American Journal of Medicine and Medical Sciences 2025, 15(3): 749-757
DOI: 10.5923/j.ajmms.20251503.55

The Role and Place of Forecasting Methods in the Prevention of Crohn's Disease Recurrence

Khamdamov Bakhtiyar Zarifovich[1,*], Navruzov Behzod Sarimbekovich[2], Sattarov Jasur Elmurodovich[3], Khamdamov Ilkhomjon Bakhtiyorovich[3]

[1]DSc, Professor, Bukhara State Medical Institute, Uzbekistan
[2]DSc, Professor, Tashkent Medical Academy, Uzbekistan
[3]Bukhara State Medical Institute named after Abu Ali Ibn Sina, Uzbekistan

Abstract The effectiveness of our method for predicting Crohn's disease recurrence in the postoperative period, due to the importance of including immunological criteria, makes it possible to increase the sensitivity of the test by 3.5 times, specificity by 1.9 times, and the prognostic value of the method by 3.3 times. The use of the developed therapeutic and diagnostic algorithm for the prevention of Crohn's disease recurrence made it possible to reduce the incidence of its development in mild form from 31% to 27.5%, in moderate severe form from 21.4% to 12.5% and completely avoid its severe forms.

Keywords Crohn's disease, Generalization of infection, Prognosis, Prevention

1. Introduction

Less than 100 years have passed since the first report of Crohn's disease (CD), which was presented in 1932 by the American gastroenterologist B.B. Crohn under the term "terminal ileitis". A more in-depth study in this area has led to the recognition of CD as an independent nosological unit in which the entire intestine is affected [1,3,9]. However, the iliac region of the small intestine still remains the predominant site of damage in CD [1,16,17,18,19,20,21,22,23].

The prevalence of CD in Europe ranges from less than 10 to about 150 cases per 100,000 inhabitants [2,4,10]. An adjusted prevalence of 133 cases of CD per 100,000 population was found in California, USA, at the beginning of this century [8]. One study conducted in South Korea showed a prevalence of 112 cases of CD per 100,000 population [5,7,11,24,25,26,27,28]. Recent data on the prevalence of CD in Uzbekistan, conducted by the Republican Center for Coloproctology of the Ministry of Health of the Republic of Uzbekistan, equated to 80 cases per 100,000 population [2,4,12]. From the available data, it can be concluded that CD is a very common disease today.

CD treatment is interdisciplinary [10]. Moreover, if drug treatment of Crohn's disease is aimed at healing the mucous membrane and reducing the symptoms of the disease, then surgery plays a key role in the treatment of such complications of the disease as stenosis, perforation, intestinal fistulas and abscesses of the abdominal cavity and cellular spaces [1,3,7,29,30]. CD recurrence in the postoperative period develops in more than 80% of operated patients [1,2,4,13].

Numerous studies in this area have allowed the development of various surgical strategies aimed at improving treatment outcomes and reducing the incidence of CD recurrence in the postoperative period [6].

Some improvement in the results of surgical operations in CD was achieved after the introduction of laparoscopic technology. However, they also failed to affect the regression of CD recurrence rate in the postoperative period [8,10]. All this influenced the formation of a certain concept about the purpose of performing surgical operations in CD as creating conditions for slowing the onset of relapse, which is considered inevitable in the future.

Developments in this area are continuing and surgical treatment of CD has yet to be discovered.

There is weak epidemiological evidence of an association between exposure to nonselective nonsteroidal anti-inflammatory drugs and the occurrence or recurrence of CD [5,6,7].

Modern aspects of the development of Russian medicine include many measures aimed at improving the results of treatment of patients, including those with inflammatory bowel diseases.

All of the above has determined the main direction of this work.

The purpose of the study. improving the results of treatment of patients with CD by developing pathogenetically based clinical and immunological criteria for predicting and preventing the recurrence of this disease.

* Corresponding author:
xamdamov.baxtiyor@bsmi.uz (Khamdamov Bakhtiyar Zarifovich)
Received: Feb. 25, 2025; Accepted: Mar. 13, 2025; Published: Mar. 17, 2025
Published online at http://journal.sapub.org/ajmms

2. Material and Methods

The results of a comprehensive examination and treatment of 82 patients with Crohn's disease (CD) are analyzed. The patients were divided into 2 study groups: the control group (42 patients) and the main group (40 patients). A distinctive feature of the patient groups was the use of different approaches in predicting and preventing CD recurrence. As reference values, 20 healthy individuals were examined, who were recognized as practically healthy by the medical commission. Male patients prevailed in the control and main groups of patients (59% and 55%, respectively), and the average age varied between young and middle (according to the WHO classification).

CD mainly affected the terminal ileum (61%). Combined lesions of the terminal ileum and large intestine were diagnosed in 24.4% of patients. Isolated colon lesion was diagnosed in 14.6% of patients. In each study group, patients with lesions of the terminal ileum prevailed. Perianal lesions were more characterized by the presence of rectal fistulas (75%), anal fissures (37.5%), narrowing of the lower ampullary rectum (8.3%), strictures of the anal canal (4.2%) and long-term non-healing wounds (4.2%).

The chronology of the course of the disease depended on the affected part of the intestine in CD. Thus, it took the least amount of time to damage the terminal part of the ileum (89.7±13.4 months). For the development of CD with damage to the large intestine, the course of the disease was on average for 121.3±33 months. Combined lesions of the terminal ileum and colon were diagnosed in patients with a CD history of 179.8±43.8 months.

