ORIGINAL ARTICLE

CONTENTS

Anastomotic leak: genetic aspects of prediction and choice of surgical treatment tactics

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ABSTRACT

Aim: To improve the treatment results of patients with anastomotic leaks by studying genetic predisposition.

Materials and Methods: The object of this prospective study were 17 patients with anastomotic leaks. A group of 80 practically healthy people was tested as control. Real-time PCR was used to investigate polymorphisms: C-1306 →T (MMP2), rs243865 та G303→A (TIMP2), rs9900972.To assess the state of connective tissue metabolism. Free oxyproline in blood serum and the level of glycosaminoglycans (GAG) in urine were studied.

Results: Having investigated the relationship of some clinical and laboratory indicators of patients with postoperative complications with the genotypes of the studied polymorphisms, we found data indicating the pathogenetic significance of the C/C allele of the MMP-2 gene (C-1306→T) and the G/G variant of the TIMP gene 2 (G303→A) as a risk factor for the failure of anastomotic sutures, which, unlike other groups of genetic polymorphisms, are statistically reliably accompanied by hypoproteinemia, elevated indicators of markers of protein catabolism, namely free blood oxyproline and urine GAGs. Thus, in the research group with AL, the carriers of the homozygous CC genotype of the MMP2 gene had significantly lower levels of total serum protein. Indicators of urinary GAGs and free oxyproline were almost three times higher than those of carriers of the minor TT genotype.

Conclusions: Molecular genetic research is a new promising direction for the development of modern personalized diagnostic criteria and models for predicting the development and course of postoperative abdominal complications, in particular, anastomotic leaks.

KEY WORDS: postoperative complications, anastomotic leak, MMP2, TIMP2 genes, method of genetic prediction, prognostic-treatment algorithm

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INTRODUCTION

Anastomosis formation is a complex, cellularly mediated process that restores the continuity of hollow digestive organs [1]. It involves classic inflammatory processes: alteration, exudation, proliferation, and specific reparative processes influenced by the suture technique, suture material, presence of infection, and other factors [2]. Anastomotic leak (AL) is one of the most challenging complications in abdominal surgery. According to various authors, the frequency of such complications ranges from 2% to 19% [3]. AL is accompanied by high mortality of 2 - 21,7% [4], which, with the development of generalized peritonitis, increases up to 32.2% - 82,9% [5,6]. To date, the surgical community does not have a single point of view on the causes of AL, and there is no practical way of predicting this complication. It is crucial to consider the multiple risk factors associated with the development of AL, including microcirculation disorders, tissue regeneration disorders, infection, increased intra-intestinal pressure, changes in the rheological properties of blood, and gross violations of homeostasis. Literature data suggests that these factors can contribute to the development of AL [7]. Tactical and technical errors are a separate group of risk factors in creating anastomoses [8].

AIM

To improve the treatment results of patients with intestinal suture failure by studying pathogenetic mechanisms of development, genetic determination, and the development of new informational methods of diagnosis and prognosis of this complication's course and surgical treatment.

MATERIALS AND METHODS

The object of this prospective study were 17 patients with anastomotic leaks, who were treated at the Shalimov`s National Scientific Centre of Surgery and Transplatation. To assess the polymorphism of genes in the population, group of 80 practically healthy people,

which are comparable in age and gender to the subjects were examined. Real time PCR was used to investigate polymorphisms: $C^{-1306} \rightarrow T$ (MMP2), rs243865 та $G^{303} \rightarrow A$ (TIMP2), rs9900972.

To assess the state of connective tissue metabolism. Free oxyproline in blood serum and the level of glycosaminoglycans (GAG) in urine were studied.

To assess the properties of connective tissue, immunohistochemical studies were performed with the following markers (Thermo Scientific, USA): monoclonal antibodies (MAT) to Collagen IV (clone CIV22), α-smooth muscle actin α-SMA (clone CIV22). Evaluation of the expression of markers was carried out according to the visual-analog scale. The intensity of expression was evaluated from 0 - «absent» to +++ - «expressed» [10].

