

Chechkin V.M. Prirodno-klimaticheskie i antropogennye faktory riska dlya zdorov'ya v sub'ektivnykh ocenках zhitelej gorodov Krajnego Severa [Natural, climatic and anthropogenic health risk factors in the subjective assessments of residents of the cities of the Far North]. *Zdorov'e naseleniya i sreda obitaniya* [Population health and habitat. 2020; 7 (328): 8-13 (In Russ.).] doi: 10.35627/2219-5238/2020-328-7-8-13.

9. Patrakeeva V.P. Osobennosti proliferativnoy aktivnosti kletok v zavisimosti ot rajona prozhivaniya cheloveka [Features of cell proliferative activity depending on the area of human residence]. *Ekologiya cheloveka* [Human ecology. 2010; 10: 23-26 (In Russ.).]

10. Pashinskaya K.O., Samodova A.V., Dobrodeeva L.K. Transportnye funktsii immunoglobulinov u zhitelej Evropejskoj territorii Arktiki Rossijskoj Federacii [Transport functions of immunoglobulins in the inhabitants of the European territory of the Arctic of the Russian Federation]. *Izvestiya RAN. Seriya biologicheskaya* [Biology Bulletin. 2023; 5: 537-545. doi: 10.31857/S1026347022600364.

11. Dobrodeeva L.K., Samodova A.V., Patrakeeva V.P., et al. Povyshennye koncentracii dofamina v krovi i sostoyanie immunnoj sistemy u prakticheski zdorovykh zhitelej severnykh terri-

torij [Increased concentrations of dopamine in the blood and the state of the immune system in practically healthy residents of the northern territories]. *Fiziologiya cheloveka* [Human Physiology. 2024; 50 (5): 95-105 (In Russ.).] doi: 10.31857/S0131164624050107, EDN: ANYZYF.

12. Repina V.P. Vliyaniye razlichnykh koncentracij katekholaminov na funkcionirovaniye immunokompetentnykh kletok ekologiya [The effect of different concentrations of catecholamines on the functioning of immunocompetent cells ecology]. *Ekologiya cheloveka* [Human ecology. 2008; 2: 30-33 (In Russ.).]

13. Ziyabishcheva V.N., Tipisova E.V., Elfimova A.E., et al. Tipologicheskie izmeneniya urovnya dofamina, kortizola i tireoidnykh gormonov u muzhchin g. Arhangel'ska v dinamike fotoperiodov goda [Typological changes in the levels of dopamine, cortisol and thyroid hormones in Arkhangelsk men in the dynamics of photoperiods of the year]. *Sibirskij nauchnyj medicinskij zhurnal* [Siberian Scientific Medical Journal. 2023; 43(6): 63-69 (In Russ.).] doi: 10.18699/SSMJ20230607.

14. Trotsenko A.A. Vliyaniye arkticheskogo klimata na nespecificheskuyu rezistentnost' zhitelej Krajnego Severa [The influence of the Arctic climate on the nonspecific resistance of the inhabitants of the Far North]. *Rossiya v global'nom mire*

[Russia in the global world. 2016; 9 (32): 211-218 (In Russ.).]

15. Khasnulin V.I., Khasnulin P.V. Sovremennye predstavleniya o mekhanizmah formirovaniya severnogo stressa u cheloveka v vysokikh shirotah [Modern concepts of the mechanisms of formation of northern stress in humans at high latitudes]. *Ekologiya cheloveka* [Human ecology. 2012; 1: 3-11 (In Russ.).]

16. Shubik V.M. Problemy ekologicheskoy immunologii na Krajnem Severe [Problems of ecological immunology in the Far North]. *Biosfera* [Biosphere. 2011; 3 (3): 390-408.

17. Engeroff, P., Fellmann, M., Yerly D., et al. A novel recycling mechanism of native IgE-antigen complexes in human B cells facilitates transfer of antigen to dendritic cells for antigen presentation. *Journal of Allergy and Clinical Immunology*. 2018; 142 (2): 557-568 (In Russ.).] doi: 10.1016/j.jaci.2017.09.024.

18. Liu CZ, Zhu JX. The source, metabolism, and function of dopamine in the digestive tract. 2020; 72 (3): 336-346.

19. Xue R., Zhang H., Pan J., et al. Peripheral Dopamine Controlled by Gut Microbes Inhibits Invariant Natural Killer T Cell-Mediated Hepatitis. *Front. Immunol*. 2018; 9: 2398. doi: 10.3389/fimmu.2018.02398.

SCIENTIFIC REVIEWS

DOI 10.25789/YMJ.2025.90.23

UDC 616.351-006

I.A. Shamanov, B.S. Dombaanaï

ANALYSIS OF RISK FACTORS FOR ANASTOMOTIC LEAKAGE IN PATIENTS AFTER SURGICAL TREATMENT OF COLORECTAL CANCER: A SYSTEMATIC LITERATURE REVIEW

This systematic literature review analyzes the risk factors for anastomotic leakage (AL) in the surgical treatment of colorectal cancer. Based on 42 studies, key risk predictors for AL were identified. The incidence of AL in the studies included in this review ranged from 2,8% to 24,7%. The introduction of the RALAR scale significantly improved the objective assessment of AL risk. A comprehensive approach to prevention, based on risk stratification and treatment personalization, can significantly improve the outcomes of surgical treatment for colorectal cancer.

Keywords: colorectal cancer, anastomotic leakage, risk factors, systematic review, PRISMA

For citation: Shamanov I.A., Dombaanaï B.S. Analysis of risk factors for anastomotic leakage in patients after surgical treatment of colorectal cancer: a systematic literature review. *Yakut Medical Journal*. 2025; 90(2): 91-97. <https://doi.org/10.25789/YMJ.2025.90.23>

Introduction. Colorectal cancer (CRC) ranks among the leading oncological diseases in terms of both incidence

and mortality [18, 36]. According to the World Health Organization, CRC is the third most common malignant neoplasm worldwide [95]. In 2022, more than 1.9 million new cases of CRC were reported, along with approximately 903,000 deaths related to the disease [36]. In the Russian Federation, CRC also holds a leading position in the structure of oncological morbidity, with a rising trend in the number of patients affected by this pathology, potentially reaching 2.2 million cases by 2030 [2, 3].

