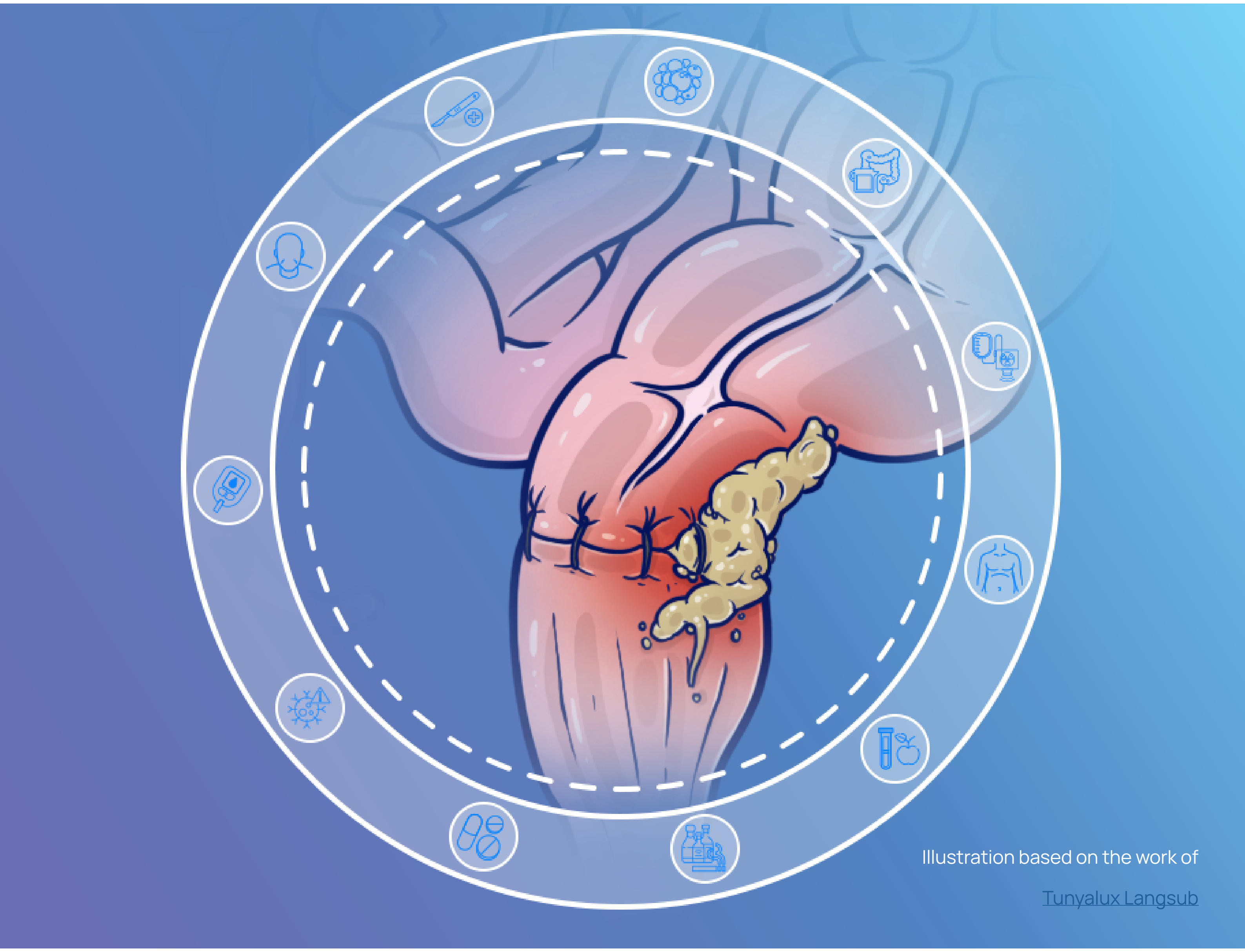

Risk Factors for Anastomotic Leaks in Colorectal Surgery

A Focus on Pre-operative Considerations

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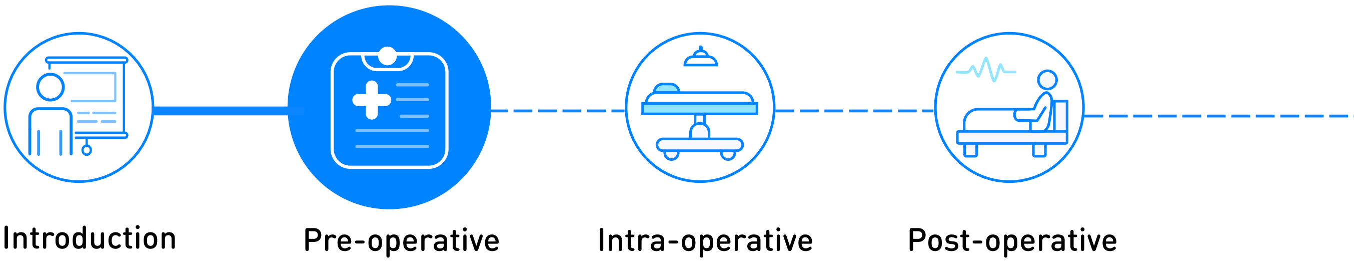
Anastomotic Atlas Series



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INTRODUCTION

Research conducted thus far has identified recurring pre-operative, intra-operative, and post-operative risk factors for anastomotic leaks (AL) after colorectal procedures. In this second article, focus will be directed to pre-operative risk factors that elevate a patient's likelihood of suffering from AL. Consideration of risk factors is relevant in the decision-making process for physicians at various levels of a patient's care – including surgeons. Identifying patients at higher risk may allow for more informed pre-operative patient counselling, planning, and preparation before surgery.

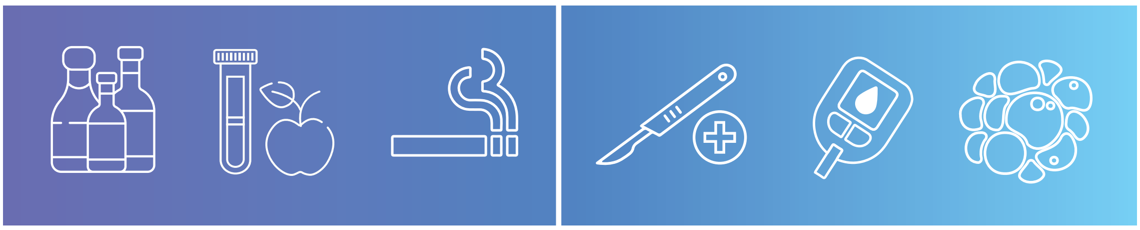
The aim of the following article is to provide an overview of the current literature on modifiable and non-modifiable pre-operative risk factors contributing to the occurrence of AL after colorectal surgery. Such risk factors include alcohol consumption, smoking, and obesity (modifiable), as well as biological sex, age, and co-morbid conditions (non-modifiable), among others. Attention will also briefly be given to the utility of FluidAI's (formally NERv Technology Inc.) Stream™ Platform as a means for early detection of AL, thereby minimizing the devastating impact of leaks, should they occur. Subsequent articles will specifically explore intra-operative and post-operative risk factors in more detail.

Modifiable	Non-Modifiable
Alcohol consumption	Biological sex (male)
Smoking	Age
Obesity	Diabetes
Medications	Elective vs. Emergency surgery
Immunosuppression	Surgery-related risk factors[b]
Nutrition & Hypoalbuminemia	Tumor factors
ASA Physical Status Classification	Pre-operative chemoradiotherapy
Mechanical Bowel Prep & Pre-op	History of radiotherapy
Antibiotics	

Table 1. Modifiable and Non-modifiable Pre-Operative Risk Factors for AL[a] (1–5)

