https://doi.org/10.33878/2073-7556-2023-22-1-83-90

Does the type of anastomosis affect the risk of recurrence in Crohn disease?

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ABSTRACT *AIM: to evaluate the effect of intestinal anastomosis type on risk of Crohn's disease (CD) recurrence.*
PATIENTS AND METHODS: the retrospective cohort study included 130 patients with CD who underwent surgery for a complicated CD in 2012–2017. Ileocecal resection with anastomosis was performed in 112/130 (86.2%) patients. Resection of the terminal ileum with resection of the right side of the colon with the formation of an ileo-transverse anastomosis. In 18/130 (13.2%) cases. Stapled "side-to-side" anastomosis was formed in 57/130 (43.8%) patients, while hand sewn "end-to-end" — in 73/130 (56.2%) patients. Post-op complications occurred in 21/130 (16.2%) cases. After surgery, most patients were treated by azathioprine as an anti-recurrence therapy — 112/130 (86.2%) patients, while in 31/112 (23.8%) cases, additional biological therapy was done. In 14/130 (10.7%) patients, anti-recurrence therapy was carried out in mono mode with a biological drug.
RESULTS: mean follow-up was 28.5 (1.9–95.4) months. Recurrence occurred in 54/130 (41.5%) patients on average 18 ± 5 (12–41) months after surgery. Thus, the operative time exceeding 200 minutes was significantly associated with an increase in the recurrence rate ($p = 0.03$). It was found that the type of anastomosis does not affect the recurrence risk. Moreover, among the significant factors was the operative time. It increases the chance of recurrence by 2.9 times in the univariate model ($p < 0.05$), and in the multivariate model — by 6.3 times, when exceeding 155 minutes.
CONCLUSION: the type of anastomosis does not affect the recurrence risk. The operation time exceeding 155 minutes increases the chance of recurrence by 6 times ($p < 0.01$).

KEYWORDS: *Crohn's disease, recurrence, anastomosis*

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

FOR CITATION: Vardanyan A.V., Anosov I.S., Michalchenko V.A., Nanaeva B.A. Does the type of anastomosis affect the risk of recurrence in Crohn disease? *Koloproktologia.* 2023;22(1):83–90. (in Russ.). https://doi.org/10.33878/2073-7556-2023-22-1-83-90

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Received — 28.11.2022 *Revised — 31.01.2023* *Accepted for publication — 20.02.2023*

INTRODUCTION

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that requires surgery in 80% of cases, regardless of the type of conservative treatment [1]. At the same time, the surgery does not completely cure patients and the recurrence rate remains high: a year after the surgery, endoscopic recurrence develops in 35–85% of patients, and clinical recurrence — in 10–38% of cases. By the third year of follow-up, the recurrence rate increases to 85–100% and 34–86%, respectively [2]. According to the literature, the CD recurrence detected during endoscopy develops either in the "neoterminal" ileum, or directly in the anastomosis [3,4]. This fact has caused concern among surgeons as to which type of anastomosis is accompanied by a low risk of ischemia, minimizes reflux of intestinal contents into the small intestine and prevents excessive bacterial growth in the ileum [5,6]. A number of studies have been published in which it is claimed that stapled "side-to-side" anastomosis is associated with a low incidence of postoperative recurrence [7–9]. In a retrospective study by Scarpa M., et al., 141 patients with CD were presented. No significant differences in recurrence rate was detected between the stapled and hand sewn method of anastomosis [10]. The results obtained were confirmed in a randomized controlled trial of McLeod R.S. Among 139 patients after 12 months, endoscopic recurrence occurred in 42.5% of patients after hand sewn anastomosis and in 37.9% after