Surgical intervention remains the primary treatment for CRC, where anas-

tomosis formation is a key stage determining functional outcomes and patients' quality of life [4, 84]. Anastomotic leakage (AL), occurring in 2–19% of cases, continues to be a serious complication [79, 96].

The International Study Group on Rectal Cancer defines AL as a defect in the integrity of the intestinal wall at the anastomotic site [24]. This complication is associated with high morbidity (20–30%), mortality (up to 22%), prolonged hospitalization, increased risk of recurrence, reduced survival rates, and diminished quality of life [59, 89, 90].

SHAMANOV Ibragim Aubekirovich – PhD, Associate Professor of the Department of Surgical Diseases, North Caucasus Academy ORCID: 0009-0006-7276-4415, magibr67-09@yandex.ru; **DOMBAANAÏ Baiyr Sergeevich** – Analyst of the Department of Scientific Foundations of Healthcare Organization, Scientific Research Institute for Healthcare Organization and Medical Management of the Moscow Healthcare Department, ORCID: 0000-0002-5887-6545, dombaanaï@mail.ru.

Despite numerous studies on AL in CRC, risk factors for this complication remain a subject of debate. Current literature identifies multiple potential predictors of AL, which can be categorized into several groups: patient-specific (age, sex, comorbidities, nutritional status, harmful habits), tumor-related (location, stage, preoperative therapy), surgical (type of intervention, anastomotic level, operation duration, intraoperative complications), and perioperative factors (use of drains, preventive stoma, antibiotic prophylaxis) [35, 61, 69].

Systematization and analysis of AL risk factors are crucial for developing effective prevention strategies, especially considering emerging data and advancements in surgical techniques in recent years [56, 61]. Risk stratification of patients may help optimize preoperative preparation, intraoperative decision-making, and postoperative management, potentially reducing AL rates and improving CRC treatment outcomes [35, 89].

The aim of this review is to analyze recent literature (within the last five years) to identify and evaluate the significance of risk factors for AL in patients undergoing surgery for CRC.

Materials and Methods. A systematic literature review was conducted following the PRISMA guidelines [92]. The search was performed in electronic databases (PubMed, Google Scholar, and eLibrary) from January 2019 to February 2025 using the following key terms and their combinations in English and Russian: "colorectal cancer", "колоректальный рак", "anastomotic leak", "несостоятельность анастомоза", "risk factors", "факторы риска".

Inclusion Criteria

Studies were selected based on the following criteria: Research on risk factors for AL in surgical treatment of CRC; Articles reporting statistically significant risk factors for AL ($p < 0.05$); Publications in English or Russian; Full-text articles in peer-reviewed journals; Original studies, systematic reviews, and meta-analyses.

Study Selection Process

A two-stage screening was applied: 1. Initial screening of titles and abstracts. 2. Full-text review of selected articles. From each publication, the following data were extracted: Authors, study design, sample size; AL incidence rate; Statistically significant risk factors with corresponding metrics.

Out of 1,522 initially identified records, after removing duplicates and applying inclusion criteria, 42 studies were included in the final analysis (Figure 1).

Results and Discussion. General

al Characteristics of Included Studies. This systematic review included 42 studies published between 2019 and 2025. A summary of the included studies is presented in Table.

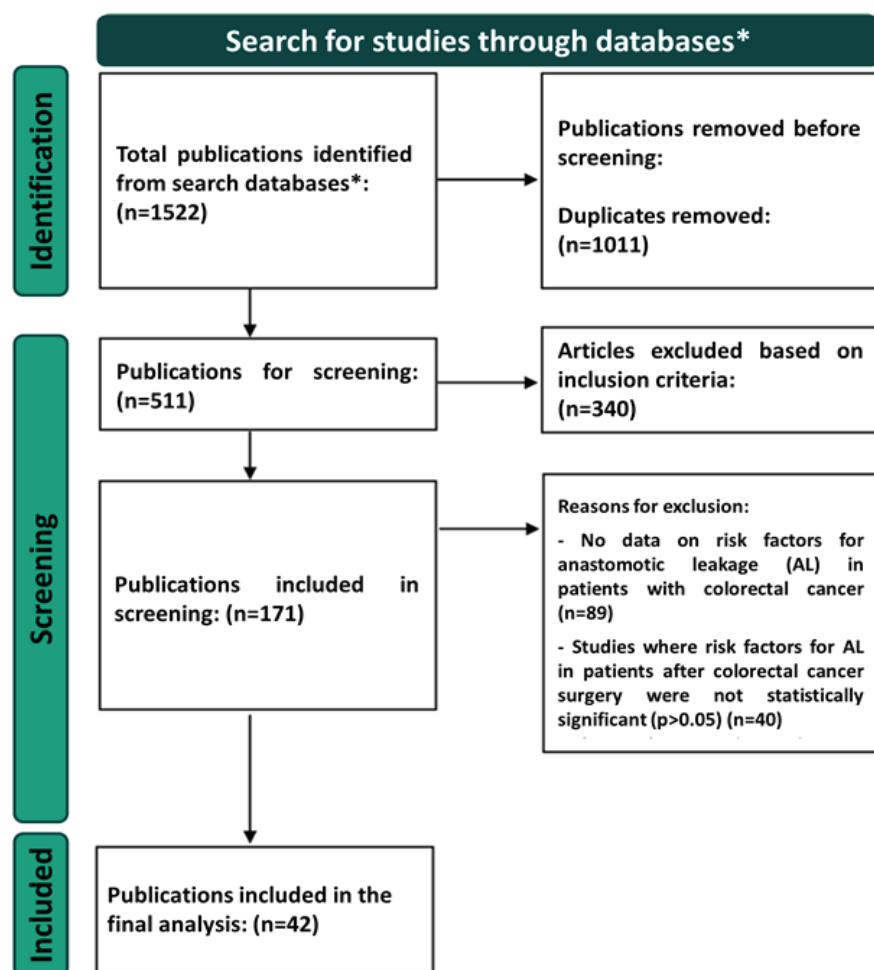
The incidence of AL across the analyzed studies ranged from 2.8% to 24.7%, reflecting significant heterogeneity in methodological approaches to defining and diagnosing this complication. In most studies ($n=31$, 73.8%), AL was defined according to the criteria of the International Study Group of Rectal Cancer [24], allowing for a more standardized analysis.

