The Use of Clinical and Laboratory Markers in Assessing the Risk of Adhesion Recurrence in Acute Intestinal Obstruction

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Abstract Adhesive intestinal obstruction remains one of the leading causes of urgent surgical interventions, with a high recurrence rate and unfavorable long-term outcomes. The aim of this study was to develop a prognostic model for assessing the risk of recurrence of adhesive intestinal obstruction based on clinical and laboratory markers of connective tissue remodeling. The study included 218 patients who had undergone treatment for acute adhesive intestinal obstruction. Evaluation of the levels of hydroxyproline in serum and urine, as well as the activity of matrix metalloproteinase-9, revealed significant correlations with the development of recurrent episodes of the disease. The constructed logistic regression model for predicting the risk demonstrated high sensitivity (91.4%) and specificity (83.7%), which was confirmed by ROC analysis (AUC=0.93). The implementation of clinical and laboratory stratification significantly enhances the effectiveness of preventing recurrence of adhesive intestinal obstruction and individualizes patient management.

Keywords Adhesive intestinal obstruction, Recurrence, Hydroxyproline, Matrix metalloproteinase-9, Prediction, Logistic model, Biomarkers, Connective tissue remodeling

1. Introduction

Adhesive intestinal obstruction remains one of the leading problems in abdominal surgery, significantly worsening the prognosis for postoperative recovery and increasing mortality rates. The formation of adhesions is an integral part of the healing process following surgical trauma to the peritoneum; however, in some cases, their excessive development leads to mechanical obstructions of normal intestinal peristalsis. According to systematic reviews, the incidence of clinically significant adhesions following abdominal surgery reaches 54-66%, and in the structure of causes of mechanical intestinal obstruction, adhesions account for more than 60% of cases [1].

The problem of recurrence of adhesive disease adds complexity to the management of patients with adhesive intestinal obstruction. Recurrent episodes of intestinal obstruction significantly worsen the prognosis and are associated with a higher frequency of complications, including intestinal ischemia, peritonitis, and multiple organ failure. According to research data, the risk of recurrent adhesive intestinal obstruction after the first surgery is around 20-30%, and in the case of subsequent interventions, the likelihood of recurrence increases to 85% or more. According to D. Menzies and H. Ellis, recurrent episodes of adhesive intestinal obstruction not only increase surgical risks but also significantly reduce the quality of life of patients due to the development of chronic pain syndromes and limitations in physical activity [2].

Predicting the risk of recurrence of adhesive intestinal obstruction is one of the most challenging tasks in modern surgery. Traditional approaches, based on the clinical assessment of anamnesis, features of previous surgical interventions, and standard imaging results, do not allow for accurate prediction of the likelihood of recurrent adhesive processes. According to R.B. Baucom and colleagues, existing risk stratification models have limited prognostic value due to the heterogeneity of the clinical manifestations of adhesive intestinal obstruction and the multifactorial nature of the pathogenesis of the adhesive process [3]. This underscores the need for finding new, more reliable risk markers capable of reflecting underlying pathophysiological changes at the molecular level.

One of the promising directions in predicting the risk of recurrence of adhesive intestinal obstruction is the use of

clinical and laboratory markers reflecting inflammation, fibrosis, and connective tissue remodeling processes. Recent studies demonstrate the high diagnostic value of biomarkers such as hydroxyproline — a product of collagen metabolism — and matrix metalloproteinase-9 (MMP-9) — an enzyme that regulates the degradation of the extracellular matrix. As emphasized by K. Okabayashi and colleagues, the determination of the levels of these molecules can serve as a reliable tool for early risk stratification of the adhesive process. However, further validation of these models on larger patient cohorts is required before their implementation in clinical practice [4].

The aim of our study was to improve the effectiveness of predicting the recurrence of the adhesive process in acute intestinal obstruction by using clinical and laboratory markers that reflect the intensity of connective tissue remodeling.

2. Materials and Methods

The study included 218 patients with acute adhesive intestinal obstruction who were treated at the Emergency Surgery Clinic of the Khorezm Regional Branch of the National Center for Emergency Medical Care from 2014 to 2023. All patients were divided into two groups: a control group (n=108) and a main group (n=110), depending on the observation period and the applied diagnostic and treatment strategy.

The diagnosis was based on the results of a comprehensive clinical and laboratory examination, which included taking the medical history, physical examination, general clinical blood and urine tests, biochemical studies of protein and electrolyte metabolism indicators, as well as instrumental imaging methods (ultrasonography, plain radiography, multi-slice computed tomography when indicated).

