86.0%, respectively.

Based on the obtained results, an algorithm for predicting the risk of IBD in patients with no non-specific laboratory criteria of inflammation is proposed taking into account the immunological and biochemical parameters of blood serum, which is presented in Figure 2.

The algorithm is implemented as follows:

l) All patients with suspected IBD should undergo general clinical and biochemical blood tests in accordance with clinical guidelines.

2) In the presence of 2 or more non-specific metabolic criteria of inflammation (leukocytosis/ increased ESR/ increased CRP), a corresponding conclusion is made about the risk of IBD. It is necessary to conduct a comprehensive examination of patients according to clinical guidelines, including colonoscopy with biopsy, ultrasound examination of the abdominal organs, magnetic resonance imaging of the abdominal organs, computed tomography of the abdominal organs with contrast of the intestine.

3) In the absence of non-specific metabolic criteria of inflammation or the presence of one parameter, apply a model to determine the risk of IBD in patients with no non-specific metabolic criteria of inflammation based on biochemical and immunological parameters of blood serum. If the corresponding risk is detected, conduct a set of studies according to established clinical guidelines for IBD.

4) In the absence of a prognosis for the risk of IBD, it is recommended to continue the diagnostic search; consultations with relevant specialists are required.

Thus, the data obtained based on the study of the characteristics of the immunological and biochemical mechanisms of formation made it possible to identify additional criteria for the risk of the presence of inflammatory bowel diseases in patients with the absence of non-specific metabolic criteria of inflammation.

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ТАБЛИЦЫ

Table 1. Analysis of immunological and biochemical parameters of blood serum in patients from the control group and patients with IBD without laboratory signs of inflammation (LSI).

Parameters	Categories	Me	$Q_1 – Q_3$	n	p
Immunological parameters					
IL-1β, pg/ml	IBD without LSI	1.82	1.37 – 2.41	43	< 0.001
	Control	0.07	0.06 – 0.07	50	
IL-4, pg/ml	IBD without LSI	1.72	0.62 – 2.44	43	< 0.001
	Control	0.03	0.02 – 0.09	50	
TNFα, pg/ml	IBD without LSI	1.03	0.04 – 2.02	43	< 0.001
	Control	0.03	0.02 – 0.03	50	
Biochemical parameters					
Total protein, g/l	IBD without LSI	67.00	54.20 – 69.95	43	< 0.001
	Control	74.75	69.00 – 78.78	50	
C-reactive protein, mg/l	IBD without LSI	3.40	3.12 – 4.40	43	< 0.001
	Control	1.52	1.00 – 2.27	50	
Urea, mmol/ L	IBD without LSI	4.40	2.75 – 5.55	43	0.013
	Control	5.50	4.46 – 6.42	50	
Creatinine, μmol/l	IBD without LSI	79.80	66.00 – 90.00	43	0.870
	Control	80.00	72.25 – 89.00	50	
Glucose, mmol/ L	IBD without LSI	5.90	4.80 – 6.20	43	< 0.001
	Control	4.71	4.05 – 5.45	50	
ALT, U/L	IBD without LSI	26.00	16.00 – 34.00	43	0.952
	Control	23.00	18.25 – 31.00	50	
AST, U/L	IBD without LSI	21.00	16.00 – 24.75	43	0.189
	Control	27.00	20.00 – 32.75	50	
Sodium, mmol/L	IBD without LSI	141.00	126.00 – 142.50	43	0.061
	Control	139.25	137.00 – 146.75	50	
Potassium, mmol/L	IBD without LSI	4.00	3.51 – 4.42	43	0.821
	Control	4.17	3.90 – 4.67	50	
Chlorides, mmol/L	IBD without LSI	97.00	90.00 – 101.00	43	< 0.001
	Control	102.00	99.00 – 105.00	50	

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РИСУНКИ

Figure 1. ROC-curve characterizing the dependence of the probability of the presence of IBD in patients with the absence of non-specific laboratory criteria of inflammation on the value of the logistic function P.