Among the surgical operations in the anamnesis, appendectomy should be distinguished, which was performed in 9 (21.4%) patients of the control group and in 15 (37.6%) patients of the main group. Operations aimed at opening acute paraproctitis were performed significantly more often (in the control group 35.7% of cases and in the main group of patients in 40% of cases, respectively). The list of operations also included excision of pararectal fistulas (in the control group 16.7% of cases and in the main group of patients in 22.5% of cases, respectively), excision of rectal fissures (in the control group 11.9% of cases and in the main group of patients in 15% of cases, respectively), diagnostic laparotomy (in the control group 7.1% and laparoscopy (in the control group of 14.3% of cases and in the main group of patients in 15% of cases, respectively) and laparoscopy (in the control group of 14.3% of cases and in the main group of patients in 20% of cases, respectively).

In 54.9% of cases, patients had previously received hormone therapy, while steroid resistance was diagnosed in 53.7% of cases.

In 84.1% of cases, patients were diagnosed with chronic continuous CD. Chronic recurrent course of the disease was detected in 12.2%. The acute course of CD was diagnosed in 3 (3.7%) patients.

The study design was based on an open, cross-sectional retrospective and prospective cohort study.

All the patients included in the study were operated on by us for CD complications. In this regard, the complex of examination of patients was not only preparatory, but also dynamic, aimed at assessing the general condition of the patient, the course of the postoperative period and the characteristics of changes in cellular and humoral immunity in CD.

For immunological studies, blood was taken from the ulnar vein into a centrifuge tube treated with 5.0 ml heparin.

The assessment of the state of the immune system of the patients was carried out by the expression of CD-differentiation and activation antigens. The following markers of immunocompetent cells were determined: CD3+-, CD4+, CD8+-, CD16+- CD25+- CD83+-lymphocytes. CD receptor expression was performed in the rosette formation reaction using LT series monoclonal antibodies manufactured by Sorbent LLC (RF) according to the method of Gharib F.Yu. et al. (1995).

Interleukins (cytokines) were determined in the blood serum of the examined by solid-phase enzyme immunoassay. To implement this option, two monoclonal antibodies with different etiotropic specificity for interleukins TGF-β, IL-4, IL-17, IL-21, INF-γ and TNF-α were used using special kits for enzyme immunoassay using a standard technique.

Blood sampling for immunological studies was performed in the preoperative period and on the 7th, 14th, 30th, 90th, and 180th days of the postoperative period. At the same time, the results obtained on days 7-14 were interpreted by us as the results of the early postoperative period, and on days 30-180 - the long-term postoperative period.

Instrumental diagnostic methods were performed without fail. The entire range of instrumental research methods included the following methods: ultrasound examination of the abdominal cavity and perineum; multispiral computed tomography with intravenous contrast and enterography; magnetic resonance imaging of the abdominal cavity according to individual indications with questionable MSCT data; video colonoscopy with mandatory examination of the Baugin flap and terminal ileum. This made it possible to assess the degree of CD development using a simple endoscopic scale (SES-CD).

When assessing the immediate results of treatment, we used a scale developed by A.O. Okhunov and A.D. Sapaev (2018). According to this method, a distinction was made between good, satisfactory and unsatisfactory immediate treatment results.

CD recurrence was determined by the appearance of typical symptoms of the disease in clinical remission, spontaneous or medically supported.

The severity of CD recurrence was determined according to the criteria of the Society for the Study of Inflammatory Bowel Diseases at the Association of Coloproctologists of Russia (2009).

3. The Results and Their Discussion

The obtained results on the frequency and nature of Crohn's disease recurrence in the postoperative period, on the one hand, and the peculiarities of changes in cellular-humoral immunity indicators in the dynamics of the study, on the other hand, created the conditions for the formation of a picture of the relationship. This will allow us to identify criteria for predicting the development of Crohn's disease recurrence and options for their prevention.

Identification of the causes of Crohn's disease recurrence and criteria (markers) for their prediction was carried out by direct and cross-correlation analysis of the data obtained, dividing them into early and late postoperative periods.

The overall dynamics of the postoperative period in Crohn's disease was characterized by high correlations of CD16+/CD3+ cells (R=0.905), as well as CD3+/CD4+ cells (R=0.781).

We found a high inverse correlation between the level of change in CD3+/CD8+ cells (R=-0.745), CD25+/CD83+ cells (R=-0.762), CD16+/CD25+ cells (R=-0.737), and CD3+/CD25+ cells (R=-0.699).

In other cases, the correlation was moderate (CD4+/CD8+ cells, R=-0.576; CD8+/CD83+ cells, R=-0.530 and CD3+/CD83+ cells, R=0.595) or low (CD3+/CD16+ cells, R=0.450; CD4+/CD16+-cells, R=-0.174; CD8+/CD16+-cells, R=-0.341; CD4+/CD25+-cells, R=-0.290; CD8+/CD25+-cells, R=0.208; CD4+/CD83+-cells, R=0.023).

In general, of the 15 indicators, the presence of a low correlation was noted the most (40%).

When assessing the cross-correlation with the division of the postoperative period into early and late periods between patients with relapse and remission of Crohn's disease, an ambiguous picture was revealed.

The correlation coefficient of CD3+ cell dynamics, which was R=0.939, was characterized by a relatively low correlation in the early postoperative period (R=0.805) and a high correlation in the late postoperative period (R=0.963). In both cases, they were directly correlated.

The reverse pattern of correlation variance was revealed by us when assessing the dynamics of CD4+ cell changes, the level of which in the early postoperative period was higher than the overall dynamics (R=0.634), and in the late postoperative period was lower (R=0.567) than the overall dynamics (R=0.500). As in the previous case, the changes were of a direct nature of dependence.