The identified statistically significant risk factors for AL were categorized into four groups (Figure 2). This classification is based on: pathophysiological mechanisms affecting anastomotic healing, chronological sequence of the treatment process, modifiable vs. non-modifiable risk factors. This approach has clinical significance for: preoperative risk stratification, development of predictive mod-

els, personalization of surgical treatment. The proposed classification aligns with current scientific approaches, emphasizing the multidisciplinary nature of AL in patients undergoing CRC surgery.

Patient-Specific Risk Factors for Anastomotic Leakage. Male Gender. Multiple studies with high statistical significance have identified male sex as an independent risk factor for AL. Alekseev et al. [42] demonstrated that male patients have nearly a fourfold increased risk of AL (OR 3.8, 95% CI 1.9-7.7, $p < 0.001$). These findings were corroborated by Degiuli et al. [70] (OR 1.55, 95% CI 1.27-1.88, $p < 0.001$) and Dias et al. [64], who reported a relative risk of 1.56 (95% CI 1.40-1.75, $p < 0.05$) for male patients. Further supporting evidence comes from Kryzauskas et al. [74] (OR=2.40, $p=0.004$) and a comprehensive meta-analysis by He et al. [11] involving 115,462 patients ($p < 0.0001$).

The elevated AL risk in male patients may be attributed to anatomical char-



* Literature search conducted in PubMed, Google Scholar, eLibrary databases.

Fig. 1. Flowchart of the systematic literature review conducted according to the PRISMA protocol

Main characteristics of the studies included in the review

Study and year of publication	Study type	Number of patients
Alekseev et al. (2022) [42]	Retrospective cohort study	429
Arron et al. (2021) [93]	Multicenter retrospective study	70229
Artus et al. (2020) [46]	Retrospective cohort study	200
Awad et al. (2021) [87]	Prospective cohort study	315
Brisinda et al. (2022) [12]	Multicenter retrospective study	583
Danardono et al. (2024) [23]	Retrospective cohort study	85
Degiuli et al. (2022) [70]	Multicenter retrospective study	5398
Dias et al. (2022) [64]	Systematic literature review and meta-analysis	184110
Foppa et al. (2023) [80]	Prospective cohort study	643
Harada et al. (2025) [76]	Retrospective cohort study	304
He et al. (2023) [11]	Systematic literature review and meta-analysis	115462
Herrod et al. (2019) [66]	Retrospective cohort study	169
Ito et al. (2024) [13]	Retrospective cohort study	102
Koskenvuo et al. (2024) [48]	Multicenter prospective study	565
Kryzauskas et al. (2020) [74]	Multicenter prospective study	900
Kryzauskas et al. (2020) [43]	Systematic literature review and meta-analysis	7115
Litchinko et al. (2024) [79]	Literature review	H/Д
Nordholm-Carstensen et al. (2019) [53]	Multicenter retrospective study	1414
Nugent et al. (2021) [54]	Systematic literature review and meta-analysis	32953
Phan et al. (2019) [28]	Systematic literature review and meta-analysis	896
Rodriguez et al. (2024) [77]	Multicenter retrospective study	360
Simillis et al. (2023) [55]	Systematic literature review and meta-analysis	59813
Simpson et al. (2024) [57]	Retrospective cohort study	522
Tan et al. (2021) [91]	Systematic literature review and meta-analysis	666886
Toyoshima et al. (2020) [49]	Retrospective cohort study	117
Tsai et al. (2022) [82]	Retrospective cohort study	1249
Tsalikidis et al. (2023) [61]	Literature review	H/Д
Wada et al. (2022) [20]	Retrospective cohort study	593
Wallace et al. (2020) [33]	Systematic literature review and meta-analysis	H/Д
Wang et al. (2022) [10]	Retrospective cohort study	1013
Yang et al. (2019) [65]	Systematic literature review and meta-analysis	8456
You et al. (2020) [37]	Retrospective cohort study	322
Yu et al. (2021) [38]	Retrospective cohort study	1058
Yue et al. (2023) [47]	Systematic literature review and meta-analysis	8852
Zarnescu et al. (2021) [96]	Literature review	H/Д
Zhang et al. (2023) [9]	Retrospective cohort study	292
Zhou et al. (2020) [32]	Retrospective cohort study	208
Zouari et al. (2022) [34]	Retrospective cohort study	163
Ahmetzyanov et al. (2021) [6]	Literature review	H/Д
Balkarov et al. (2021) [5]	Prospective cohort study	115
Darbishgadzhev et al. (2023) [7]	Retrospective cohort study	248
Polishchuk et al. (2021) [1]	Retrospective cohort study	74