Statistical calculations of research results were performed using the program «Statistica 12.6» (SPSS) and Excel 2020. When comparing quantitative characteristics in the case of a normal distribution law in two groups, the Student's criteria was used; when the distribution law differs from the normal one, non-parametric criteria were used: Mann-Whitney U Test; Wilcoxon Matched Pairs Test. Fisher's two-sided exact test was used to compare the frequency of qualitative features in two groups. The reliability of differences in average values in groups with different genotypes was determined using the method of one-factor statistical analysis (URL: http://www.dgmp.kyiv.ua/index.php/snip-ka). The appropriateness of the distribution of genotypes was checked using the Hardy-Weinberg test and the chi-square test.

RESULTS

In the studied group of patients with anastomotic leaks treated in the clinic, the vast majority (66,7%) were patients operated on in other medical institutions of Ukraine, which were transferred to the National Scientific Centre of Surgery and Transplantation for further treatment.

Notably, a great number of complications (60.2%) occurred after planned interventions, which can be explained by the predominantly elective demographic of our patients.

To identify a possible association of polymorphic variants of the MMP-2 ($C^{-1306} \rightarrow T$) and TIMP2 ($G^{303} \rightarrow A$) genes with the risk of intestinal suture failure, we performed a univariate statistical analysis of the frequency of genotypes in the studied patient groups [10].

Analysis of the multiplicative model of inheritance of the MMP-2 gene

($C^{-1306} \rightarrow T$), when comparing the control group (n=80) and the experimental group with suture failure (n=17), confirmed the conformity of the distribution of genotypes to the Hardy-Weinberg law (p>0,05). Which in the control group was tested using the $\chi 2$ test with 1 degree of freedom, without using the Yates correction. Using the $\chi 2$ test with 2 degrees of freedom, we did not find statistically significant differences in the distribution of genotypes in the group of patients and the group of practically healthy people (p>0.05).

Notably, the experimental group has half as many carriers of the homozygous TT genotype compared to the control: 5.9% versus 10% (p>0.05), respectively. However, carriers of the dominant CC genotype were present in all groups. They were most prominent in the group with suture failure: 64,7% versus 47,5% (p>0.05) in the control (Fig. 1).

When analyzing TIMP-2 ($G^{303} \rightarrow A$) inheritance patterns, we managed to find statistically significant differences in the distribution of genotypes in control group and experimental group (p<0.05).

Thus, in the group of patients with anastomotic leak, the distribution of genotype carriers was significantly different from the control. Therefore, the dominant GG variant almost doubled, reliably, the indicators of the control and experimental group (82.4% vs. 47,5%, p<0.05). The heterozygous GA genotype in the experimental group occurred more than twice as often as in the control group (17.6% versus 42,5%). Carriers of the homozygous AA genotype in the group with suture failure were not detected, while a similar variant in the control occurred in 10% of cases (Fig. 2).

As a result of genetic and statistical analysis of MMP2 ($C^{-1306} \rightarrow T$) and TIMP2 ($G^{303} \rightarrow A$) gene polymorphisms, genotype variants were determined that are associated with the risk of developing anastomotic leak. Thus, in the experimental group with AL, carriers of the homozygous SS genotype of the MMP2 gene met 1.36 times more often than the control group. At the same time, minor TT homozygotes in the group of patients with suture failure were almost twice less than in controls (5.9% vs. 10% (p>0.05)).

When analyzing carriers of TIMP-2 genotypes, we obtained statically reliable data: in the group with AL, the GG variant was 82.4%, 1,7 times higher than the indicators of the control group (82,4% vs. 47,5%, p< 0.05). Carriers of minor AA genotype homozygotes were not found in the group with suture failure, while a similar genotype in the control group occurred in 10%.