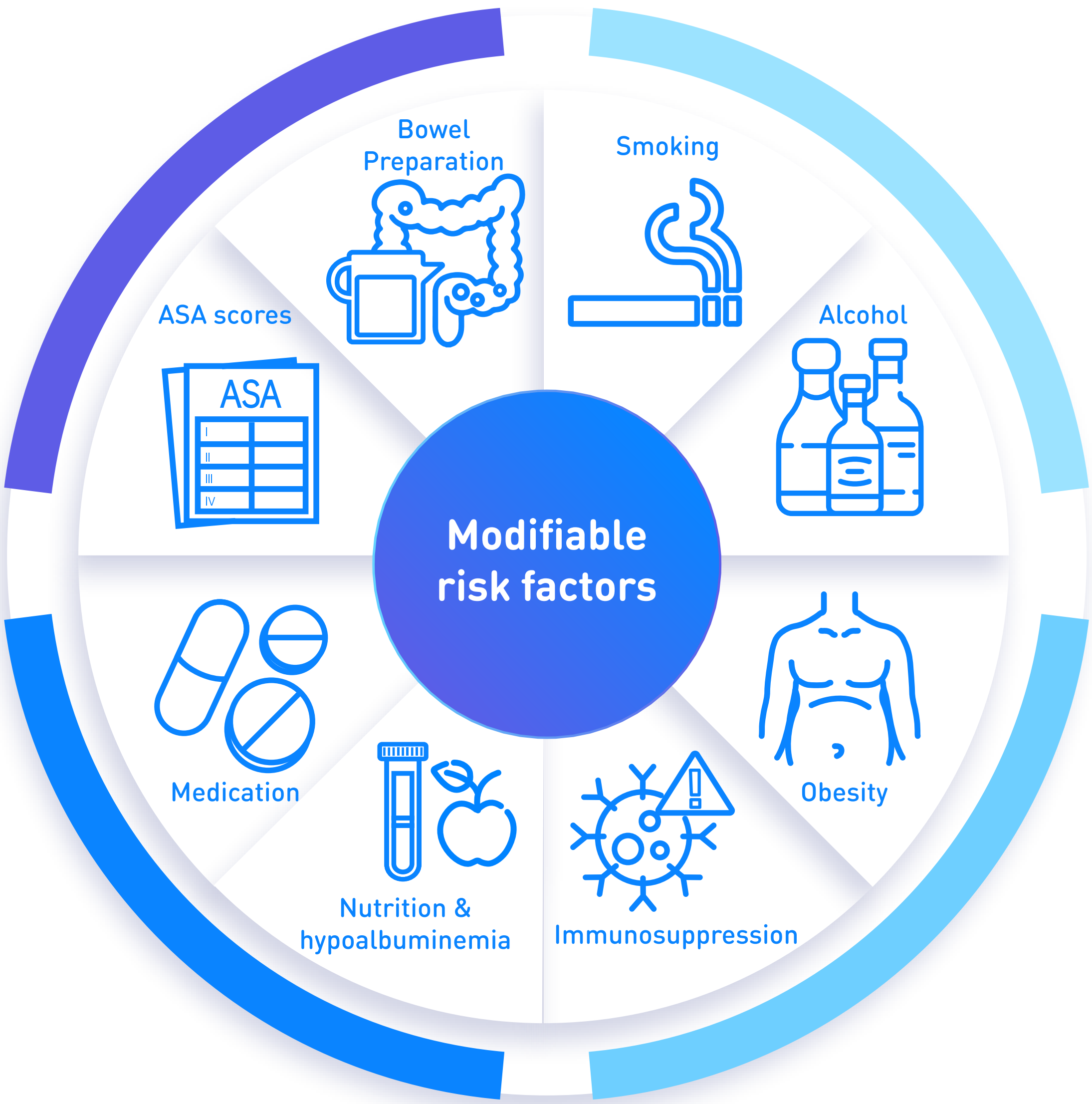
[a] While some risk factors are consistently described in the literature, others are controversial. For completeness and transparency, we include all reported risk factors, noting where controversy has been identified. Ongoing/future research in this area may provide additional clarity about the impact of specific risk factors.

[b] Surgery-related risk factors include the type of resection and anastomosis, proper surgical technique, surgical duration, urgency, and blood transfusion. These factors will be discussed in more detail in the subsequent article, on intra-operative risk factors. (5–7)



Modifiable Risk Factors

As with any significant procedure, the risks associated with colorectal surgery may be increased or decreased in accordance with factors that are modifiable. Given that many of these risks can be mitigated with lifestyle changes, it is critical that a patient's care team explore ways to manage such risks in advance, or (if this is not possible) recognize higher-risk patients and manage the approach to surgery accordingly. This includes considerations about the risk of post-operative complications such as AL, which has shown a significant association with many of the modifiable risk factors explored below.