Thus, the nature of the correlation between the dynamics of changes in CD3+ and CD4+ cells in the blood in Crohn's disease in the postoperative period, both in the remission phase and in the relapse phase of the disease, had no special differences except for a decrease or increase in correlation. This pattern of changes was apparently associated with an early reaction of the body's immune system in differentiating naive T-lymphocytes and T-helper cells when macrophages present primary antigens.

The cross-correlation of the overall dynamics of CD8+ cell changes had a high direct correlation (R=0.877) between patients with different phases of Crohn's disease. In other words, the recurrence and remission of Crohn's disease have the same mechanism of activation of cytotoxic cells in both the first and second links of the body's immune response and in the perception of antigen presentation by macrophages.

Evidence of our judgments can be found in the data on changes in the CD8+ correlation coefficient in the early postoperative period (R=1,000). The nature of the changes was so similar that, apparently, it determined the minimum level of Crohn's disease recurrence during these follow-up periods.

In the long-term postoperative period, the correlation of changes in CD8+ cells in the blood also had a positive value (R=0.979), which, apparently, determined the activity of T-cytostatic cells in the cellular immune system and its relationship with Th1-cell T-helper cells.

The overall dynamics of CD16+ cells in the postoperative period in patients of the main and comparative groups was characterized by a high direct correlation (R=0.782). A separate analysis of the timing of the postoperative period revealed that in the early stages, the correlation between Crohn's disease in remission and relapse was identical in nature, with differentiation only in terms of the level of values. In the long-term period of the postoperative course, the correlation acquired the opposite character between patients with different phases of Crohn's disease (R=-0.243).

Thus, the involvement of T-suppressors in the development of Crohn's disease recurrence was minimal, and its involvement in the immune response was characterized by the general course of the postoperative period. At the same time, the activity of natural killer cells was of greater importance already in the late postoperative period, during which we noted a high proportion of the development of Crohn's disease recurrence. These changes, apparently, were already associated with the active involvement of CD16+ cells in the immune response in patients with recurrent Crohn's disease in the long-term period after surgery.

The correlation between the overall dynamics of CD25+ and CD83+ cell changes between patients with different phases of Crohn's disease was characterized by low positive values (R=0.479 and R=0.202, respectively), which was apparently due to the different directions of their expression both in different phases of the disease and in different periods of the postoperative course diseases.

The multidirectional nature of the expression of T-regulatory (CD25+ cells) and dendritic (CD83+ cells) cells was revealed by us among patients with Crohn's disease, regardless of the phase of the disease. The role and significance of these lymphocytes in terms of the timing of Crohn's disease recurrence was also different. Thus, in the early postoperative period, a high correlation was found between patients with different phases of Crohn's disease in relation to the dynamics of CD83+ cell changes, which was reversed (R= -0.905). In contrast, the dynamics of CD25+ cell changes turned out to be more dependent in the long-term period of the postoperative course in the form of a direct high correlation (R=0.801).

Thus, the correlational nature of the changes in T-regulating lymphocytes and dendritic cells was multidirectional and determined by the timing of the postoperative period in Crohn's disease.

Analysis of the dynamics of changes in blood cytokines in the context of the correlation coefficient of 15 indicators revealed the presence of a high direct relationship in the overall dynamics of the postoperative period in 10 (66.7%) cases. In the remaining 5 cases, the correlation was reversed and was related to the dynamics of the transformative growth factor. At the same time, we noted the maximum difference in the dynamics of TGF-β to IL-4 (R=-0.562) and further in descending order to TNF-α (R=-0.415), to IL-21 (R=-0.402), to INF-γ (R=-0.396) and to IL-17 (R=-0.304).

It is noteworthy that the severity of the correlation value of tissue growth factor was noted by us in the early postoperative period than in the late period, which indicates the possibility of using this marker in predicting the recurrence of Crohn's disease.

The correlation coefficient of TGF-β in the blood between patients with different phases of Crohn's disease in the early postoperative period was positive (R=0.232), although it was insignificant.

At the same time, the level of the correlation coefficient of the dynamics of IL-17 changes in the blood of patients in the comparative and main groups was pronounced reversed (R=-0.972).

The fact that the dynamics of TGF-β and IL-17 changes between patients with different phases of Crohn's disease in the late postoperative period (R=-0.932 and R=-0.980, respectively), which indicates a single mechanism of their transformation in the pathogenesis of this disease.

In general, the severity of the distinctive properties of changes in the level of cytokines TGF-β (R=-0.758) and IL-17 (R=-0.982) in the blood of patients in the postoperative period was characterized by opposite values between cases of recurrence and remission of Crohn's disease. Moreover, the importance of IL-17 exceeded the nature of the dynamics of the TGF-β change.

An inverse correlation between remission and recurrence of Crohn's disease was also revealed by the dynamics of changes in the level of proinflammatory cytokines IL-21 (R=-0.860) and TNF-α (R=-0.942), and the level of change in the latter indicator was relatively more pronounced. In the early postoperative period in patients of the main group, the dynamics of changes in the proinflammatory cytokine TNF-α changed in the opposite direction of the dynamics of patients with remission of the disease, which was characterized by a negative correlation coefficient (R=-0.853). A similar pattern of changes, but with a lower intensity, could be observed with respect to IL-21 (R=-0.573).

In the long-term period after surgery, the level of correlation between patients with different phases of Crohn's disease in terms of TNF-α and IL-21 was the opposite. Moreover, if in the first case (TNF-α) the correlation coefficient between remission and recurrence of the disease in the long-term period after surgery was the opposite (R=-0.930), then in the case of IL-21 it acquired a positive character (R=0.798).