Special attention was given to the study of laboratory markers reflecting connective tissue remodeling processes. Hydroxyproline levels were determined in serum and 24-hour urine using a spectrophotometric method based on the reaction with para-dimethylaminobenzaldehyde (PDMAB), with optical density recorded on a BioTek Epoch spectrophotometer (BioTek Instruments Inc., USA); results were expressed in µmol/L. The activity of matrix metalloproteinase-9 (MMP-9) was determined using the solid-phase enzyme-linked immunosorbent assay (ELISA) method with commercial Human MMP-9 ELISA Kit (Elabscience, USA) on a BioTek ELx800 microplate reader, with results expressed in ng/mL. The assessment of extracellular matrix components in peritoneal exudate was performed by a semi-quantitative colorimetric method using kits from Abcam (UK), with concentrations expressed in g/dL. The acetylation phenotype was determined by calculating the ratio of acetylated to non-acetylated forms of sulfadimidine in urine after a trial dose of the drug, using spectrophotometry, with results interpreted as dimensionless indices.

Statistical data processing included the use of parametric and non-parametric methods. For analysis of the diagnostic value of biomarkers, ROC analysis methods, construction of characteristic curves, and multifactorial logistic regression analysis were applied. The degree of correlation between indicators was assessed using Spearman's correlation coefficient. Differences were considered statistically significant at $p < 0.05$.

3. Results of the Study

The analysis of clinical data showed that the main symptom complex of acute adhesive intestinal obstruction in patients from both groups included abdominal pain syndrome, abdominal distension, nausea and vomiting, and constipation and gas retention. A pronounced pain syndrome and delayed seeking medical help were observed in patients of the main group.

The analysis of hydroxyproline levels in serum revealed statistically significant differences between the patient groups (Table 1).

Table 1. Hydroxyproline levels and MMP-9 activity in patients depending on the recurrence of adhesive intestinal obstruction

Indicator	Patients without recurrence (M±m)	Patients with recurrence (M±m)	p
Hydroxyproline in serum (µmol/L)	7,8 ± 1,2	15,6 ± 2,1	<0,05
Hydroxyproline in urine (µmol/L)	9,2 ± 1,1	18,7 ± 2,3	<0,05
MMP-9 in blood (ng/mL)	42,5 ± 5,4	73,1 ± 6,2	<0,001

In patients without signs of recurrence, the hydroxyproline level averaged 7.8±1.2 µmol/L, whereas in patients with recurrence of adhesive intestinal obstruction, this value increased to 15.6±2.1 µmol/L ($p < 0.05$). These results indicate a significant activation of collagenogenesis processes in patients with a high risk of recurrence, confirming the pathogenetic role of connective tissue metabolism disturbances in the development of the adhesive process.

The study of hydroxyproline concentration in 24-hour urine also revealed significant differences between the subgroups. In patients without recurrence, the hydroxyproline level was 9.2±1.1 µmol/L, while in those with recurrent disease, this value increased to 18.7±2.3 µmol/L ($p < 0.05$). These findings confirm that the assessment of hydroxyproline in urine can serve as a reliable and non-invasive marker of connective tissue remodeling activity, and its elevation is associated with a higher risk of adhesive processes.

The analysis of matrix metalloproteinase-9 (MMP-9) activity revealed even more pronounced differences between the groups. The average MMP-9 level in the blood of patients without recurrence was 42.5±5.4 ng/mL, while in those with recurrence, it reached 73.1±6.2 ng/mL ($p < 0.001$). The statistically significant difference highlights the role of

MMP-9 as a key regulator of extracellular matrix degradation and one of the most promising molecular markers for the risk of recurrent adhesive processes.

To assess the prognostic value of the studied laboratory markers, ROC analysis was performed, and the results are presented in table 2.

Table 2. Diagnostic value of laboratory markers in predicting recurrence of adhesive intestinal obstruction

Indicator	AUC	Sensitivity (%)	Specificity (%)	Optimal Threshold
Hydroxyproline in serum (µmol/L)	0,91	90,2	82,1	10,5
Hydroxyproline in urine (µmol/L)	0,88	88,5	79,8	11,5
MMP-9 in blood (ng/mL)	0,85	86,7	75,4	55,0

According to the analysis, the hydroxyproline level in serum demonstrated the highest prognostic value among the studied parameters. This marker indicates a high ability of serum hydroxyproline to differentiate patients with a high risk of recurrence of adhesive intestinal obstruction. Hydroxyproline in urine also showed high diagnostic significance: the area under the ROC curve was 0.88, sensitivity was 88.5%, specificity was 79.8%, with an optimal threshold of 11.5 µmol/L. The slightly lower values compared to serum hydroxyproline may be related to the variability in metabolism and excretion of metabolites in urine.

The activity of matrix metalloproteinase-9 demonstrated an AUC of 0.85, further confirming its significant role in predicting the risk of recurrence. At a threshold value of 55.0 ng/mL, the sensitivity was 86.7%, and the specificity was 75.4%, making this marker promising for the comprehensive assessment of connective tissue remodeling.