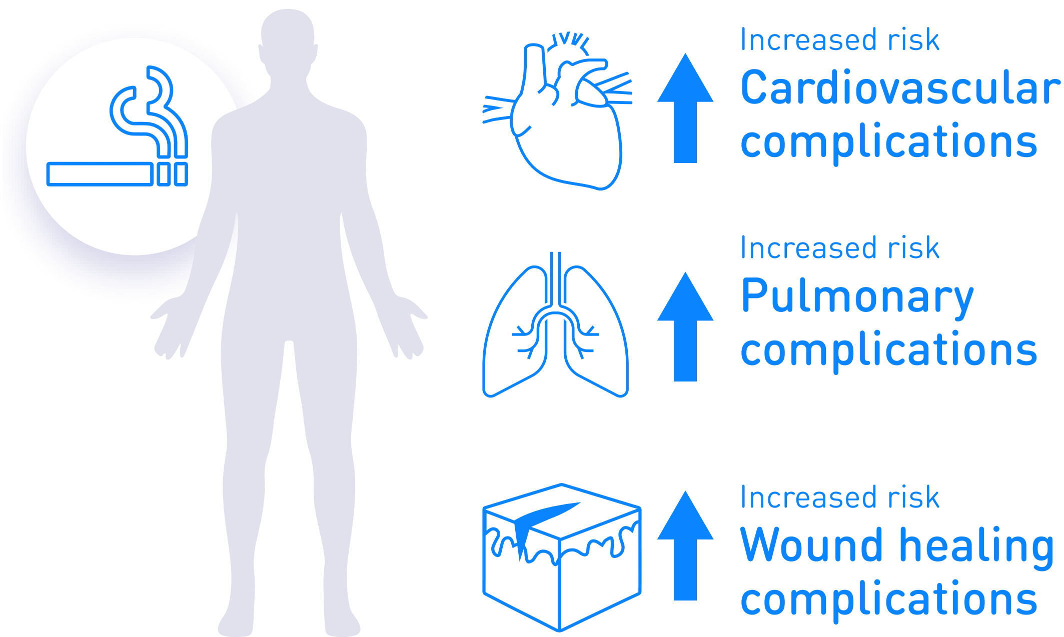


Smoking

Substance use, including alcohol and tobacco, have been found to be risk factors for AL across numerous studies. The factors contributing to increased risk of surgical complications are complex, including other lifestyle factors that may augment the effect of smoking and/or drinking alone.

Smoking is established to have a negative impact on surgical outcomes, regardless of the procedure being performed, with active smoking linked to increased risk of perioperative cardiovascular, pulmonary, and wound healing complications, including infections, anastomotic dehiscence, reintubation, and respiratory failure (8). For these reasons, preoperative smoking cessation is highly recommended for improving postoperative results. The optimal duration of smoking cessation to confer operative benefits remains under study, and is explored in more detail below (9).

Across several studies, smoking has been found to put patients undergoing anterior or low anterior resection at risk for AL. Research conducted by Kruschewski et al. (2007) found that smokers had an increased risk of anastomotic leakage following anterior or low anterior resection (multiple regression analysis; OR = 6.42, 95% CI: 2.68-15.36). In this study, coronary heart disease was also found to be a significant risk factor (OR = 7.79, 95% CI: 2.52-24.08) (10). Of note, smoking is known to have a negative impact on cardiovascular health, and so patients with pre-existing coronary heart disease, who also smoke, are likely at an even greater risk than either health concern alone. Similar conclusions were obtained in work by Bertelsen et al. (2009), in a study which aimed to identify risk factors for clinical AL following anterior resection for rectal cancer (11). These findings were based on a national cohort consisting of 1,495 patients who had curative anterior resection surgery between May 2001 and December 2004. Overall, 11% of patients (n = 163) experienced AL. A significantly higher risk of AL was found in smokers compared to non-smokers (OR = 1.88, 95% CI: 1.02-3.46), once again supporting the link between smoking and this significant post-operative complication.



Numerous other studies, undertaken to explore the association between smoking and AL, have yielded similar conclusions (12–14).