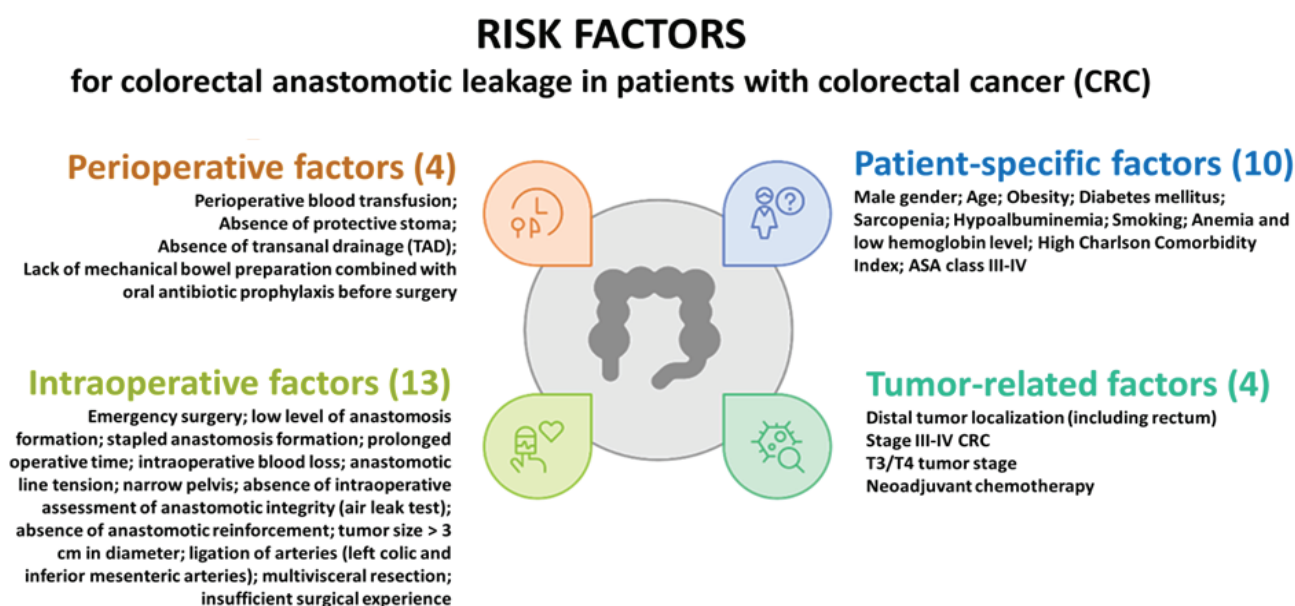


Fig. 2. Summary of risk factors for anastomotic leakage included in the study

acteristics of the male pelvis, which is typically narrower and deeper, creating technical challenges during anastomosis formation, particularly in low rectal resections [74]. Additionally, hormonal factors may influence microcirculation at the anastomotic site, potentially increasing the risk of ischemia and subsequent leakage [26]. These findings underscore the importance of considering male sex as a significant risk factor in surgical planning and postoperative monitoring.

Age. The influence of age on AL risk was confirmed in two studies. Rodriguez et al. [77] showed that age ≥ 65 years is associated with an increased risk of AL (OR=2.48, 95% CI 1.24–4.97, $p=0.003$). Similar results were obtained by Danar-dono et al. [23], where age over 50 years was a statistically significant risk factor ($p=0.05$).

The increased risk of AL in elderly patients may be associated with age-related changes in microcirculation, reduced tissue regenerative capacity, impaired collagen formation, and a higher incidence of comorbidities [31, 88]. These factors collectively may negatively affect the anastomotic healing process [62].

Obesity. Obesity was identified as a significant risk factor for AL in two studies. Nugent et al. [54] demonstrated that visceral obesity increases the risk of AL by 2.15 times (OR=2.15, 95% CI 1.46–3.15, $p<0.05$), with this risk being particularly high in patients with colon cancer (OR=2.88) and rectal cancer (OR=2.74). The meta-analysis by He et al. [11] also confirmed a statistically significant association between body mass index (BMI) and the risk of AL ($p=0.03$).

The negative impact of obesity may be explained by technical difficulties during surgery associated with increased visceral fat, impaired tissue perfusion, and higher intra-abdominal pressure [60, 72]. Additionally, obese patients often present with chronic inflammation, which may adversely affect tissue regeneration and wound healing processes [8].

Diabetes Mellitus. Diabetes mellitus was identified as a risk factor for AL in three studies. A systematic review by Dias et al. [64] established that diabetes nearly doubles the risk of AL (RR=1.97, 95% CI 1.44–2.70, $p<0.05$). An even stronger association was reported in a meta-analysis by Tan et al. [91], where the OR was 2.407 (95% CI 1.837–3.155, $p<0.001$). The study by Zouari et al. [34] also confirmed this relationship ($p=0.04$).

The pathophysiology of the increased risk of AL in diabetic patients involves several mechanisms. Diabetic microangiopathy leads to impaired tissue perfusion at the anastomotic site [81]. Chronic hyperglycemia disrupts neutrophil and macrophage function, potentially delaying the inflammatory phase of wound healing [52]. Moreover, collagen protein glycation reduces the tensile strength of the anastomosis [16]. It is important to note that even short-term episodes of hyperglycemia in the perioperative period can negatively affect healing processes, highlighting the need for strict glycemic control [27].

Nutritional Status. Nutritional status disorders, particularly hypoalbuminemia, were identified as significant risk factors for AL in five studies. Rodriguez et al. [77]

established that a preoperative albumin level <3.5 g/dL significantly increases the risk of AL (OR=22.2, 95% CI 11.5–42.9, $p<0.001$). Zhang et al. [9] also confirmed that low albumin levels (<37.5 g/L) are an independent risk factor ($p=0.006$). Similar findings were reported by Danar-dono et al. [23] ($p=0.01$), Zouari et al. [34] ($p=0.01$), and Awad et al. [87] ($p=0.015$).

Sarcopenia, as an indicator of malnutrition, was also identified as an independent risk factor for AL in the study by Herrod et al. [66], where a lumbar muscle density ≤ 43.5 HU on computed tomography was associated with a 14-fold increased risk of AL (OR=14.37, $p=0.026$).

Malnutrition negatively affects protein synthesis necessary for tissue repair, weakens the immune response, and impairs regeneration processes [29]. Low albumin levels may reflect both insufficient protein intake and ongoing inflammatory processes, which together worsen the prognosis of anastomotic healing [63].

Smoking. Active smoking was identified as a significant risk factor for AL in four studies. In the systematic review by Dias et al. [64], the relative risk for smokers was 1.48 (95% CI 1.30–1.69, $p<0.05$). Tsai et al. [82] found that not only active smoking at the time of surgery ($p=0.022$), but also a history of smoking with cessation less than 10 years prior ($p=0.029$), significantly increased the risk of AL. This association was also confirmed by Zouari et al. [34] ($p=0.01$) and Foppa et al. [80] ($p=0.03$).

The negative impact of smoking on anastomotic healing may be attributed to several mechanisms. Nicotine induc-

es vasoconstriction, leading to tissue ischemia. Carbon monoxide in tobacco smoke reduces oxygen transport to tissues [83]. Additionally, tobacco smoke components impair neutrophil and macrophage function, delaying wound cleansing and granulation tissue formation processes [21].

Anemia. Preoperative anemia was identified as a risk factor for AL in four studies. Harada et al. [76] found that hemoglobin levels ≤ 10.9 g/dL for men and ≤ 9.9 g/dL for women were associated with nearly a 10-fold increased risk of AL (OR=9.94, $p=0.002$). Brisinda et al. [12] showed that hemoglobin levels <10 g/dL significantly increased the risk of AL (11.8% vs. 7.0% with ≥ 10 g/dL, $p=0.02$). The association between anemia and AL was also confirmed by Danardono et al. [23] ($p=0.007$) and Zouari et al. [34] ($p<0.01$).