We analyzed several clinical and laboratory indicators to study the possible association of anastomotic leak occurrence to the studied genotypes during the study. The analysis of the results, according to the genotype, in patients with suture failure is presented in Table 1, where the data are given only for those indicators,

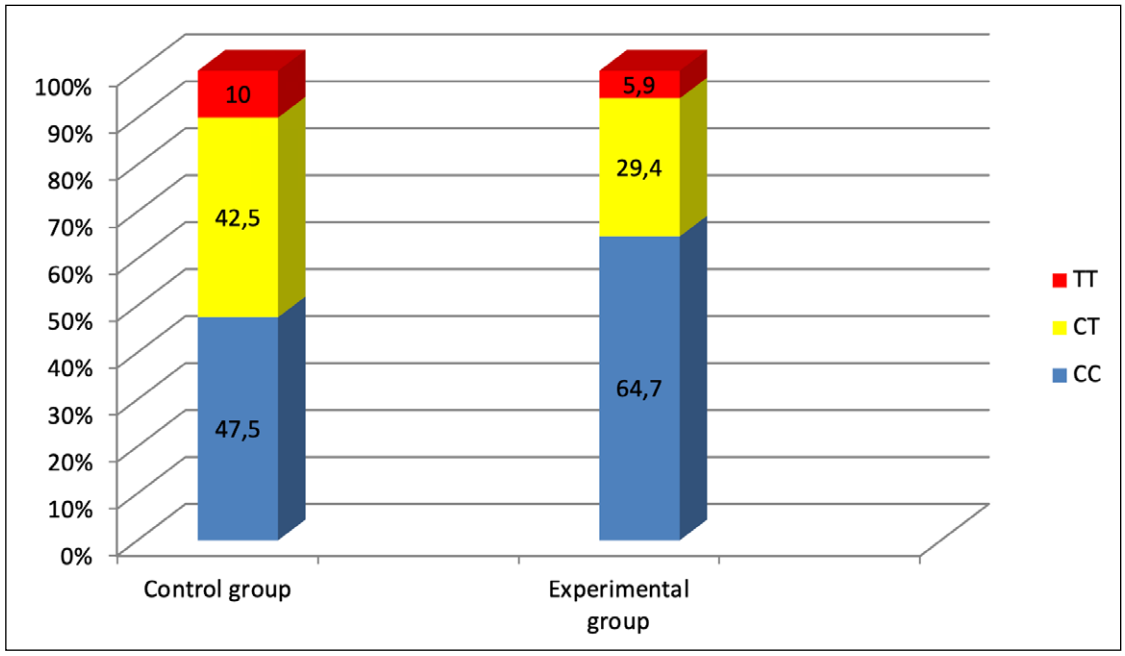

Fig. 1. Distribution of the frequency of allelic polymorphism (%) of the gene promoter MMP2 (C-1306 ⟶T).