In 2012, Richards et al. evaluated 233 patients (identified from a prospective database) undergoing low anterior resection for benign and malignant disease over a 10-year period at a single surgical unit. In this cohort, the overall anastomotic leak rate was 14% (33/233) (15). On multivariate analysis, current smokers (OR 3.68; 95% CI: 1.38-9.82; P = 0.009) and patients with evidence of metastatic malignant disease (OR 3.43; 95% CI: 1.29-9.13; P = 0.013) were at increased risk of anastomotic leak. The authors concluded that both smoking and the presence of metastatic disease are major risk factors for the development of AL following low anterior resection. It is notable that smoking – a modifiable factor – carries as much, if not more risk, than metastatic disease itself. Furthermore, in a 2015 study conducted by Baucom et al., the effect of smoking on clinical leaks after left-sided anastomoses was evaluated (16). From the sample of 246 patients included in the study, the anastomotic leak rate was 6.5% (n=16). Importantly, a significant difference was found in leak rates between smokers and non-smokers (17% and 5%, respectively), with smokers experiencing an over four times greater chance of leak (OR 4.2, 95% CI: 1.3-13.5, P = 0.02). From these results, smoking was concluded to be a significant risk factor for AL after left colectomy.

Additional work has demonstrated that not only is smoking associated with AL, but also a patient's smoking history (e.g. heavy smoking) confers additional risk. A 2011 publication from Kim et al. utilized univariate analysis to demonstrate that both smoking history and smoking amount were related to the risk of AL, with a heavy smoking history (more than 40 pack-years) an independently significant risk factor for anastomotic complications after low anterior resection in rectal cancer patients (17). Along similar lines, evaluations about the impact of smoking cessation on reducing AL risk have also been conducted. A recent study by Tsai et al. (2022) investigated the optimal duration of smoking cessation to reduce the risk of anastomotic leaks (9). Here, a total of 1,246 patients who underwent curative-intent sphincter-preserving surgery without preventative stoma were enrolled between 2000 and 2012. Using a receiver operating characteristic (ROC) curve, a cut-off value of 10.5 years of smoking cessation was identified. Moreover, on multivariate analysis, current smoking (P = 0.022), as well as former smoking with less than ten years of smoking cessation (OR = 2.725, P = 0.029) were both found to be independently related to the development of anastomotic leakage. Thus, current evidence suggests smoking cessation for less than ten years continues to present risks for AL in patients with mid-to-low rectal cancer undergoing sphincter-preserving surgery. Additional studies completed by other research groups have led to similar conclusions regarding the importance of smoking cessation prior to colorectal surgery (8,16). In a 2016 review, short-term cessation was not found to be effective in reducing risk for anastomotic leaks; a minimum discontinuation of 4-8 weeks, if not longer, was suggested for benefit (18). Importantly, smoking cessation should occur not only prior to surgery, but also during the postoperative period.

Critically, despite approximately 30% of colon cancers warranting a right hemicolectomy (RH), little data existed until this point regarding the impact of smoking in this context. Recently, Badiani et al. (2022) conducted research to better understand the effect of smoking on postoperative complications following RH (19). Here, patients who underwent elective RH for colon cancer between 2016 to 2019 were identified from the ACS-NSQIP (American College of Surgeons National Surgical Quality Improvement Program) database. Of the 5,652 RH patients included, 1,884 (33.3%) identified as smokers. Overall, smoking was found to be a significant risk factor for a variety of serious complications, including higher rate of organ space infection (4.1% vs. 3.1%, P = 0.034), unplanned return to the operating theatre (4.8% vs. 3.7%, P = 0.045), and risk of AL (3.5% vs. 2.1%, P = 0.005). Additionally, smoking was found to be an independent risk factor for wound complications (OR = 1.32; 95% CI: 1.03-1.71; P = 0.032), primary pulmonary complications (OR = 1.50; 95% CI: 1.06-2.13); P = 0.024), and AL (OR = 1.66; 95% CI: 1.19-2.31; P = 0.003). Based on these results, it was concluded that smokers have an increased risk of developing major post-operative complications, compared to non-smokers.