Table 1. *Clinical criteria in patients with remission and recurrence*

	Recurrence (*n* = 54)	Remission (*n* = 76)	*P*
Stapled anastomosis	25 (46.3%)	32 (42.1%)	0.2
Hand sewn anastomosis	29 (53.7%)	44 (57.9%)	0.3
Gender (male)	31 (57.4%)	41 (53.9%)	0.18
Age, years (median, min-max)	28.5 (18–68)	28 (18–70)	0.5
CDIC[1]	10 (18.5%)	8 (10.5%)	0.2
Anamnesis, months (median, min-max)	48 (4–168)	33 (3–360)	0.11
Previous treatment	26 (48.1%)	33 (43.4%)	0.2
H-B[2] index (average point, min-max)	5 (3–10)	5 (2–14)	0.5
Laparoscopy	21 (38.8%)	25 (32.9%)	0.2
Operation time, minutes (median, min-max)	200 (120–390)	190 (90–450)	**0.03**
Lesion extent, cm (median, min-max)	20 (5–100)	20 (8–150)	0.3
Lesion of the jejunum	9 (16.6%)	6 (7.9%)	0.2
Abdominal mass	39 (72.2%)	60 (78.9%)	0.1
Abscess	8 (14.8%)	23 (30.2%)	**= 0.059**
Post-opcomplication	8 (14.8%)	13 (17.1%)	0.2
AZA[3]	44 (81.5%)	68 (89.5%)	0.1
BIO[4]	18 (33.3%)	27 (35.5%)	0.2

(CDIC[1] — Crohn's disease in the form of ileocolitis; H-B[2]– Harvey-Bradshaw index; AZA[3] — Azathioprine; BIO[4] — Biological therapy)

stapled anastomosis ($p = 0.55$) [11]. However, an earlier work by Muñoz-Juárez M., et al., based on an analysis of 138 patients operated on for CD, clearly indicates a significant decrease in the recurrence rate after a stapled anastomosis [12].

Taking into account these disagreements, we analyzed results in 130 patients with CD.

PATIENTS AND METHODS

The retrospective cohort study included 130 patients with CD who underwent surgery for a complicated CD in 2012–2017. Males were 72/130 (55.3%), females — 58/130 (44.7%). The median age was 28 (18–70) years. In 112/130 (86.2%) cases there was CD in the form of terminal ileitis, in the remaining 18/130 (13.2%) cases — in the form of ileocolitis. In 7 (5.4%) cases, there was an additional lesion of the jejunum.

Abdominal mass before surgery was detected in 99/130 (76.2%) cases, and intra-abdominal abscess — in 31/130 (23.8%) patients. The median disease history was 36 (3–360) months. In 112/130 (86.2%) cases, ileocecal resection with anastomosis was performed, in 18/130 (13.8%) cases — resection of the terminal ileum with the right colon and ileo-transverse anastomosis. The extent of the surgery volume was associated with the involvement of the colon in the inflammation. The extent of the lesion averaged 25 ± 1.6 (5–150) cm. 59/130 (45.4%) patients had previous prolonged conservative treatment for Me = 3 (1–7) months, including antibiotics (in 55/59 (93.2%) cases) and steroids (in 26/59 (44.1%) cases). In the remaining 71/130 (54.6%) patients, preoperative treatment, including antibacterial and steroid therapy, was carried out for Me = 7 (1–14) days. The Harvey-Bradshaw disease activity index, immediately before surgery, was Me = 5 (2–14) points. Laparoscopic procedures were performed in 46/130 (35.4%)

cases. The average operation time was 200 (90–450) minutes. Stapled "side-to-side" anastomosis was done in 57/130 (43.8%) patients, while hand sewn "end-to-end" anastomosis — in 73/130 (56.2%).

Post-op complications occurred in 21/130 (16.2%) cases. After surgery, azathioprine — 112/130 (86.2%) was used as anti-recurrence therapy for most patients, while biological therapy — in 31/112 (23.8%) patients. In 14/130 (10.7%) patients, anti-recurrence therapy was carried out in a single mode with a biological drug.

RESULTS

Follow-up had a median of 28.5 (1.9–95.4) months. Recurrence developed in 54/130 (41.5%) patients in 18.5 (12–41) months after surgery.

It should be noted that the groups were comparable by the type of the anastomosis ($p = 0.08$). Initially, we compared various clinical criteria in patients with recurrence and remission. The following signs were assessed: type of anastomosis, gender, age, presence of ileocolitis, duration of the disease, the fact of conservative treatment before the first surgery, Harvey-Bradshaw index, laparoscopic procedures, operation time, extent of lesion before primary surgery, presence of jejunum lesion in the anamnesis, abdominal mass or abscess before surgery in abdominal cavity, early postoperative complications, anti-recurrence therapy with azathioprine or biological drugs (Table 1).