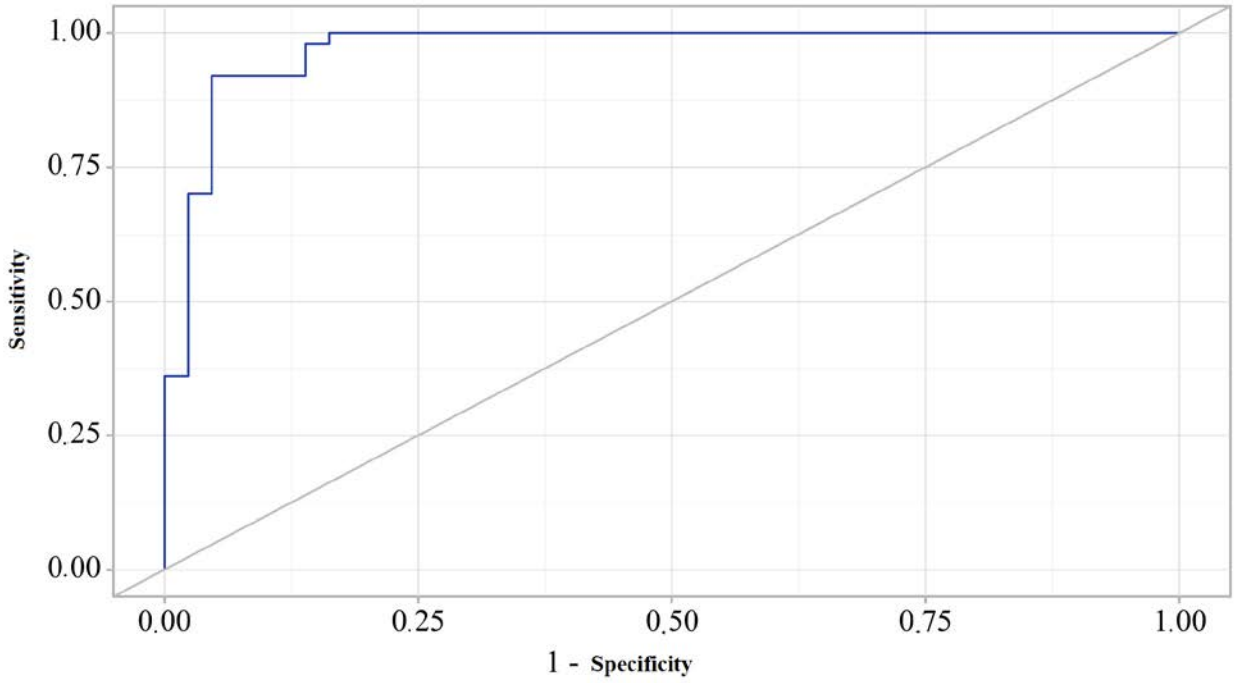

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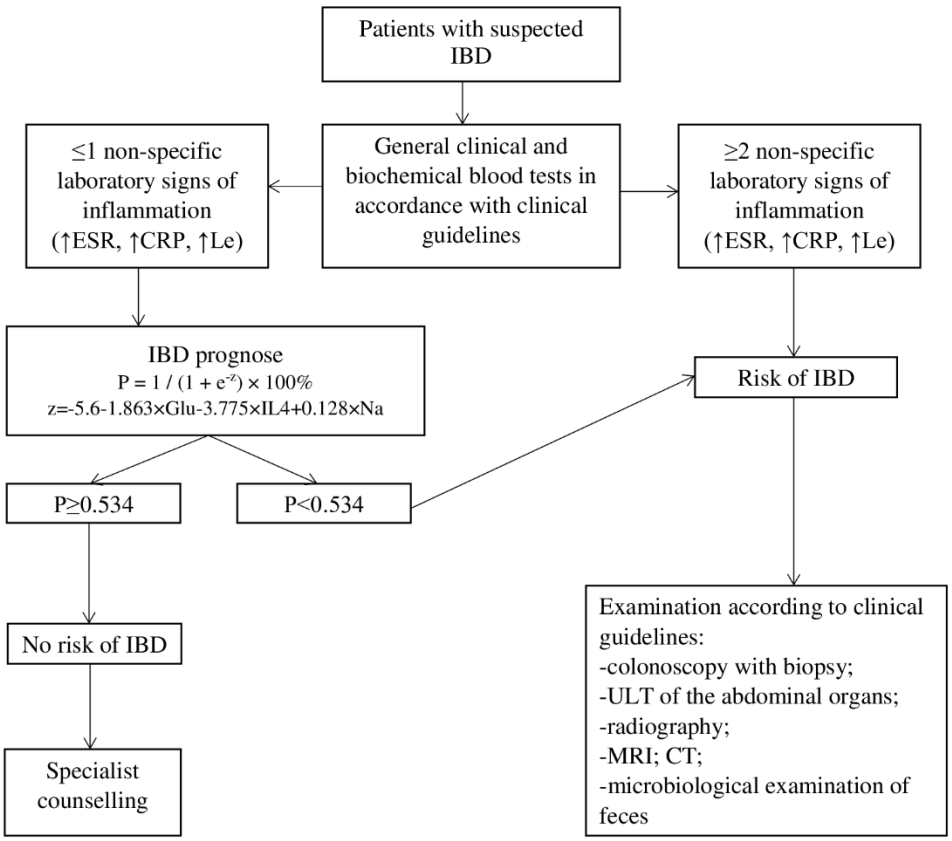
Figure 2. Algorithm for predicting the risk of IBD in patients with no non-specific metabolic criteria of inflammation based on biochemical and immunological parameters of blood serum.



Notes: IBD - inflammatory bowel disease; P – probability of absence of the risk of IBD; Glu – serum glucose, mmol/L; IL4 - serum IL4, pg/ml; Na - serum sodium, mmol/L; ULT - ultrasound examination of the abdominal organs; MRI - magnetic resonance imaging of the abdominal organs; CT - computed tomography of the abdominal organs with contrast of the intestine.

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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи

PREDICTING THE RISK OF INFLAMMATORY BOWEL DISEASE IN PATIENTS WITHOUT LABORATORY SIGNS OF INFLAMMATION
ПРОГНОЗИРОВАНИЕ РИСКА НАЛИЧИЯ ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЙ КИШЕЧНИКА У ПАЦИЕНТОВ БЕЗ ЛАБОРАТОРНЫХ ПРИЗНАКОВ ВОСПАЛЕНИЯ

Сокращенное название статьи для верхнего колонтитула:
PROGNOSIS OF INFLAMMATORY BOWEL DISEASE
ПРОГНОЗ ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЙ КИШЕЧНИКА

Keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, laboratory criteria of inflammation, C-reactive protein, erythrocyte sedimentation rate, white blood cell count, IL-4, glucose, sodium.
Ключевые слова: воспалительные заболевания кишечника, язвенный колит, болезнь Крона, лабораторные критерии воспаления, С-реактивный белок, скорость оседания эритроцитов, количество лейкоцитов, IL-4, глюкоза, натрий.

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Порядковый номер ссылки	Авторы, название публикации и источника, где она опубликована, выходные данные	ФИО, название публикации и источника на английском	Полный интернет-адрес (URL) цитируемой статьи и/или ее doi
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