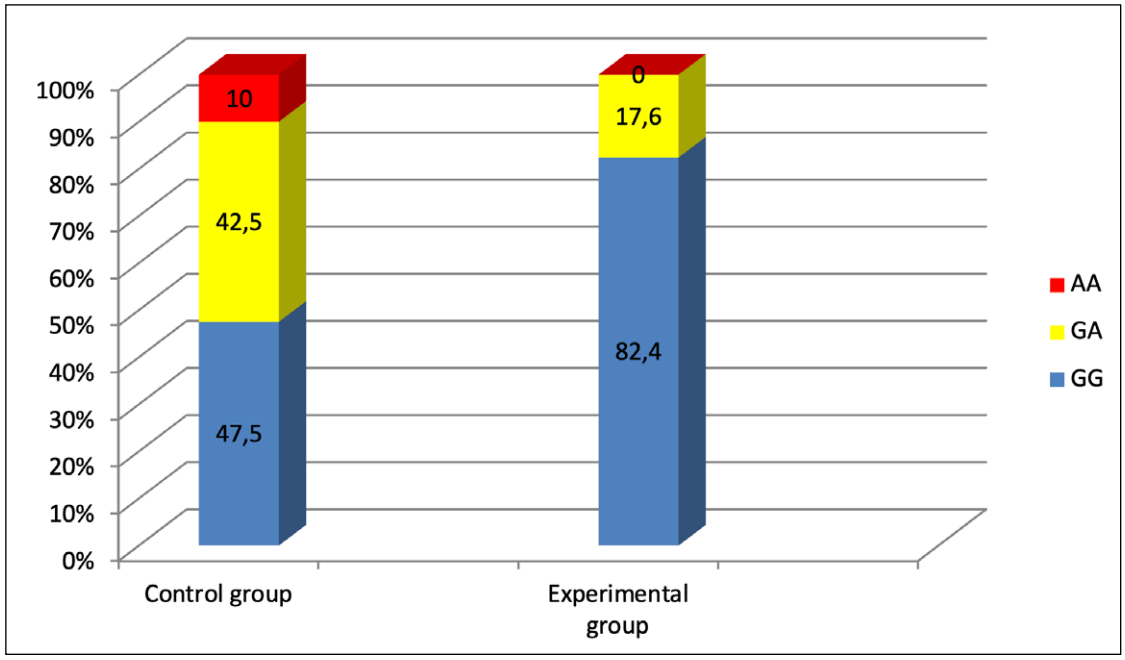

Fig. 2. Distribution of the allelic polymorphism frequency (%) of the TIMP2 gene promoter (G303⟶A).

the values of which differed statistically significantly depending on the genotype ($p<0.05$).

Having investigated the relationship of some clinical and laboratory indicators of patients with postoperative complications with the genotypes of the studied polymorphisms, we found data indicating the pathogenetic significance of the C/C allele of the MMP-2 gene ($C^{-1306}\rightarrow T$) and the G/G variant of the TIMP gene 2 ($G^{303}\rightarrow A$) as a risk factor for the failure of anastomotic sutures, which, unlike other groups of genetic polymorphisms, are statistically reliably accompanied by hypoproteinemia, elevated indicators of markers of protein catabolism, namely free blood oxyproline and urine GAGs.

Thus, in the research group with AL, the carriers of the homozygous CC genotype of the MMP2 gene had significantly lower levels of total serum protein. Indicators of urinary GAGs and free oxyproline were almost three times higher than those of carriers of the minor TT genotype.

Similar data were obtained for carriers of the GG genotype of the TIMP2 gene. In addition to significantly

Table 1. Dependence of some clinical and laboratory indicators on the genotypes of the studied polymorphisms in patients with failure of anastomoses of hollow digestive organs, n= 17

Indicator	MMP2 ($C^{-1306} \rightarrow T$)			Criteria F	P value
	C/C (n=11)	C/T (n=5)	T/T (n=1)		
Serum protein	60,12±2,74	69,44±2,20	72,50	8,193	0,04
Free Oxyproline mkmol/l	145,1±8,6	62,2±5,1	48,60	4,123	0,002
Urine GAGs Mkmol/l	140,82±7,8	68,25±4,5	50,94	5,620	0,006
	TIMP2 ($G^{303} \rightarrow A$)				
	G/G (n=14)	G/A (n=3)	A/A		
Serum protein	60,24±1,48	68,32±2,16	-	10,965	0,046
Free Oxyproline mkmol/l	187,3±9,8	55,2±3,8 *	-	5,071	0,002
Urine GAGs Mkmol/l	156,32±7,9 **	87,45±8,5 *	-	6,597	0,04
MAT Expression to α – SMA	+	++	-	-	-
MAT Expression To Collagen IV	+	++	-	-	-

Note: only statistically significant differences are given (* p1-2<0.05; ** p1-2<0.01).

lower levels of protein and high levels of free oxyproline (187.3±9.8 and 55.2±3.8, p<0.05), a reduced expression of monoclonal antibodies to α-SMA and Collagen IV was detected.