It is interesting to note that in the group of patients with remission, cases with diagnosed abdominal abscess prevail, while there is a borderline reliability of the results ($p = 0.05$). This fact will be separately verified with further multivariate analysis. Moreover, unexpected

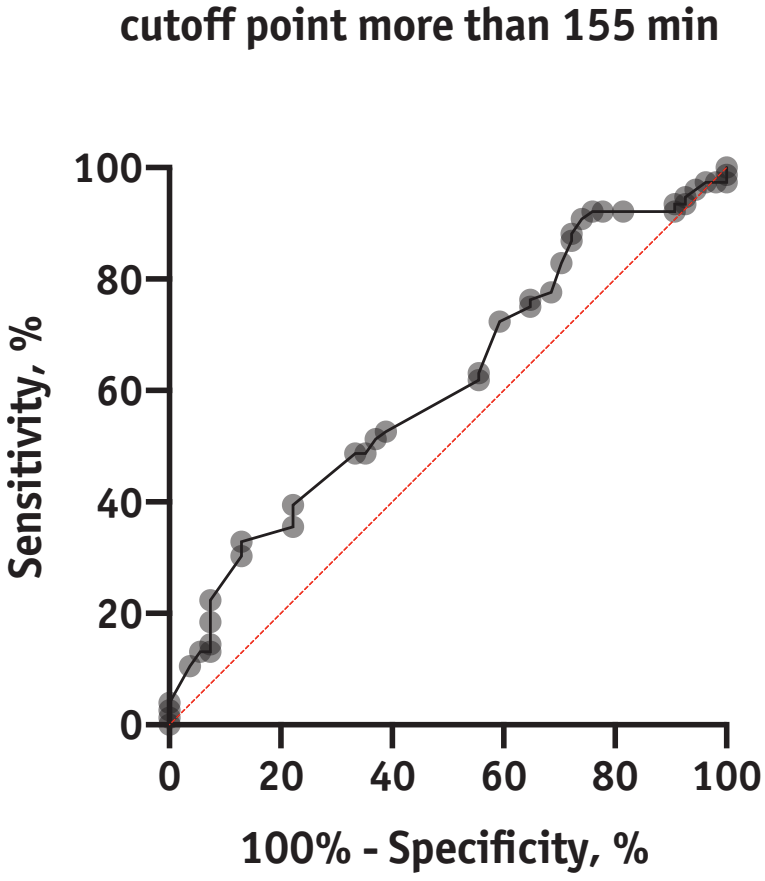

Figure 1. *ROC curve for determining the cut-off point for the duration of operations*

Table 2. *Odds ratio and confidence interval for risk factors for CD recurrence*

Predictors	Column A	Column B	Column C
	Univariate models (each variable is included separately) OR (CI)	**Multivariate model (all variables are included simultaneously) OR (CI)**	**Multivariate model (some variables are excluded) OR (CI)**
Stapled anastomosis	(0.587–2.393)	1.468 (0.576–3.744)	
Gender	1.151 (0.570–2.324)	1.955 (0.791–4.835)	
Age, years	1.000 (0.969–1.032)	1.005 (0.965–1.046)	
CDIC[1]	1.932 (0.708–5.273)	3.102* (0.842–11.43)	
Anamnesis, months	1.001 (0.994–1.007)	1.000 (0.991–1.008)	
Previous treatment	1.210 (0.601–2.438)	1.592 (0.644–3.937)	1.168 (0.541–2.521)
H-B[2]index	1.033 (0.872–1.224)	1.041 (0.841–1.290)	1.055 (0.881–1.264)
Laparoscopy	1.339 (0.646–2.776)	1.135 (0.412–3.128)	
Operation time, minutes	1.005* (1.000–1.010)		
Surgery duration over average (200 minutes)	1.371 (0.674–2.792)		
Operation time over 155 minutes	**2.914** (1.146–7.405)**	**6.278*** (1.799–21.91)**	
Lesion extent, cm	0.990 (0.970–1.011)	0.994 (0.969–1.019)	
Lesion of the jejunum	2.333 (0.778–7.001)	1.938 (0.514–7.312)	
Abdominal mass	0.693 (0.308–1.561)	0.501 (0.155–1.615)	0.872 (0.360–2.112)
Abscess	**0.401** (0.164–0.982)**	**0.293** (0.0945–0.909)**	**0.415* (0.156–1.108)**
Post-opcomplication	0.862 (0.330–2.251)	1.126 (0.351–3.619)	1.206 (0.424–3.435)
AZA[3]	0.518 (0.190–1.413)	0.504 (0.138–1.838)	0.428 (0.137–1.341)
BIO[4]	0.907 (0.435–1.893)	0.524 (0.192–1.433)	0.674 (0.289–1.573)