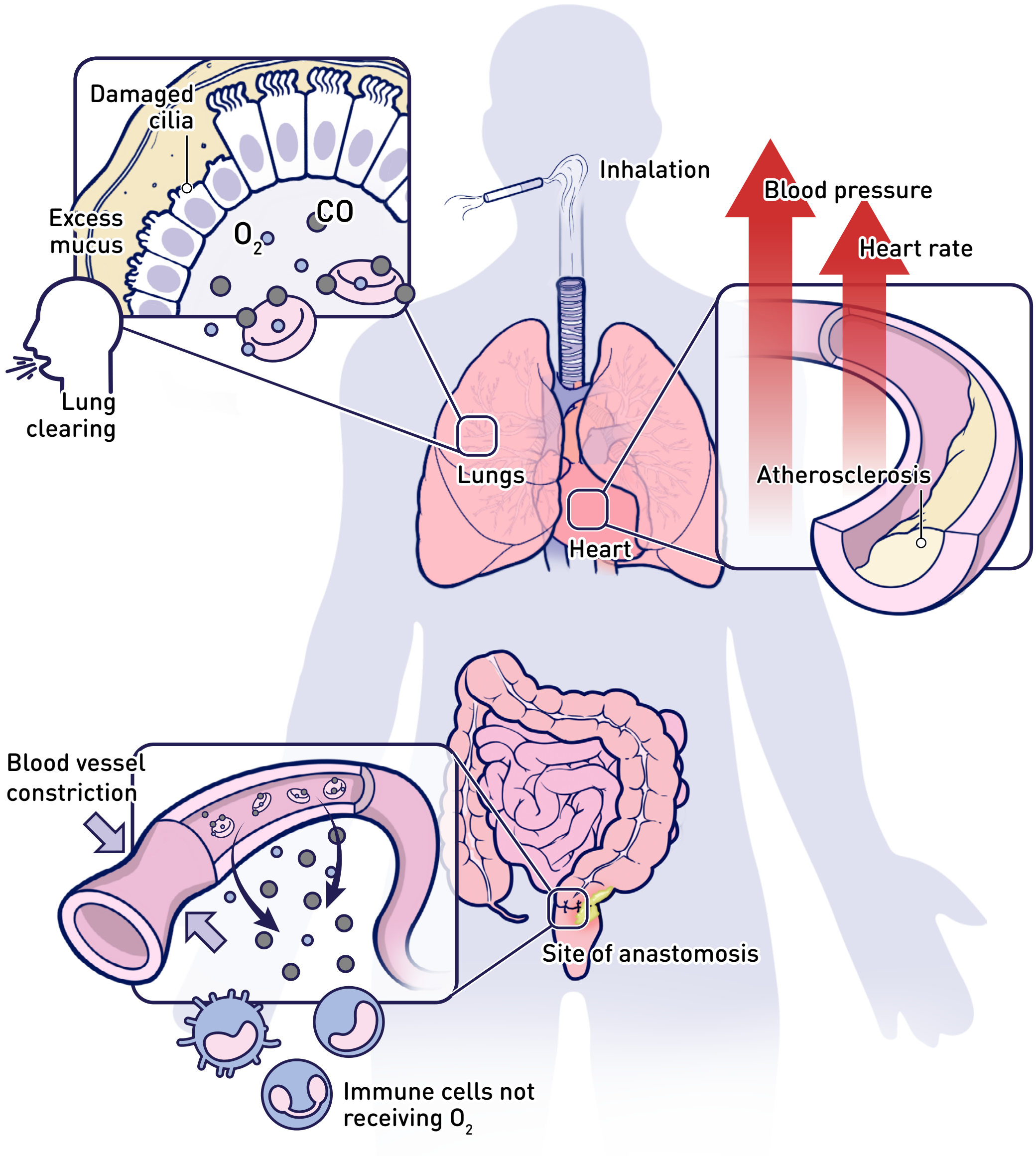


Fig 1. Pathophysiology of smoking in AL patients.

Other studies have focused on multiple lifestyle/concomitant factors that are known to have negative impacts on overall health, including smoking and alcohol consumption (discussed in more detail below). One such early article comes from Sørensen et al. (1999), which focused specifically on the association between AL and smoking and alcohol consumption (20). Based on 333 patients who underwent colonic or rectal resection with anastomosis between 1993 and 1996, the rate of clinical AL was 15.9% (n = 53). Multiple regression showed that smokers, compared with non-smokers, had an increased risk of anastomotic leakage (relative risk (RR) = 3.18 (95% CI: 1.44-7.00), as did alcohol abuse (RR = 7.18 (95% CI: 1.20-43.01). Thus, smoking and alcohol abuse were considered to be important risk factors for anastomotic leakage after colonic and rectal resection.