At the same time, carriers of risk alleles of TIMP-2 gene polymorphisms were distinguished by reduced expression of MAT to α-SMA, namely «+» for the G/G variant of the genotype and «++» for the G/A variant. The same trend was observed for the expression of MAT to Collagen IV, with the indicator «+» for the G/G genotype variant and «++» for the G/A variant. Thus, the indicated genetic alleles have a morphological confirmation of a genetic trigger in the pathogenesis of the development of anastomotic leak and intestinal fistulas.

The obtained data indicates the pathogenetic significance of alleles of polymorphisms of the MMP2 and TIMP2 genes, which are at risk for failure. Unlike the comparison group, presence of these alleles is accompanied by hypoproteinemia and significantly high levels of biochemical markers indicating collagen biodegradation.

Reduced expression of α-SMA cells correlates with the activation of fibrogenesis and reflects the phenotypic presence of myofibroblasts. The phenotype of myofibroblasts in the expression of α-SMA and the production of extracellular matrix coupling is regulated by β-transforming growth factor (TGF-β). The contractile properties of myofibroblasts are associated with α-SMA expression and are involved in inflammation, healing, fibrosis, and carcinogenesis [11].

All these factors have pathogenetic significance for the development of AL and are signs of connective tissue dysplasia [12].

We discovered the differences in the allelic variants of the studied genes in the groups with failure of anastomotic sutures. This became the basis for determining molecular genetic markers and developing a method of predicting the failure of anastomotic sutures.

We have proposed a method that involves a genetic study of the polymorphism of the MMP-2 ($C^{-1306} \rightarrow T$) and TIMP-2 ($G^{303} \rightarrow A$) genes and is distinguished by the fact that when the GG variant of the TIMP-2 gene ($G^{303} \rightarrow A$) is detected, we predict the development of AL if the AA variant of the genotype is detected, anastomotic leak is unlikely.

Based on the role of connective tissue pathology in anastomotic leaks, we have identified morphological signs of reparative regeneration disorders and proteolysis activation. We have also established a connection between these signs and genetic polymorphisms of MMP-2 ($C^{-1306} \rightarrow T$) and TIMP-2 ($G^{303} \rightarrow A$). Using this knowledge, we have developed a predictive treatment algorithm to prevent complications and increase treatment reliability at all stages. Our approach involves preventive measures and pathogenetically justified treatment of complications, as shown in Fig.3.

The developed prognostic-treatment algorithm involves screening patients for the presence of undifferentiated connective tissue dysplasia using the developed method (patent No. 120158) followed by genetic research of polymorphisms of the MMP-2 ($C^{-1306} \rightarrow T$) and TIMP-2 ($G^{303} \rightarrow A$). The determination of genetic polymorphism allows for the prediction of the development of postoperative complications. Patients who are carriers of alleles of the GG-variant of the TIMP-2 genotype and the CC-variant of the MMP-2 genotype are a risk group for the development of suture failure and require