The correlation value between patients with different phases of Crohn's disease in terms of INF-γ and IL-4 was generally the opposite (R=0.582 and R=-0.779, respectively). Moreover, the severity of such changes was in favor of IL-4.

An interesting fact remains the identity of changes depending on the phase of Crohn's disease in both the dynamics of INF-γ and IL-4 in the early (R=0.920 and R=0.984, respectively) and late (R=-0.996 and R=-0.964, respectively) postoperative periods.

Thus, the correlation analysis of changes in the level of pro-inflammatory cytokines and indicators of cellular immunity allowed us to combine them into a single scheme of the mechanism of development of Crohn's disease recurrence, which, in our opinion, may look like the following scenario. At the first stage, antigens, represented by macrophages and dendritic cells, as components of innate immunity, affect the initial (naive T helper) Th0 lymphocytes. As a result of this reaction, Th0 lymphocytes are amplified and differentiated into various subsets of subpopulations, in particular into Th1, Th2, Th17 and regulatory T cells. It should be noted that an imbalance of T-cell subpopulations at this stage of the immune response can cause excessive release of cytokines and chemokines, leading to the development of a pronounced inflammatory reaction.

Activation of various links of T-lymphocyte subpopulations occurs under the influence of the expression level of cytokines such as INF-γ (for the Th1 cell link), IL-4 (for the Th2 cell link) and TGF-β for the remaining T cells. At the same time, a sufficient amount of this cytokine is required to trigger the expression of T-regulatory cells. A lack (low level) of TGF-β in the blood leads to the expression of T-helper cells in their regulatory link.

As is known, INF-γ secreted by antigen-presenting cells acts on the signal transmission of the original Th cells and stimulates the differentiation of the original Th cells into Th1 cells. Th1 cells secrete various pro-inflammatory cytokines, in particular TNF-α, which was clearly noted by us among patients with recurrent Crohn's disease. Similar changes in Crohn's disease have been noted by other researchers. At the same time, the IL-4 cytokine secreted by antigen-presenting cells acts on receptors on the surface of the initial Th cells and induces the expression of transformation of the initial Th0 cells into Th2 cells and promotes their proliferation. Inflammatory factors such as IL-4 are also secreted by Th2 cells. IL-4 expression increases at the onset of Crohn's disease recurrence.

Thus, already at this stage of the analysis, it can be assumed that Th2 cells are associated with the pathogenesis of Crohn's disease. The Thl cell response is enhanced in the early phase of Crohn's disease recurrence, while the Th2 cell response dominates in the late period. Under normal conditions (control group), Th1 cells and Th2 cells were in dynamic equilibrium. Insufficient formation of IL-4 expressed by Th2 cells creates an obstacle to regulating the reaction of the Th1 cell link, which prevents the suppression of the

active production of proinflammatory cytokines, in our case TNF-α, an overabundance of which leads to the triggering of an immunological response with a chronic course of autoimmune inflammation. It is an autoimmune reaction that develops as a result of an imbalance of Th1/Th2 cell subpopulations that can be considered one of the variants of the recurrence of the inflammatory process in Crohn's disease.

In general, it can be noted that the balance of Thl- and Th2-lymphocyte cells determines the balance of pro-inflammatory and anti-inflammatory cytokines, which then determine whether and which immune reactions occur. Key cytokines for balancing Thl and Th2 lymphocytes may play a major role in the development of treatments and prevention of Crohn's disease recurrence.

The presentation of antigens by dendritic cells leads to the differentiation of Th17- and T-regulatory cells. In this case, everything depends on the abundance of TGF-β, a low level of which leads to the stimulation of Th17 cell expression and the response synthesis of IL-17, which was increased in patients with recurrent Crohn's disease. The subsequent reaction leads to increased formation of IL-21, which induces the transfer of immune cells to peripheral tissues and simultaneously activates natural killer cells (NF-kB), promoting apoptosis and the release of TNF-α. In general, it can be noted that Th17 cells and its cytokine derivatives play an important role in the early diagnosis and prediction of Crohn's disease recurrence.

Th17 cells and T-regulating lymphocytes are in dynamic equilibrium under normal conditions. The balance is disrupted by an excessive increase in Th17 cells, an excessive increase in immunogenicity, and a decrease or malfunction of T-regulating lymphocytes, which leads to a recurrence of Crohn's disease.

The original T cells differentiate into Th17 cells at low concentrations of TGF-β. At the same time, our studies have shown that Th17 cell production is inhibited at high concentrations of TGF-β. It is a sufficient amount of T-regulatory lymphocyte formation under the action of TGF-β that leads to suppression of the immune response and, accordingly, to remission of Crohn's disease. Thus, regulating the balance between Th17/T-regulating cells may become a new method for the prevention and treatment of Crohn's disease.

In any case, abnormal innate immune responses cause an imbalance of acquired immunity. In particular, pro-inflammatory cytokines produced by macrophages, eosinophils, and granulocytes increase damage to cellular immunity, weaken intestinal barrier functions, and worsen inflammation, thus forming a vicious circle. All of this can be fundamental to preventing the recurrence of Crohn's disease.

Thus, in Crohn's disease, there is an imbalance between Th1/Th2 cells and Th17/T-regulating cells, the intensity of which determines the outcome of the disease in the form of remission or relapse. Immunological disorders in Crohn's disease recurrence are based on the mechanisms of formation of an autoimmune reaction due to increased cell apoptosis due to the expression of proinflammatory cytokines TNF-α, IL-17 and IL-21 through the induction of natural killer cells against a background of low concentrations of TGF-β. Relatively high stimulation of TGF-β production by naive T-helper cells stimulates T-regulating lymphocytes, increasing their role in the development of tissue regeneration, and, consequently, creating favorable conditions for the onset of the remission phase of Crohn's disease.