A 1996 study conducted by Fawcett et al. further supports more recent data exploring the connection between smoking, vascular health, and risk of AL (21). Both smoking and hypertension, which contribute to microvascular disease, were found to be associated with increased incidence of anastomotic dehiscence. Treatment with serotonin antagonists in the perioperative period may be beneficial, to maintain microvascular flow (increased serum serotonin and vessel hypersensitivity to serotonin has been observed in smokers, hypertensives, and after surgery).

In 2020, an analysis from the National Surgical Quality Improvement Program (NSQIP) identified both smoking and hypoalbuminemia as risk factors for AL after proctectomy and ileal pouch anal anastomosis (22). From 910 patients included in this analysis, an overall leak rate of 4.0% (n = 36) was observed. On multivariate analysis, smoking was found to be the only significant risk factor associated with AL (P = 0.0016). Subgroup analysis of patients with preoperative serum albumin levels revealed that low preoperative albumin was a significant risk factor for AL (P = 0.023).

Research has also been conducted to better understand the pathophysiology behind smoking and increased risk for surgical complications, including anastomotic leaks (23). Given the well-established adverse effect of chronic smoking on peripheral vasculature, the negative impact of smoking on rectal mucosal blood flow is posited to play a role. One study measured rectal mucosal blood flow (MBF) in 80 subjects (44 smokers and 36 non-smokers), using laser Doppler flowmetry (23). Results demonstrated that chronic smokers had significantly lower MBF at the posterior and ventral sites of the rectum compared to non-smokers (P = 0.04 and P = 0.03, respectively). Reduced MBF is thought to impair healing following surgery, increasing the risk of complications such as AL. Additional work found that regular smoking was significantly associated with AL (OR = 6.529, P = 0.007), with the authors suggesting that vascular ischemia from nicotine-induced vasoconstriction and microthromboses, along with carbon monoxide-induced cellular hypoxia, may impair anastomotic circulation in smokers (24).

In summary, across numerous studies, smoking has been shown to be an important risk factor for anastomotic leaks. While any reduction in smoking is a major win for patients and providers, most evidence points to significant risk reduction only when smoking cessation has taken place over months to years. Patients with any recent smoking history should thus be monitored carefully for AL following surgery, and additional risk factors should be considered which may further elevate their likelihood of complications, alongside smoking.

Study name	Design	Sample size	Conclusion
Kruschewski et al. (2007)	Multiple regression analysis	N/A	Smoking is known to have a negative impact on cardiovascular health, and so patients with pre-existing coronary heart disease, who also smoke, are likely at an even greater risk than either health concern alone
Bertelsen et al. (2009)	National co-hort study	1,495 patients	Smokers have a significantly higher risk of clinical anastomotic leakage following anterior resection for rectal cancer.
Richards et al. (2012)	Prospective database study	233 patients	Both smoking and the presence of metastatic disease are major risk factors for the development of AL following low anterior resection.
Baucom et al. (2015)	Retrospective cohort study	246 patients	Smoking is a significant risk factor for anastomotic leakage after left colectomy.
Kim et al. (2011	Univariate analysis	154 patients	Heavy smoking history is an independently significant risk factor for anastomotic complications after low anterior resection in rectal cancer patients.
Tsai et al. (2022)	Prospective cohort study	1246 patients	Current and former smoking with less than ten years of smoking cessation are independently related to the development of anastomotic leakage. The optimal duration of smoking cessation to reduce the risk of anastomotic leaks is 10.5 years.