(CDIC[1] — Crohn's disease in the form of ileocolitis; H-B[2]– Harvey-Bradshaw index; AZA[3] — Azathioprine; BIO[4] — Biological therapy)
*(*p > 0.05; ** p < 0.05; ***p < 0.01)*

results were obtained when comparing the operative. Thus, the surgery duration exceeding 200 minutes was significantly associated with an increase in the recurrence rate of the disease ($p = 0.03$). Since the difference between the two groups is 10 minutes, we made additional analysis to identify the cut-off point using the ROC curve and the Yuden index (Fig. 1). As a result, the value of the point < 155 minutes was obtained, which will be used in further analysis.

To identify the predictors of recurrence, univariate and multivariate analysis was carried out.

The first step was to consider each of the above factors separately in univariate models, then all the factors in one model.

The odds ratio and coincidence intervals with confidence can be seen in Table 2. Figure 2 shows the results of univariate (each coefficient is included in turn) and multivariate (coefficients are included all together) models.

As a result of this analysis, it was revealed that the type of anastomosis does not affect the risk of the disease recurrence. Moreover, among the significant factors is the operation time.

Its exceeding 155 minutes in the univariate model increases the chance of recurrence by 2.9 times ($p < 0.05$), and in the multivariate model — by 6.3 times. In addition, in the univariate model (Table 2, column A), the presence of an abscess reduces the chances of recurrence by about 2.5 times (1/OR = 1/0.4), and in the multivariate model (Table 2, column B) — by about 3.4 times (1/OR = 1/0.29). On the conjugacy table, the presence of an abscess is less common in patients with recurrence ($p = 0.05$). We assumed that due to the inclusion of a large number of signs, this factor is most likely associated with other characteristics and therefore gives a contradictory result. In this regard, we conducted another multivariate analysis (optimized), in which we excluded several variables and left only the fact of previous therapy and other characteristics of the patient indicated in Table 2 in column B (Fig. 3). At the same time, the significance of the presence of an abscess