Anemia may negatively affect anastomotic healing by reducing oxygen delivery to tissues, which is especially critical in the context of relative ischemia at the anastomotic site [14]. Inadequate tissue oxygenation can impair cellular proliferation, collagen synthesis, and neoangiogenesis processes, which collectively compromise anastomotic strength and integrity [17].

Comorbidity. A high Charlson Comorbidity Index (CCI) was associated with an increased risk of AL in two studies. Artus et al. [46] showed that CCI >5 is an independent risk factor for AL in rectal surgery ($p=0.025$). Wada et al. [20] found that CCI ≥ 2 increased the risk of AL by nearly fivefold (hazard ratio=4.91, 95% CI 2.23–10.85, $p<0.001$).

A high American Society of Anesthesiologists (ASA) physical status classification III–IV was also identified as a risk factor for AL in three studies: Dias et al. [64] (RR=1.70, 95% CI 1.37–2.09, $p<0.05$), Kryzauskas et al. [74] (OR=3.23, 95% CI 1.10–9.50, $p=0.013$), and Rodriguez et al. [77] ($p=0.032$).

A high comorbidity burden reflects the general health status of the patient and may affect anastomotic healing through various mechanisms, including impaired microcirculation, reduced regenerative capacity of tissues, and altered immune response. Moreover, patients with a high comorbidity index often take multiple medications, some of which (e.g., non-steroidal anti-inflammatory drugs, corticosteroids) can negatively influence healing processes [62, 74].

Tumor-Related Risk Factors. *Tumor Location.* Distal tumor location in the rectum was identified as one of the most significant risk factors for AL in six studies.

Rodriguez et al. [77] found a statistically significant association between rectal tumor location and the risk of AL ($p=0.001$). This association was also confirmed by Zhang et al. [9] ($p=0.007$) and Brisinda et al. [12] ($p=0.006$). Kryzauskas et al. [74] showed that the incidence of AL after rectal resection was 10.7% compared to 5.1% after sigmoid resection ($p<0.05$). Wang et al. [10] established that tumor distance from the anal verge ≤ 5 cm and 5–10 cm were independent risk factors for AL ($p=0.009$ and $p=0.018$, respectively). Polishchuk et al. [1] also confirmed that tumor location 5–10 cm from the anal canal significantly increases the risk of AL ($p=0.021$).

The increased risk of AL in distal tumor locations may be explained by several factors. Technical difficulties in forming a low anastomosis within the confined space of the pelvis increase the risk of anastomotic failure [72]. Additionally, the blood supply to the distal rectum is less abundant compared to the proximal sections, which may predispose the anastomosis to ischemia [15]. Finally, radiotherapy, commonly used in rectal cancer, may negatively affect tissue healing [45].

Tumor Stage and Size. Stage III–IV CRC was associated with an increased risk of AL in the study by Rodriguez et al. [77] (OR=2.71, 95% CI 1.34–5.48, $p=0.005$). Kryzauskas et al. [74] also identified tumor stage T3/T4 as an independent risk factor for AL (OR=2.25, $p=0.017$). Tsalikidis et al. [61] noted in their study that a tumor diameter greater than 3 cm may also increase the risk of AL ($p<0.05$).

Stages III–IV and larger tumor size may increase the risk of AL through several mechanisms. More extensive resections required to remove large tumors can lead to greater anastomotic tension [71]. Moreover, tumors at more advanced stages are often accompanied by systemic metabolic disturbances, which may negatively affect the healing process [86].

Neoadjuvant Therapy. Preoperative chemoradiotherapy was identified as a risk factor for AL in the systematic review and meta-analysis by Dias et al. [64], where the relative risk was 2.16 (95% CI 1.17–4.02, $p<0.05$).

Neoadjuvant therapy potentially impairs anastomotic healing through endothelial damage and tissue fibrosis caused by radiotherapy [41], as well as through suppression of cellular proliferation and collagen synthesis during chemotherapy. The combination of these methods may exacerbate negative effects [44]. However, recent studies have not confirmed an increased risk of AL in CRC patients

undergoing neoadjuvant treatment [39, 51, 58, 85].

Intraoperative Risk Factors. *Type of Surgery.* Emergency surgery was identified as a significant risk factor for AL in two studies. Dias et al. [64] demonstrated that emergency CRC surgeries are associated with an increased risk of AL (OR=1.61, 95% CI 1.26–2.07, $p<0.05$). Awad et al. [87] also confirmed this association in their study ($p=0.043$).

Emergency surgeries increase the risk of anastomotic leak due to the inability to adequately prepare the bowel, leading to higher bacterial contamination at the anastomotic site [75]. Additionally, unstable hemodynamics in emergency situations negatively affect tissue perfusion. Technical aspects of emergency interventions are often less optimal compared to elective procedures [67].

Anastomotic Level and Type. A low anastomotic level was identified as one of the most significant risk factors for AL in four studies. Litchinko et al. [79] noted that a low anastomotic level significantly increases the risk of AL ($p<0.05$). Tsalikidis et al. [61] also confirmed this association ($p<0.05$). Another study [7] demonstrated the relationship between anastomotic height and AL risk: the incidence of AL was 0% at 9 cm and above, 5.2% at 5–8 cm, and 13% at 4 cm or lower from the dentate line ($p=0.006$). Brisinda et al. [12] also found that the mean distance from the anal verge in patients with AL was 71.0 ± 32.0 mm, compared to 89.0 ± 21.0 mm in patients without AL ($p=0.0001$).

The type of anastomosis may also influence the risk of AL. Nordholm-Carstensen et al. [53] reported that stapled anastomosis was associated with a higher risk of AL compared to hand-sewn anastomosis ($p=0.004$).

The higher risk of AL in low anastomoses is due to technical difficulties in forming the anastomosis within the confined pelvic space, which can compromise sealing [73]. Additionally, the distal rectum has a less abundant blood supply, increasing the likelihood of anastomotic ischemia [15]. The stapling technique may traumatize tissues and impair microcirculation along the anastomotic line [40].