When developing a therapeutic and diagnostic algorithm for the prevention of Crohn's disease recurrence, along with the results of immunological studies, the clinical manifestations of the disease should also be taken into account, which, based on the immediate results of treatment, can determine the likelihood of developing unsatisfactory results.

This conclusion was formed by us based on the purpose of the surgical methods of treatment for Crohn's disease, which are primarily aimed at removing (resecting) areas of the intestine that have undergone morphostructural changes and do not allow for the normal functioning of both the passage of food and the digestive process as a whole. At the same time, in general, the possibility of recurrence of the disease remains very high starting from the 14th day of the postoperative period, acquiring an increasing character in the dynamics of the postoperative period.

Certain difficulties in choosing drug therapy for Crohn's disease result in the limitation of the possibility of using hormone therapy due to the development of resistance to this type of treatment. At the same time, hormonal dependence also creates side effects of the treatment.

An attempt to analyze the pathogenesis of immunological disorders during the development and recurrence of Crohn's disease has shown us the significance of changes in cellular immunity values from the perspective of a change in regulation, resulting in an imbalance in the cytokine profile of the blood, in particular, high values of TNF-α, IL-17 and IL-21 and low values of TGF-β.

As our studies in the control group of patients have shown, stool frequency, body temperature, heart rate, and a history of early postoperative complications according to the Clavien-Dindo classification can be identified as clinical parameters of the prognostic probability of Crohn's disease recurrence after surgical treatment. Body temperature and the number of stools per day exceeded the significance of heart rate and the presence of postoperative complications. At the same time, the last criterion exceeded the previous one only slightly. In this case, a detailed breakdown of complications showed the importance of such types as grade III, which are most likely to be associated with a recurrence of Crohn's disease (grade III a complications accounted for 37.9%, while grade III b complications accounted for 63.1%). The same differentiated level was acquired by the number of stools per day, the gradation of which turned out to be at the level of 4.6 ± 0.5 times per day.

The regressive difference in the significance of the main immunological criteria for predicting Crohn's disease recurrence in the postoperative period turned out to be ambiguous. This was probably due to the different levels of variance of values in the postoperative period and in the difference in the manifestation of Crohn's disease.

The distribution parameters revealed a high sensitivity to TGF-β, moderate sensitivity to TNF-α and IL-21, and a relatively low sensitivity to IL-17. In this case, the confidence interval of the selected values in all cases has a reliable value ($p<0.001$).

This allowed us to grade these indicators as criteria for the likelihood of recurrence of Crohn's disease in the postoperative period according to the following parameters that need to be evaluated over time (dynamic prognosis).

The prognostic probability of Crohn's disease recurrence will be low with a stool frequency of up to 2 times a day; normal body temperature and heart rate; absence of postoperative complications or if they are only at grade I according to the Clavien-Dindo classification; deviations in blood levels of no more than one of the following parameters: TGF-β, TNF-α, IL-71 and IL-21 are more than 10% of the reference value.

The prognostic probability of Crohn's disease recurrence will be high with a stool frequency of 3 or more times a day; the presence of persistent subfebrile body temperature; the presence of tachycardia; the presence of postoperative complications at grade II and higher according to the Clavien-Dindo classification; blood abnormalities of two or more of the following parameters: TGF-β, TNF-α, IL-71 and IL-21 are more than 10% of the reference value.

Preventive measures for Crohn's disease recurrence were initiated during surgery by intraperitoneal administration of the drug Infliximab (Adalimumab) diluted in saline solution at a dose of 5 mg per 1 kg of patient weight. The intraenteric administration of this drug was technically performed in the affected area of the intestine after resection. If the patient had several intestinal lesions, the dose of the administered drug was evenly divided by the number of sites.

It is known that this drug has an affinity for TNF-α, and, accordingly, by rapidly binding to this proinflammatory cytokine, it reduces its functional activity.

In the postoperative period, this drug is administered intravenously at a rate of no more than 2 ml per 1 minute. The total infusion time should not have been less than 2 hours. A system with an apyrogenic filter and low protein binding activity was used for intravenous infusion of the drug.

With a high probability of recurrence of Crohn's disease, Infliximab (Adalimumab) was administered every 5 days at a dose of 10 mg per 1 kg of patient's weight until the level of prognostic parameters decreased. Against this background, the drug Entivio® (Vedolizumab) was administered intravenously once every 7 days at a dose of 300 mg. With a low probability of recurrence of Crohn's disease, Infliximab (Adalimumab) was administered every 10 days at a dose of 5 mg per 1 kg of patient's weight until the level of normal values of prognostic parameters was reached. Against this background, Entivio® (Vedolizumab) was administered intravenously once every 14 days at a dose of 300 mg.

In the absence of the likelihood of a recurrence of Crohn's disease, conservative therapy was continued by prescribing Prednisone at a dose of 1 mg per 1 kg per day (according to the reduction-to-withdrawal scheme) and Azathioprine at a dose of 3 mg per day in tablet forms. The patients remained under dynamic control.

This therapy regimen was also acceptable for active forms of Crohn's disease, if detected later.

The therapeutic and diagnostic algorithm developed by us allows not only to predict and prevent the recurrence of Crohn's disease, but also to determine the timing of reconstructive operations, which have more opportunities to achieve effective effectiveness.