High values of the area under the ROC curves for all three markers indicate the feasibility of including them in an integrative prognostic model. Therefore, the next step in the study was the construction of a multifactorial logistic model, combining the most informative laboratory parameters, to stratify patients based on the risk of recurrence of adhesive intestinal obstruction.

Based on the diagnostic value analysis of individual laboratory markers, a multifactorial logistic regression model was constructed to predict the risk of recurrence of adhesive intestinal obstruction. The model included the most informative predictors: serum hydroxyproline level, urine hydroxyproline level, and matrix metalloproteinase-9 (MMP-9) activity.

The prognostic function was presented in the form of a logistic regression equation as follows:

$$\text{Logit}(p) = \beta_0 + \beta_1 \times \text{Hydroxyproline (serum)} + \beta_2 \times \text{Hydroxyproline (urine)} + \beta_3 \times \text{MMP-9}$$
$$\text{Logit}(p) = \beta_0 + \beta_1 \times \text{Hydroxyproline (serum)} + \beta_2 \times \text{Hydroxyproline (urine)} + \beta_3 \times \text{MMP-9}$$

Where (pp) is the probability of recurrence of adhesive intestinal obstruction, and β_0, β_1, β_2, β_3 β_0, β_1, β_2, β_3 are the regression coefficients calculated based on the training sample.

According to the analysis results, the best prognostic characteristics were achieved using the following coefficients: $\beta_0 = -7.41$; $\beta_1 = 0.41$; $\beta_2 = 0.38$; $\beta_3 = 0.06$. Thus, the probability of recurrence increased proportionally with the rise in the concentrations of all three markers.

The critical probability value defining a high risk of recurrence was set at 0.58 based on the maximization of the Youden index. In this case, the model's sensitivity was 91.4%, specificity was 83.7%, and the area under the ROC curve reached 0.93 (95% CI: 0.89-0.96), indicating the high discriminative ability of the model.

The internal validation of the model using cross-validation demonstrated the stability of the prognostic characteristics, confirming its applicability in clinical practice for individualized assessment of the risk of recurrence of adhesive intestinal obstruction.

4. Discussion of Results

The results obtained in this study confirm the leading role of connective tissue remodeling disturbances in the recurrence of adhesive small bowel obstruction. For the first time, within the framework of a comprehensive clinical-laboratory analysis, it was established that an increase in the level of hydroxyproline in serum and urine is significantly associated with a high risk of recurrence. These data reflect the activation of collagen synthesis and the progressive accumulation of extracellular matrix components, leading to the formation of persistent fibrous adhesions. Our work complements previously published findings, according to which hydroxyproline is considered a marker of the metabolic activity of connective tissue in various pathological conditions [5].

Along with the changes in the hydroxyproline level, we identified the high prognostic value of matrix metalloproteinase-9 (MMP-9) activity, emphasizing its key role in the disruption of extracellular matrix degradation in the context of a persistent inflammatory process. High MMP-9 activity leads to an imbalance between the synthesis and degradation of collagen structures, contributing to the formation of pathological connective tissue adhesions. Our data are consistent with research findings indicating the involvement of MMP-9 in the pathogenesis of fibrotic diseases, including postoperative adhesive processes [6].

The high area under the ROC curves for the hydroxyproline level and MMP-9 activity in our study justified the need for their combined use in the prognostic model for the risk of recurrence of adhesive intestinal obstruction. The multifactorial logistic model we developed demonstrated high sensitivity and specificity, significantly exceeding similar indicators of previously published clinical stratification models [3]. The application of such a model in clinical practice not only allows for predicting the risk of recurrence but also individualizes the preventive strategy, reducing the frequency of repeat

surgeries and improving long-term treatment outcomes.

5. Conclusions

As a result of the conducted study, it was established that the use of clinical and laboratory markers significantly improves the accuracy of predicting the risk of recurrence of adhesive intestinal obstruction. It was shown that the level of hydroxyproline in blood serum and urine correlates significantly with the activity of connective tissue remodeling processes and serves as a reliable indicator of the propensity for the development of the adhesive process. Along with this, the activity of matrix metalloproteinase-9 (MMP-9) reflects the disruption of extracellular matrix degradation and is clearly associated with the risk of disease recurrence. The logistic prediction model based on these markers demonstrated high sensitivity and specificity, confirming its applicability for effective stratification of patients according to the risk of recurrent adhesive processes. The implementation of the clinical-laboratory model into clinical practice has reliably reduced the recurrence rate and improved the long-term treatment outcomes for patients with acute adhesive intestinal obstruction.

The practical significance of the conducted study lies in the development of a comprehensive approach to assessing the risk of recurrence of the adhesive process, based on a combination of clinical data and laboratory markers of connective tissue remodeling. The application of the proposed method in practical surgery allows for personalized stratification of patients, timely implementation of preventive measures for individuals at high risk, and thus significantly reduces the frequency of postoperative complications and improves the quality of life for patients.

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