Technical Aspects of Surgery. Operation duration was identified as a risk factor for AL in four studies. Zouari et al. [34] found that procedures lasting more than 180 minutes significantly increased the risk of AL ($p=0.04$). Zhou et al. [32] showed that an operation time ≥ 140 minutes was an independent risk factor for AL (OR=5.427, 95% CI 1.355–21.727,

$p < 0.001$). Zarnescu et al. [96] and Litichinko et al. [79] also noted in their reviews that surgeries lasting over 3 hours were associated with a higher risk of AL ($p < 0.05$).

Intraoperative blood loss was associated with an increased risk of AL in the study by Simillis et al. [55], which showed that greater blood loss increased AL risk: for losses >250 – 300 ml, $OR = 2.06$ ($p < 0.001$), and for >400 – 500 ml, $OR = 3.15$ ($p < 0.001$). Tsalikidis et al. [61] also confirmed this relationship ($p < 0.05$).

Anastomotic tension was identified as a risk factor for AL in the study by Ito et al. [13], where tension at the anastomotic line was associated with an increased AL rate (31.3% in the high-tension group vs. 2.2% in the non-tension group, $OR = 6.97$, 95% CI 1.45–33.6, $p = 0.016$).

A narrow pelvis, particularly in men, was also identified as a risk factor for AL in two studies. Yu et al. [38] demonstrated that pelvic dimensions were independent predictors of AL risk ($p < 0.05$). Toyoshima et al. [49] found that a narrow pelvic inlet area ($\leq 10,074$ mm²) was a significant risk factor ($p = 0.012$).

Ligation of arteries (left colic artery and inferior mesenteric artery) [37, 65], as well as multivisceral resections [93], were also reported to affect AL risk.

Surgeon experience may also influence AL risk. Studies by Zarnescu et al. [96] and Wallace et al. [33] confirmed the impact of surgeon experience on AL development risk ($p < 0.05$).

The negative influence of prolonged surgery and blood loss may be attributed to several factors. Lengthy operations are often associated with technical difficulties, increasing the risk of anastomotic failure. Additionally, prolonged anesthesia exposure and hypothermia may negatively impact tissue perfusion. Significant blood loss can lead to hypovolemia and tissue ischemia, which impair anastomotic healing [68, 74].

Anastomotic tension reduces blood supply and increases mechanical stress, while a narrow pelvis complicates anastomosis formation in low resections. Arterial ligation compromises collateral circulation, predisposing the anastomosis to ischemia and subsequent failure [26, 71].

Assessment of Anastomotic Integrity. Lack of intraoperative assessment of anastomotic integrity (air leak test) was identified as a risk factor for AL in the meta-analysis by Kryzauskas et al. [43], which showed that using intraoperative tests significantly reduces the risk of AL ($OR = 0.52$, 95% CI 0.34–0.82, $p < 0.001$).

Lack of anastomotic reinforcement was also associated with an increased

risk of AL in two studies. Balkarov et al. [5] found that the AL rate was 8.3% in the group with additional anastomotic reinforcement compared to 25.5% in the control group without reinforcement ($p = 0.01$). Foppa et al. [80] also showed that using a single-layer transanal reinforcement technique was associated with a lower risk of AL compared to the double-layer technique (6.48% vs. 15.28%, $p = 0.002$).

Intraoperative assessment of anastomotic integrity allows for immediate detection and correction of defects during surgery, significantly reducing the risk of postoperative AL [40]. Reinforcing the anastomosis using various methods (additional sutures, biological glues, fibrin sealants) can improve mechanical strength and sealing, thereby reducing the risk of leakage [30].

Perioperative Risk Factors. Blood Transfusion. Perioperative blood transfusion was identified as a risk factor for AL in two studies. Simpson et al. [57] found that blood transfusion significantly increased the risk of AL ($p < 0.0001$). Zouari et al. [34] also confirmed this association ($p < 0.01$).

The negative impact of blood transfusion on anastomotic healing may be due to its immunomodulatory effects, which can disrupt the normal inflammatory response and regenerative processes. Furthermore, the need for blood transfusion often reflects significant blood loss and hemodynamic instability, which themselves can adversely affect anastomotic healing [22, 50].

Preventive Measures. The absence of a protective stoma was identified as a risk factor for clinically significant AL in the meta-analysis by Phan et al. [28]. The study showed that the formation of a diverting stoma significantly reduced the risk of AL (6.3% vs. 18.3%, $OR = 0.36$, 95% CI 0.24–0.54, $p < 0.00001$).

The absence of transanal drainage (TAD) may also increase the risk of AL, as shown in the systematic review by Akhmetzyanova et al. [6] ($p < 0.05$). However, research results on this topic remain controversial.

The lack of mechanical bowel preparation combined with antibiotic prophylaxis was associated with an increased risk of AL in two studies. Yue et al. [47] found that combined preparation (mechanical bowel preparation + oral antibiotics) significantly reduced the risk of AL compared to mechanical preparation alone ($p = 0.009$). Koskenvuo et al. [48] also confirmed this association ($p < 0.05$).

A protective stoma reduces the risk of clinically significant consequences of AL by diverting intestinal contents proximally

from the anastomosis, which decreases intraluminal pressure and minimizes bacterial contamination of the anastomotic area [25]. TAD may also reduce intraluminal pressure and promote evacuation of contents, potentially decreasing the risk of AL [94]. Mechanical bowel preparation with antibiotic prophylaxis reduces bacterial load in the intestine, which may positively influence anastomotic healing and reduce the risk of infectious complications [78].

According to the study by Carus et al. [19], intraoperative assessment of anastomotic perfusion using indocyanine green fluorescence angiography reduced the incidence of AL by 48%. Identification of inadequate perfusion, observed in 3.4% of cases, prompted changes in surgical strategy, including the formation of a new anastomosis or creation of a protective stoma.

A significant advancement in AL prevention was the development of the RALAR score, which allows prediction of AL risk based on nine independent variables. Although a protective stoma does not reduce the incidence of AL itself, it significantly decreases the severity of the complication, the need for reoperation, and complication-related mortality. The RALAR score enables surgeons to make informed decisions regarding the formation of a protective stoma in high-risk patients, aligning with the modern concept of a personalized surgical approach [70].