Thus, the basis of the therapeutic and diagnostic algorithm for the prevention of Crohn's disease recurrence is the dynamic monitoring of cytokine levels (TNF-α, IL-17, IL-21 and TGF-β) in the blood, as well as clinical signs of the postoperative course (stool frequency per day, body temperature, heart rate, the presence of postoperative complications and their degree according to the Clavien-Dindo classification), which make it possible to determine the level (low or high) of the probability of an attack, on the one hand, and apply differentiated approaches to the anti-cytokine regimen (Infliximab and Vedolizumab), hormonal (Prednisone) and immunosuppressive (Azathioprine) therapy is on the other hand.

The methods we developed for predicting and preventing the recurrence of Crohn's disease were used by us among patients in the main group, who did not differ in their initial clinical and pathognomonic characteristics from patients in the control group.

When going to the clinic, abdominal pain bothered patients 9.4% more often than in the control group. Nausea, which was noted in 30% (12 patients) of cases, was also 3.8% more common than among patients in the control group. Cases of flatulence were also more often prevalent among patients in the main group (by 4.3%). In the main group of patients, there were 2.1 times more cases of fistulas of the anterior abdominal wall of the abdomen than among patients in the control group, and 1.5 times more frequent stools during the day.

There were relatively fewer patients with pain in the anus (only 1.5% less), cases of stool incontinence (1.9 times) and the presence of blood in the stool (1.3 times).

In general, the balance of the number of complaints among patients in the main group (an average of 2.1 complaints per 1 patient) corresponded to the frequency of complaints in the control group (an average of 2 complaints per 1 patient).

During the examination of patients, in 55% of cases (22 patients), Crohn's disease was localized in the terminal part of the ileum, and in another 11 (27.5%) patients, such a lesion was combined with pathology of the large intestine. Only 7 (17.5%) patients had Crohn's disease, which was manifested by lesions of the large intestine, which was 5.6% more than among patients in the control group.

Among patients with ileokolitis, jejunum lesion was noted in 81.8% of cases, and among patients with terminal ileitis, combined jejunum lesion was noted in 36.4% of cases. In total, jejunum lesion was noted among 17 patients in the main group, which amounted to 42.5% and was 1.5 times

more than among patients in the control group.

Perianal lesions were noted in 24 (60%) patients of the main group.

In total, 17% more resections of the ileum and subtotal resections of the colon with ileosigmoid anastomosis were performed among the patients of the main group. Resections of jejunum segments were also performed 1.5 times more often.

Infiltrates in the abdominal cavity were detected in 62.5% of patients during surgery. At the same time, 17 (42.5%) patients were also diagnosed with intestinal fistulas, which were mainly located between the affected segments of the ileum and the sigmoid colon.

In 12 (30%) patients, intercellular fistulas were sutured after their separation, and only in 5 (12.5%) patients of the main group, resections of the affected intestinal tract with the formation of a colorectal anastomosis were performed.

Intra-abdominal abscesses were diagnosed in 5 (12.5%) patients of the main group.

By applying a stoma (single-barrel ileostomy), operations were completed in 11 (27.5%) patients, which was 2 times less than in the control group. In other cases, intestinal resection was performed with the formation of an anastomosis without a preventive stoma.

Thus, the nature of Crohn's disease, the volume of intestinal damage and the nature of complications among patients in the main group did not differ much from the control group as a whole.

At the first stage of Crohn's disease recurrence prevention, at the end of surgery, Infliximab was administered intraperitoneally to patients of the main groups at a dose of 5 mg/ kg of patient weight. This stage of the operation affected the parameters of humoral immunity that we studied.

The use of anti-TNF-α therapy disrupts the continuity of the vicious circle of autoimmune processes, creating conditions for immunosuppression and thus the likelihood of recurrence of Crohn's disease. At the same time, as can be seen from the change in the nomogram curve, the initial values of cytokine content in the blood were more disturbed among the patients of the main group, which ultimately did not prevent them from normalizing the dynamics of changes.

In the postoperative period, complications were noted in 13 (32.5%) patients of the main group, which was 1.8 times less than among patients of the control group.

According to the Clavien-Dindo classification, postoperative complications were predominantly grade I (20%), less than grade II (7.5%) and grade III (5%).

Parastomal complications were noted in 5 (12.5%) patients, and in 4 cases (10% each), wound infection and infiltration of the abdominal cavity were noted, which did not require repeated surgical interventions.

In general, in the main group of patients, in 47.5% of cases, the immediate treatment results were assessed as good, which was 1.7 times more than among patients in the control group.

The proportion of satisfactory immediate results also exceeded the frequency of cases in the control group of patients and amounted to 42.5%.

We noted unsatisfactory treatment results in 4 (10%) patients, which was 3.1 times less than in the control group.

Targeted anti-cytokine and immunosuppressive therapy during surgery and in the early postoperative period allowed us to improve treatment outcomes and reduce the average length of hospital stay from 26.9±7.5 beds/days to 13.6±2.1 beds/days, which was almost 2 times less than among patients in the control group.

The use of methods for predicting and preventing autoimmune manifestations of the postoperative course of Crohn's disease allowed the main group to reduce the recurrence rate of the disease from 59.5% to 40%.

At the same time, the reduction in the proportion of Crohn's disease recurrence in the form of a moderate form was reduced by 1.7 times and severe forms of disease recurrence were completely avoided.

The use of the preventive measures we have developed has also allowed us to delay the development of Crohn's disease recurrence.