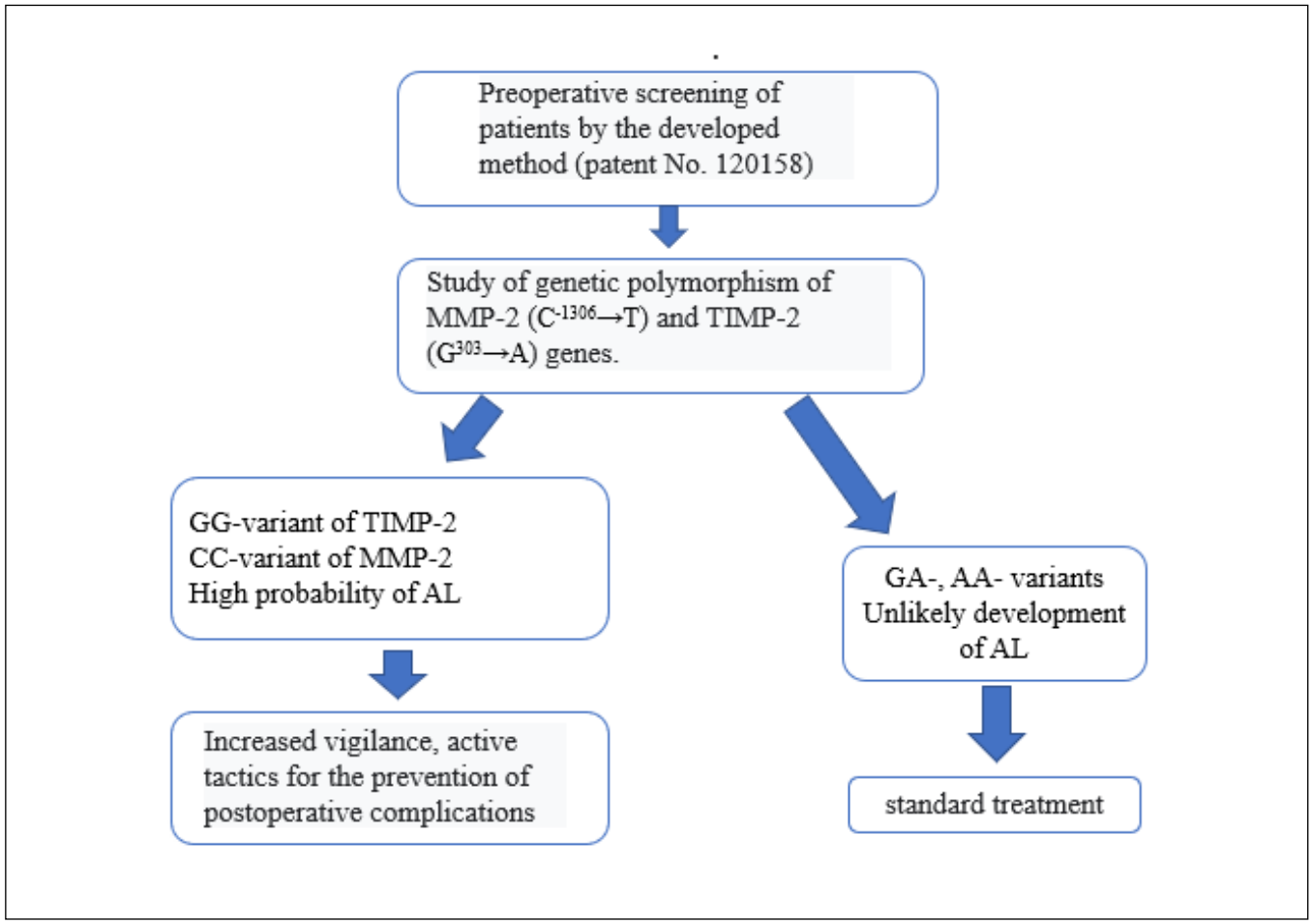

Fig. 3. A prognostic and therapeutic algorithm for the prevention of anastomotic leak in patients with undifferentiated connective tissue dysplasia.

comprehensive preventive and therapeutic measures starting from the pre-, intra-, and postoperative-stages.
Preoperative stage:
- Sparing food intake.
- Mechanical bowel preparation.
- Bowel decontamination.
- Epidural anesthesia.

Intraoperative stage:
- Precise technique of anastomosis and minimization of the tension in the anastomosed area;
- giving preference to the "side to side" small-intestinal, small-large-intestinal anastomosis
- Use of monofilament long-absorbable suture material.
- Use of "reinforcing" sutures in staple lines of colo-rectal and esophago-jejunal anastomosis
- Feeding Microjejunostomy formation in operations on proximal sections of GI tract
- Expansion of indications for protective stomas during operations on the distal parts of the hollow digestive organs (colonic and colo-anal anastomoses);
- Colonic lavage with use of antiseptic solutions.