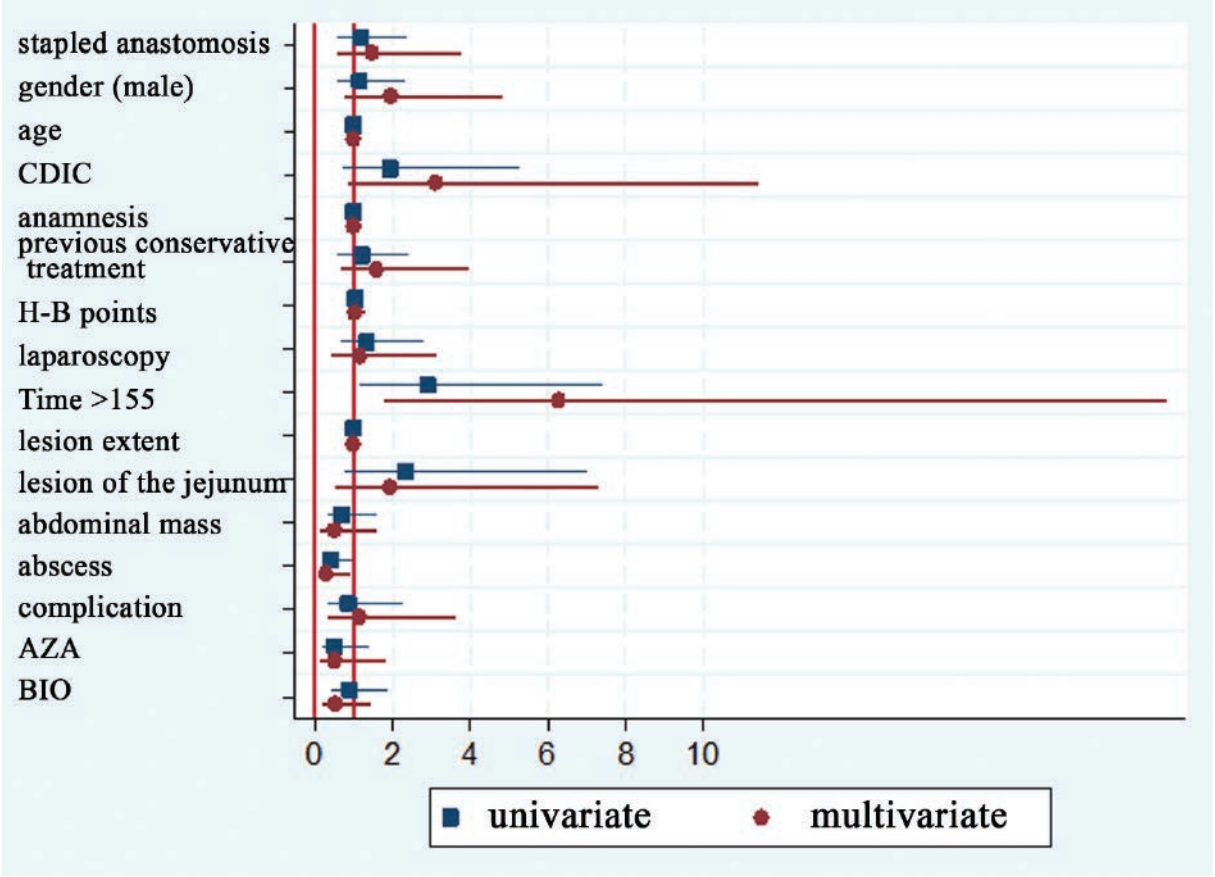

Figure 2. *Univariate and multivariate model for analyzing risk factors for the likelihood of CD recurrence*