In the main group of patients, the use of the therapeutic and diagnostic algorithm developed by us for predicting and preventing recurrence of Crohn's disease made it possible to avoid its development within 1 month after surgery, and to reduce the frequency by an average of 1.3 times by 90-180 days after surgery.

The effectiveness of the criteria we developed for predicting Crohn's disease recurrence in the postoperative period was carried out using ROC analysis methods according to the principles of evidence-based medicine. At the same time, the main leitmotif of such an analysis was to determine the significance of immunological criteria in increasing the prognostic value of the method, which were applied among patients in the main group, whereas in the control group of patients we mainly focused on clinical criteria in the likelihood of recurrence of Crohn's disease in the postoperative period.

The results of applying clinical criteria for predicting Crohn's disease recurrence averaged 10.5±5.9% true positive results, 33.3±2.9% true negative results, 25.7±5.1% false positive results, and 30.5±4.4% false negative results. In general, the use of clinical criteria for predicting Crohn's disease recurrence made it possible to increase their diagnostic sensitivity from 6.67% on the 14th day after surgery to 33.3% on the 180th day after surgery, and specificity from 46.15% on the 14th day after surgery to 57.14% on the 180th day after surgery. The prognostic value of clinical criteria on the 14th day was 6.3%, on the 30th day after surgery - 14.3%, on the 90th day after surgery – 30.8%, and on the 180th day after surgery – 42.9%. On average, the diagnostic value was 28.9±14.4%.

The use of prognostic criteria with the inclusion of indicators of humoral immunity as a whole made it possible to increase the diagnostic sensitivity of the method by 3.5 times, diagnostic specificity by 1.9 times, and the prognostic value of the criteria for predicting the recurrence of Crohn's disease by 3.3 times.

Thus, the effectiveness of our method for predicting Crohn's disease recurrence in the postoperative period, due

to the importance of including immunological criteria, makes it possible to increase the sensitivity of the test by 3.5 times, specificity by 1.9 times, and the prognostic value of the method by 3.3 times. The use of the developed therapeutic and diagnostic algorithm for the prevention of Crohn's disease recurrence made it possible to reduce the incidence of its development in mild form from 31% to 27.5%, in moderate form from 21.4% to 12.5% and completely avoid its severe forms under the influence of pathogenetically based differentiated and targeted anti-cytokine, hormonal and immunosuppressive therapy.

4. Conclusions

1. Traditional approaches in the treatment of CD in 57.1% of cases are accompanied by the development of postoperative complications, among which parastomal types (33.3%) and wound infection (25%) prevail, leading to a high frequency (31%) of unsatisfactory immediate treatment results. CD recurrence with traditional approaches to the treatment of the disease is noted in 59.5% of cases, mainly occurring in mild and moderate type (88%). The chronology of the increase in the incidence of CD recurrence is directly proportional to the increase in the duration of the postoperative period.
2. The basis of the therapeutic and diagnostic algorithm for predicting and preventing CD recurrence is the dynamic monitoring of cytokine levels (TNF-α, IL-17, IL-21 and TGF-β) in the blood, as well as clinical signs of the postoperative course (stool frequency per day, body temperature, heart rate, the presence of postoperative complications and their degree according to the Clavien -Dindo classification), which make it possible to determine the level (low or high) of the probability of an attack, on the one hand, and apply differentiated approaches to the anti-cytokine regimen (Infliximab and Vedolizumab), hormonal (Prednisone) and immunosuppressive (Azathioprine) therapy – on the other hand.
3. The effectiveness of the developed method for predicting CD recurrence in the postoperative period, due to the importance of including immunological criteria, makes it possible to increase the sensitivity of the test by 3.5 times, specificity by 1.9 times, and the prognostic value of the method by 3.3 times. The use of the developed therapeutic and diagnostic algorithm for the prevention of CD recurrence made it possible to reduce the incidence of its development in mild form from 31% to 27.5%, in moderate form from 21.4% to 12.5% and completely avoid its severe forms under the influence of pathogenetically based differentiated and targeted anti-cytokine, hormonal and immunosuppressive therapy.

REFERENCES

[1] Manasyan N.Y. Crohn's disease // Smolenskiy medical almanac. – 2019. – № 1. – C. 196-199.

[2] Morozova V.V., Nezhenets S.P. On the issue of morphological diagnosis of ulcerative colitis and Crohn's disease // Modern problems of science and education. – 2024. – No. 2. – S. 9.

[3] Navruzov S.N., Navruzov B.S. Modern methods of diagnosis and treatment of Crohn's disease // Monograph, Tashkent – 2021. – 238 p..

[4] O.N. Nazarenko, O.N. Romanova, D.S. Matyushko, D.N. Dankova, Non-specific ulcerative colitis, crohn's disease in children: practical experience and application of various treatment options // Pediatric dietetics Issues. – 2017. – Trofim. 15, No. 2. – p. 68.

[5] Assessment of immunity in patients with ulcerative colitis and Crohn's disease / E.A. Melnikova, A.S. Solodyankina, S.N. Styazhkina et al. // Student Bulletin. – 2020. – № 47-4(145). – Pp. 78-81.

[6] Early ileocecal resection in Crohn's disease / M.A. Danilov, A.A. Demidova, A.V. Leontiev, V.V. Tsvirkun // Evidence-based gastroenterology. – 2023. – Vol. 12, No. 3. – pp. 10-17.

[7] Franze E., Dinallo V., Rizzo A. Interleukin-34 sustains pro-tumorigenic signals in colon cancer tissue. // Oncotarget. - 2018; 9(3): 3432–3445.