It is important to note that many risk factors are interrelated and may potentiate each other's effects. For example, distal tumor location often necessitates low anastomosis, which, combined with male gender and a narrow pelvis, creates a situation of very high AL risk. Similarly, patients with diabetes mellitus often have obesity, creating an unfavorable background for anastomotic healing.

The findings highlight the necessity of an individualized approach to AL prevention. Stratifying patients into risk groups allows for optimization of preoperative preparation, intraoperative strategy, and postoperative management.

Conclusion. This systematic literature review identified key risk factors for AL following surgical treatment of CRC, with an incidence ranging from 2.8% to 24.7%. The most significant risk factors include male gender, age over 65 years, obesity, diabetes mellitus, impaired nutritional status, distal tumor location, low anastomotic level, prolonged surgery (>180 minutes), and significant intraoperative blood loss.

The implementation of the RALAR score has significantly improved the ob-

jective assessment of AL risk, enabling more evidence-based decisions regarding the formation of a protective stoma during surgery.

A comprehensive approach to AL prevention, based on risk stratification and personalized treatment strategies, can substantially reduce the incidence of this complication. This, in turn, will lead to improved treatment outcomes, shorter hospital stays, reduced healthcare costs, and, most importantly, enhanced quality of life for patients undergoing CRC surgery.

The authors declare no conflict of interest in the submitted article.