Postoperative stage:
- Conservative treatment aimed at enhancing of regenerative processes in tissues;
- Rational antibiotic prophylaxis and antibacterial therapy;
- Prolonged use of epidural anesthesia;
- Early enteral nutrition.

Based on the analysis of the obtained research results, we believe that the surgical treatment of such postoperative complications as anastomotic leak in patients with identified and genetically determined pathology of connective tissue should be included in the rule «less is better,» i.e., reducing trauma and the volume of surgical intervention, with a preference for minimally invasive methods.

DISCUSSION

Anastomotic leak is a major complication that is associated with major postoperative morbidity, mortality, and prolonged hospital stay [13]. Depending on the site of anastomosis incidence ranges from 2 to 19 %, and may be up to 25 % in the case of pancreatic anastomoses [14]. Short-term consequences of AL

such as septic or hemorrhagic complications drastically increase postoperative morbidity and mortality, and long-term outcomes may require additional interventions due to a stricture formation, functional limitations to the patient`s life, and also have a negative impact on recurrence-free survival [15]. So prevention of such complications, and identification of patients, susceptible to AL with further tailored management in such cases is of great importance for reducing morbidity and mortality.

The absence of tension, adequate blood supply, and the correct opposition of tissues are fundamentals in the technical aspects of anastomotic formation [16]. Despite this, there is no common point of view on the reasons for anastomotic leak. In the conducted studies on anastomotic leaks, multiple factors that may add to the chance of AL have been described, some are non-modifiable such as male gender due to a more narrow pelvis. Some are based on preoperative therapy – radiation and chemotherapy, blood products, and patient-dependent factors: smoking, alcohol consumption, obesity, and malnutrition [17,18]. Lin et al. in their study of 999 patients that were operated on for rectal cancer link a patient`s old age to an anastomotic leak formation (P = 0.009) [19]. But there are several studies, that show that a patient`s age is not correlated with AL [20-22]. The way anastomosis should be constructed, hand-sewn, or stapled is also a point of dispute, while there are studies advocating for lower AL incidence in stapled anastomoses [23]. They are opposed by studies, some of which demonstrate a two-fold increase in anastomotic dehiscence after the use of stapling devices in comparison to hand-sewn [24,25].

In conclusion, most authors identify four main risk factors: state and morpho-functional processes occurring in anastomosed tissues, unfavorable factors for which sutures were applied, technical features of stitching, and adverse factors occurring in the postoperative period. The first group of factors is decisive and reflects the viability of tissues and the extent of reparative processes. Despite its undisputed role, research on regenerative processes in anastomosed tissues is lacking [1].

Several research papers have developed a hypothetical relationship between genetic polymorphisms in the mechanisms of inflammation development and the occurrence of anastomotic leaks. The impact of genetic factors on anastomotic healing requires further research. [9, 10]. The lack of clear prognostic criteria for the possibility of AL, the practically unexplored role of genetic predisposition for the development of anastomotic complications, and the possibility of correcting surgical tactics in such patients require new scientific research in this direction. Based on the genetic research findings, our proposed prognostic treatment algorithm promises to significantly improve the treatment outcomes for patients with intestinal suture failure.

CONCLUSIONS

1. The pathogenetic significance of alleles of polymorphisms of the MMP2 and TIMP2 genes, which are a risk factor for AL, accompanied by hypoproteinemia, high levels of biochemical markers of collagen biodegradation, and reduced expression of monoclonal antibodies to α-SMA and Collagen IV was revealed.
2. The proposed method of prognosis, which involves genetic research of MMP-2 ($C^{-1306}\rightarrow T$) and TIMP-2 ($G^{303}\rightarrow A$) gene polymorphisms, makes it possible to determine the probability of the development of anastomotic leak, which affects the choice of treatment tactics for such patients.
3. Molecular genetic research is a new promising direction for the development of modern personalized diagnostic criteria and models for prediction of postoperative abdominal complications, in particular, anastomotic leaks.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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