[8] Fujino S., Andoh A., Bamba S. Increased expression of interleukin 17 in inflammatory bowel disease. // Gut. - 2023; 52: 65–70.

[9] Inflammatory bowel disease is associated with changes of enterocytic junctions. / N. Gassler, C. Rohr, A. Schneider, et al. // Am. J. Physiol. Gastrointest. Liver Physiol. - 2021; 281: G216–228.

[10] Inflammatory bowel disease position statement of the Italian Society of Colorectal Surgery (SICCR): Crohn's disease. / G. Pellino, D.S. Keller, G.M. Sampietro, et al. // Tech. Coloproctol. - 2020; 24(5): 421–448.

[11] Khamdamov B.Z. Indicators of immunocitocine status in purulent-necrotic lesions of the lover extremities in patients with diabetes mellitus. // American Journal of Medicine and Medical Sciences, 2020, 10 (7). -P 473-478. DOI: 10.5923/j.ajmm.20201007.08.

[12] Khamdamov B.Z., Sayfiddinov S.I., Khamdamov I.B., Teshaev U.Sh. The role and place laser photodynamic therapy in prevention postoperative complications at treatment of diabetic foot syndrome. // 5th International scientific conference "European Applied Sciences: challenges and solutions" December 10th 2015. Stuttgart, Germany. -P. 27-31.

[13] Khamdamov I.B. Experimental determination of the extensibility of the anterior abdominal wall tissues at different times of pregnancy using various approaches to hernioplasty // Academicia: An International Multidisciplinary Research Journal Vol. 12, Issue 04, April 2022 SJIF 2022 = 8.252 P.193-201.

[14] Khamdamov I.B. Improving tactical approaches in the treatment of hernias of the anterior abdominal wall in women of fertile age // New day in medicine. Bukhara, 2022. -№ 10(48) - P. 338-342.

[15] Khamdamov I.B. Morphofunctional features of the abdominal press in women of reproductive age // New day in medicine. Bukhara, 2022. -№ 3(41) - P. 223-227.

[16] Hong S.C., Song J.Y., Lee J.K., Lee N.W., Kim S.H., Yeom B.W., Lee K.W. Significance of CD44v6 expression in gynecologic malignancies. // J. Obstet. Gynaecol. Res. 2016; 32(4): P. 379-386.

[17] Khamdamova M.T., Akramova D. E. Genetic aspects of genital prolapse in women of reproductive age // New day in medicine. Bukhara, 2023. - No. 5 (55). - P. 638-643.

[18] Khamdamova M.T., Akramova D. E. Genetic aspects of genital prolapse in women of reproductive age // New day in medicine. Bukhara, 2023. - No. 5 (55). - P. 638-643.

[19] Khamdamova M.T., Teshaev Sh.Zh., Hikmatova M.F. Morphological changes of the thymus and spleen in renal failure in rats and correction with pomegranate seed oil // New day in medicine. Bukhara, 2024. - N. 3(65). - P. 167-187.

[20] Khamdamova M. T. The state of local immunity in background diseases of the cervix // Eurasian journal of medical and natural sciences Innovative Academy Research Support Center. Volume 3 Issue 1, January 2023 ISSN 2181-287X R.171-175.

[21] Khamdamova M.T., Khasanova M.T. Various mechanisms of pathogenesis of endometrial hyperplasia in postmenopausal women (literature review) // New day in medicine. Bukhara. 2023. - No. 8 (58). - P. 103-107.

[22] Khamdamova M.T. Reproductive Health of Women Using Copper-Containing Intrauterine Contraception // Eurasian Medical Research Periodical Volume 28 January 2024, ISSN: 2795-7624. www.geniusjournals.org P. 39-45.

[23] Khamdamova M.T., Zhaloldinova M.M., Khamdamov I.B. The state of nitric oxide in blood serum in patients with cutaneous leishmaniasis // New day in medicine. Bukhara, 2023. - No. 5 (55). - P. 638-643.

[24] Khamdamova M.T., Zhaloldinova M.M., Khamdamov I.B. The value of ceruloplasmin and copper in blood serum in women wearing copper-containing intrauterine device // New day in medicine. Bukhara, 2023. - No. 6 (56). - P. 2-7.

[25] Khamdamov I.B. Improving tactical approaches in the treatment of hernias of the anterior abdominal wall in women of fertile age // New day in medicine. Bukhara, 2022. -№ 10(48) - P. 338-342.

[26] Khamdamov I.B. Morphofunctional features of the abdominal press in women of reproductive age // New day in medicine. Bukhara, 2022. -№ 3(41) - P. 223-227.

[27] Khamdamov A.B. The state of carbohydrate and lipid metabolism in obese patients after biliopancreatic bypass surgery // International conference on interdisciplinary science Volume 03, Issue 11, 2024. P. 169-175.

[28] Khamdamova M. T., Khasanova M.T. Genetic mechanisms of development of endometrial hyperplastic processes in women in menopacteric age // American Journal of Medicine and Medical Sciences 2025. - № 15(2): P. 372-375 DOI: 10.5923/j.ajmms.20251502.22.

[29] Khamdamov I.B. Advantages Of Laparoscopic Hernioplasty in Obesity Women of Fertile Age // Eurasian Medical Research Periodical Volume 28 January 2024, ISSN: 2795-7624. www.geniusjournals.org P. 33-38.

[30] Khamdamov B.Z., Khamdamov I.B., Teshaev U.SH. Laser photodynamic therapy in prevention postoperative complication at treatment of diabetic foot syndrome. // The 3rd International Congress of Wounds and Wound Infections. Collection of abstracts. Moscow, 2016. pp. 325-327.