References

- Polishchuk L.O., Vetshev F.P., Petrenko K.N., [et al.]. Analiz faktorov, vliyayushchikh na nesostoyatel'nost' kolorektal'nykh anastomozov: retrospektivnoe issledovanie [Analysis of factors influencing colorectal anastomotic leakage: a retrospective study]. *Klinicheskaya i eksperimental'naya khirurgiya. Zhurnal imeni akademika B.V. Petrovskogo* [Clinical and Experimental Surgery. Academician B.V. Petrovsky Journal]. 2021; 9(1): 37–44. doi: 10.33029/2308-1198-2021-9-1-37-44 (in Russ.).
- Anuffrieva E.V., Demidov D.A., Chekasina E.S. Proektniy podkhod k organizatsii skrininga kolorektal'nogo raka kak osnova uluchsheniya obshchestvennogo zdorov'ya naseleniya [Project approach to organizing colorectal cancer screening as a basis for improving public health]. *Zdorov'e naseleniya i sreda obitaniya – ZnISO* [Health of Population and Habitat]. 2023; 31(11): 7–14 (In Russ.) doi: 10.35627/2219-5238/2023-31-11-7-14
- Evsyutina Yu.V., Drapkina O.M. Naibolee effektivnye strategii skrininga kolorektal'nogo raka [Most effective colorectal cancer screening strategies]. *Profilakticheskaya meditsina* [Preventive Medicine]. 2019; 22(1): 105–108 (In Russ.). doi: 10.17116/profmed20192201105. (in Russ.)
- Cherkasov M.F., Dmitriev A.V., Groshilin V.S., [et al.]. Nesostoyatel'nost' kolorektal'nogo anastomoz: faktory riska, profilaktika, diagnostika, lechnaya taktika [Colorectal anastomotic leakage: risk factors, prevention, diagnosis, treatment tactics]. *Rossiyskiy zhurnal gastroenterologii, gepatologii, koloproktologii* [Russian Journal of Gastroenterology, Hepatology, Coloproctology]. 2019; 29(2): 27–34 (In Russ.). doi: 10.22416/1382-4376-2019-29-2-27-34.
- Balkarov A.A., Alekseev M.V., Rybakov E.G., [et al.]. Profilaktika nesostoyatel'nosti kolorektal'nogo anastomoz putyom ego ukrepleniya (rezultaty randomizirovannogo issledovaniya) [Prevention of colorectal anastomotic leakage by strengthening the anastomosis (results of a randomized trial)]. *Khirurgiya. Zhurnal im. N.I. Pirogova* [Surgery. N.I. Pirogov Journal]. 2021; (7): 18–23. (In Russ.).
- Ahmetzyanov F.Sh., Egorov V.I., Ruvinsky D.M., [et al.]. Rol' transanal'nogo drenirvaniya pri nizkikh perednikh rezektsiyakh pryamoy kishki [Role of transanal drainage in low anterior resection for rectal cancer]. *Kazanskiy meditsinskiy zhurnal* [Kazan Medical Journal]. 2021; 102(3): 335–34 (In Russ.). doi: 10.17816/KMJ2021-335.
- Darbishgadzhiev Sh.O., Baulin A.A., Ivacheva N.A., [et al.]. Rol' urovnya formirovaniya kolorektal'nogo anastomoz v razvitiy nesostoyatel'nosti i puti uluchsheniya rezultatov khirurgicheskogo lecheniya raka pryamoy kishki [Role of colorectal anastomosis level in the development of leakage and ways to improve surgical treatment outcomes of rectal cancer]. *Vestnik novykh meditsinskikh tekhnologiy* [Bulletin of New Medical Technologies]. 2020; 27(1): 21–25 (In Russ.). doi: 10.24411/1609-2163-2020-16478.
- Sahami S, Bartels S.A., D'Hoore A., et al. A multicentre evaluation of risk factors for anastomotic leakage after restorative proctocolectomy with ileal pouch-anal anastomosis for inflammatory bowel disease. *Journal of Crohn's & Colitis*. 2016; 10 (7): 773–778. doi: 10.1093/ecco-jcc/jjv170.
- Zhang Z, Sun W, Wang J, et al.] A nomogram to predict the risk of colorectal anastomotic leakage combining inflammatory-nutritional and abdominal aorta calcium index. *Frontiers in Surgery*. 2023; 9: 1008448. doi: 10.3389/fsurg.2022.1008448.
- Wang K, Li M, Liu R, et al. Analysis of risk factors for anastomotic leakage after laparoscopic anterior resection of rectal cancer and construction of a nomogram prediction model. *Cancer Management and Research*. 2022; 14: 2243–2252. doi: 10.2147/CMAR.S364875.
- He J, He M, Tang J.H., et al. Anastomotic leak risk factors following colon cancer resection: a systematic review and meta-analysis. *Langenbeck's Archives of Surgery*. 2023; 408 (1): 252. doi: 10.1007/s00423-023-02989-z.
- Brisinda G, Chiarello M.M., Pepe G, et al. Anastomotic leakage in rectal cancer surgery: retrospective analysis of risk factors. *World Journal of Clinical Cases*. 2022; 10 (36): 13321–13336. doi: 10.12998/wjcc.v10.i36.13321.
- Ito R, Matsubara H, Shimizu R, et al. Anastomotic tension "Bridging": a risk factor for anastomotic leakage following low anterior resection. *Surgical Endoscopy*. 2024; 38: 4916–4925. doi: 10.1007/s00464-024-11008-1.
- Gvrtzman R, Livovsky D.M., Tahover E., et al. Anemia can predict the prognosis of colorectal cancer in the pre-operative stage: a retrospective analysis. *World Journal of Surgical Oncology*. 2021; 19: 341. doi: 10.1186/s12957-021-02452-7.
- Rutegård M, Hassmén N, Hemmingsson O, et al. Anterior resection for rectal cancer and visceral blood flow: an explorative study. *Scandinavian Journal of Surgery*. 2016; 105 (2): 78–83. doi: 10.1177/1457496915593692.
- Reudink M, van Dieren M, Bemelman W, et al. Association between intraoperative blood glucose and anastomotic leakage in colorectal surgery. *Journal of Gastrointestinal Surgery*. 2021; 25 (10): 2619–2627. doi: 10.1007/s11605-021-04933-2.
- Paliogiannis P, Fancellu M, Cossu G, et al. Blood cell count indexes as predictors of anastomotic leakage in elective colorectal surgery: a multicenter study on 1432 patients. *World Journal of Surgical Oncology*. 2020; 18: 1. doi: 10.1186/s12957-020-01856-1.
- Siegel R.L., Miller K.D., Fuchs H.E., et al. Cancer statistics, 2022. *CA: A Cancer Journal for Clinicians*. 2022; 72 (1): 7–33. doi: 10.3322/caac.21708.
- Carus T., Pick P. Intraoperative fluorescence angiography in colorectal surgery [Intraoperative Fluoreszenzangiographie in der kolorektalen Chirurgie]. *Der Chirurg: Zeitschrift für alle Gebiete der operativen Medizin*. 2019; 90 (11): 887–890. doi: 10.1007/s00104-019-01042-4.
- Wada H, Tominaga T, Nonaka T, et al. Charlson comorbidity index predicts anastomotic leakage in patients with resected right-sided colon cancer. *Surgery Today*. 2022; 52 (5): 804–811. doi: 10.1007/s00595-022-02472-0.
- White P.C., Hirschfeld J., Milward M.R., et al. Cigarette smoke modifies neutrophil chemotaxis, neutrophil extracellular trap formation and inflammatory response-related gene expression. *Journal of Periodontal Research*. 2018; 53 (4): 525–535. doi: 10.1111/jre.12542.
- Tamini N, Deghi G, Gianotti L, et al. Colon cancer surgery: does preoperative blood transfusion influence short-term postoperative outcomes? *Journal of Investigative Surgery*. 2021; 34 (9): 974–978. doi: 10.1080/08941939.2020.1731634.
- Danaradono E., Hana N., Sahudi S. Hemoglobin level and albumin as a predictive factor for anastomotic leakage following after hemicolectomy: a prospective study for colon cancer // *Journal of Medicinal and Pharmaceutical Chemistry Research*. 2024; 6 (9): 1460–1468. doi: 10.48309/jmpcr.2024.447094.1135.
- Rahbari N.N., Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery*. 2010; 147 (3): 339–351. doi: 10.1016/j.surg.2009.10.012.
- Holmgren K, Häggström J, Haapamäki M.M., et al. Defunctioning stomas may reduce chances of a stoma-free outcome after anterior resection for rectal cancer. *Colorectal Disease*. 2021; 23 (11): 2859–2869. doi: 10.1111/codi.15836.
- Suzuki N, Yoshida S, Tomochika S, et al. Determining the protective characteristics and risk factors for the development of anastomotic leakage after low anterior resection for rectal cancer. *Surgery Today*. 2021; 51 (5): 713–720. doi: 10.1007/s00595-020-02133-0.
- Li S.J., Wang Z.Q., Li Y.J., et al. Diabetes mellitus and risk of anastomotic leakage after esophagectomy: a systematic review and meta-analysis. *Diseases of the Esophagus*. 2017; 30 (6): 1–12. doi: 10.1093/dote/dox006.
- Phan K, Oh L, Ctercteko G, et al. Does a stoma reduce the risk of anastomotic leak and need for re-operation following low anterior resection for rectal cancer: systematic review and meta-analysis of randomized controlled trials. *Journal of Gastrointestinal Oncology*. 2019. Vol. 10, No. 2. P. 179–187. doi: 10.21037/jgo.2018.11.07.
- Karabulut S, Karabulut O, Yalcin A, et al. Does nutritional status affect treatment tolerability, response and survival in metastatic colorectal cancer patients? Results of a prospective multicenter study. *Research Square*. 2020. doi: 10.21203/rs.2.22409/v1.
- Jiang T.Y., Zang L., Dong F., et al. Effect of different reinforcement methods on anastomotic leakage prevention after laparoscopic double anastomosis. *Journal of Surgical Oncology*. 2021; 123 (1): S81–S87. doi: 10.1002/jso.26333.
- Inoue Y, Kawamoto A, Okugawa Y, et al. Efficacy and safety of laparoscopic surgery in elderly patients with colorectal cancer. *Molecular and Clinical Oncology*. 2015; 3(4): 897–901. doi: 10.3892/mco.2015.530.
- Zhou S, Pei W, Li Z, et al. Evaluating the predictive factors for anastomotic leakage after total laparoscopic resection with transrectal natural orifice specimen extraction for colorectal cancer. *Asia-Pacific Journal of Clinical Oncology*. 2020; 16 (6): 326–332. doi: 10.1111/ajco.13372.
- Wallace B, Schuepbach F, Gaukel S, et al. Evidence according to Cochrane systematic reviews on alterable risk factors for anastomotic leakage in colorectal surgery. *Gastroenterology Research and Practice*. 2020; P. 9057963. doi: 10.1155/2020/9057963.

The full version of the bibliography is available from the editors.