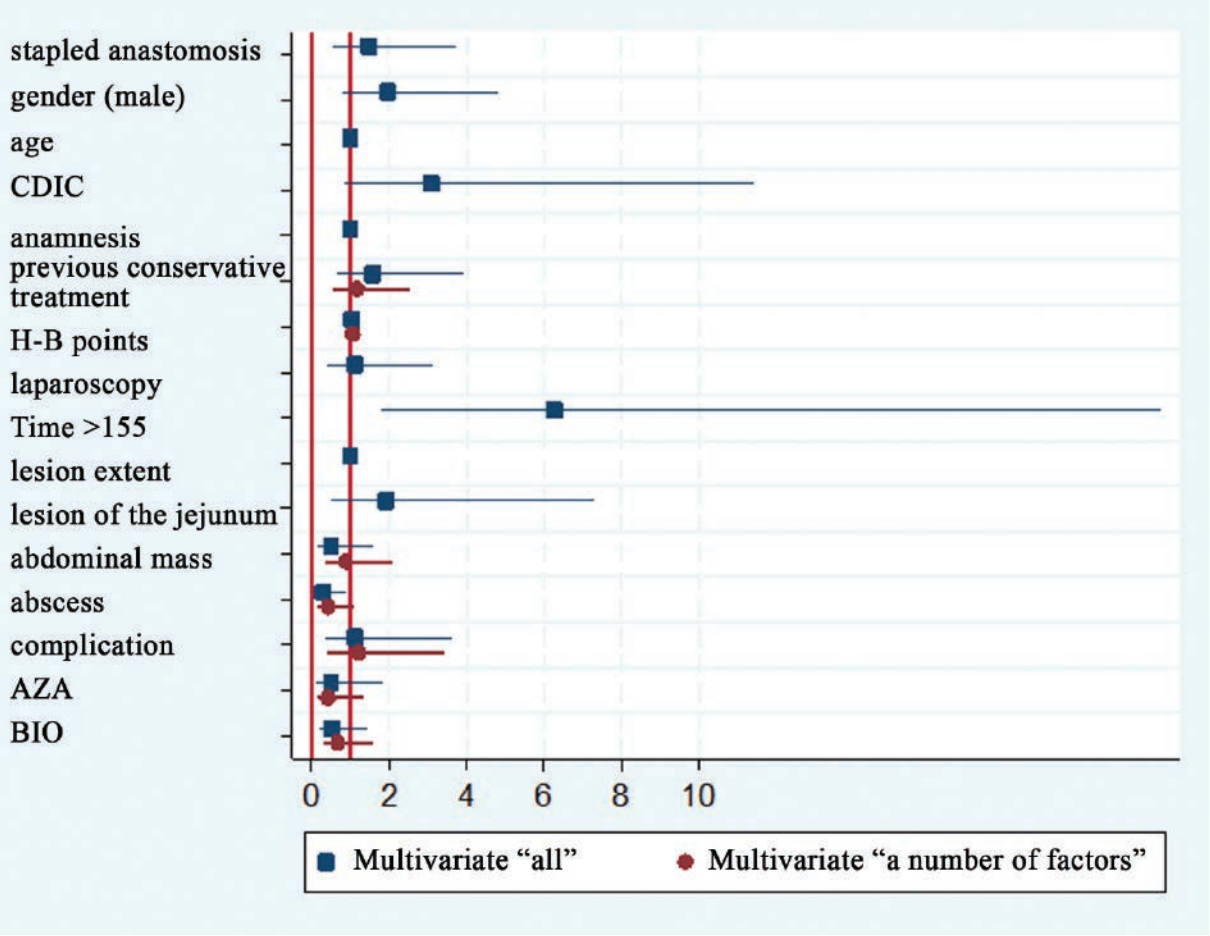

Figure 3. *Optimized univariate and multivariate model for analyzing risk factors for the likelihood of CD recurrence*

decreases ($p > 0.05$). This conclusion proves the connection of this criterion with other characteristics, which leads to a false increase in the probability of recurrence.

DISCUSSION

In 2014, a team of authors from China published a meta-analysis on the comparison of two types of anastomosis in ileocecal resection. The work included 8 studies summarizing the results of treatment in 821 patients, among whom in 396 (48.2%) cases the stapled anastomosis was performed and in 425 (51.8%)–hand sewn anastomosis. It is interesting to note that 3 out of 8 studies were randomized. A 5-fold reduction in the risk of the disease recurrence after "side-to-side" stapled anastomosis was found. It is extremely important to emphasize that after analyzing the isolated results of three randomized trials, our colleagues did not reveal any significant differences in the incidence of CD recurrences ($p = 0.2$) and re-operations for CD recurrence ($p = 0.12$) in the groups of patients with hand sewn or stapled anastomoses [13]. Another meta-analysis was done by Simillis C., et al. in 2007, which included 8 papers analyzing the effect of the type of anastomosis on the late results of CD treatment [14]. A total of 661 patients who underwent 712 intestinal resections were analyzed. In 383 (53.8%) cases, hand sewn anastomosis was formed, and in 329 (46.2%) – stapled anastomosis. When analyzing the late results, no correlation was found between the CD recurrence rate and the anastomosis type. It should be emphasized that the meta-analysis included 5 retrospective studies. McLeod R.S., et al., in their multicenter randomized study, analyzing the late results of surgery for CD for 12 months who had "end-to-end" and "side-to-side" anastomoses, demonstrated an equal CD

recurrence rate as for endoscopic signs (42.5% vs. 37.9%; $p = 0.55$), and by clinical manifestations (21.9% vs. 22.7%; $p = 0.92$) [11].

In a meta-analysis published in 2018, Feng J.S., et al. cautiously concluded that a stapled "side-to-side" anastomosis is preferable to hand sewn one [15]. However, the authors themselves noted in conclusion that the number of selected controlled studies was small, more than half of the studies were retrospective, and the follow-up time between the groups was different, which indicates the heterogeneity.

It turned out to be very interesting that on the issue of comparing different types of anastomoses in CD, a total of 4 meta-analyses were published from 2007 to 2018 [13–16]. In almost all works, the implementation of stapled "side-to-side" anastomosis is promoted, accompanied by both a lower postoperative complications rate and a CD recurrence.

However, many studies were not comparable, the groups of patients were heterogeneous, which has a negative impact on the reliability of the conclusions.

In this study, despite the retrospective nature, the lack of advantages of the stapled anastomosis in relation to the probability of postoperative recurrence was also demonstrated. It is interesting to note that the operation time, as an independent risk factor for the CD recurrence, has not been found in the available literature. The revealed pattern can be explained by the fact that longer procedures were associated with more severe and extensive complications of CD. In other words, patients with a developed recurrence initially had a more aggressive disease. Most likely, it is necessary to continue research in this area, giving preference to randomized trials.

CONCLUSION

The type of anastomosis does not affect the risk of the disease recurrence. The operation time exceeding 155 minutes increases the chance of recurrence by 6 times ($p < 0.01$).

AUTHORS CONTRIBUTION

Concept and design of the study: *Armen V. Vardanyan*

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