Table 2. Summary of findings for smoking as a risk factor

Alcohol Consumption

Similar to smoking, excessive alcohol consumption has been consistently found to be associated with increased risk for anastomotic leaks. In an early study completed by Mäkelä et al. (2003), patients who consumed alcohol were at a significantly elevated risk for AL, compared to those who abstained (OR = 6.19; 95% CI: 2.39-15.99; P = 0.001) (25). Unfortunately, more detailed patient information, including the amount of alcohol consumption patients were reporting, was not provided. A subsequent study completed by Nickelsen et al. (2005) also found a relationship between alcohol consumption and AL (26). It is important to note that statistically significant results were only obtained for those with heavy alcohol consumption (> 60g/day; OR = 2.48; 95% CI: 1.07-5.77). Those with no/low alcohol consumption were not found to be at increased risk (OR = 0.81; 95% CI: 0.50-1.31).

In a chart review of the American College of Surgeons NSQIP, patient cases (completed January 2003 – April 2006) were reviewed for evidence of anastomotic leaks for 12 months following the operating date (27). Patients were tracked for up to 10 years to determine survival, while assessing morbidity, mortality, and cost for patients who experienced a leak compared to those who did not. Multivariable regression found that AL was associated with alcohol abuse (OR = 3.7; 95% CI: 2.6-381.4, P = 0.007), among other factors such as congestive heart failure and peripheral vascular disease. Further, in a prospective study completed by Jannasch et al. (2015), alcohol history was found to be related to risk of anastomotic leaks (28). Overall, 17,867 patients with histopathologically confirmed rectal carcinoma and primary anastomosis were included. Multivariate analysis found that alcohol history was a risk factor for AL (OR = 1.628; 95% CI: 1.233-2.150, P = 0.001), although no information was provided specifying the criteria for 'alcohol history.' The authors note that lifestyle factors, such as alcohol consumption and smoking, may be biased, depending on the reliability of patient reports. A systematic review completed by McDermott et al. (2015) found that heavy alcohol intake (>21 units weekly) was associated with AL (RR = 7.18; 95% CI: 1.2-43) (29).

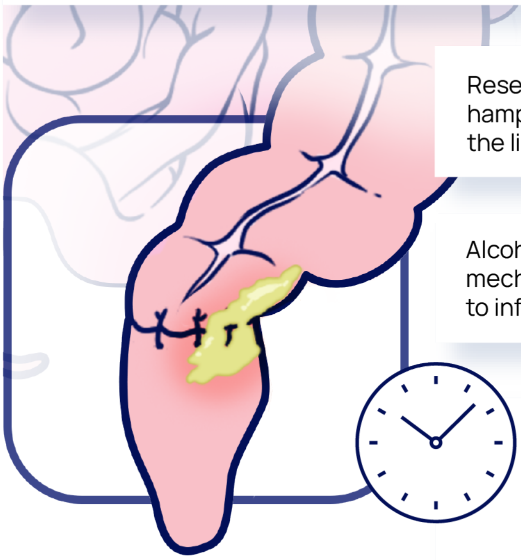
Contrary to other findings, a study by Bertelsen et al. (2010) investigating risk factors for AL after anterior resection for rectal cancer found alcohol consumption was not associated with AL (11). Other factors that were found to be insignificant in this investigation include preoperative weight loss, BMI, ASA score, and self-reported physical fitness. Results were insignificant for even the highest threshold of alcohol consumption, greater than 35 units per week (OR = 1.37; 95% CI: 0.51-3.67). The discrepancy between these results and other research may be explained by biased patient reporting.

Overall, the evidence is strongly suggestive that alcohol – a modifiable lifestyle factor – is significantly associated with anastomotic leakages in colorectal surgery. Varied findings and levels of clinical significance may be attributable to the challenge of obtaining lifestyle data from patients, who may under- or overestimate their alcohol consumption. Additionally, some studies failed to define quantities of alcohol consumed, at times only grouping patients into binary categories (alcohol – yes/no). All this considered, due to the known detrimental effects on alcohol for surgical outcomes and health overall, encouraging patients to decrease alcohol consumption (particularly for heavy drinkers) is advised to minimize AL risk.

Pathophysiology of Alcohol Consumption and Impaired Wound Healing

The consumption of alcohol has been linked to several negative impacts on the body, such as hindered wound healing and heightened vulnerability to infections. Prolonged alcohol consumption can weaken the immune system, disrupt the formation of new blood vessels (angiogenesis), and interfere with the synthesis of collagen. These processes are vital for effective wound healing.

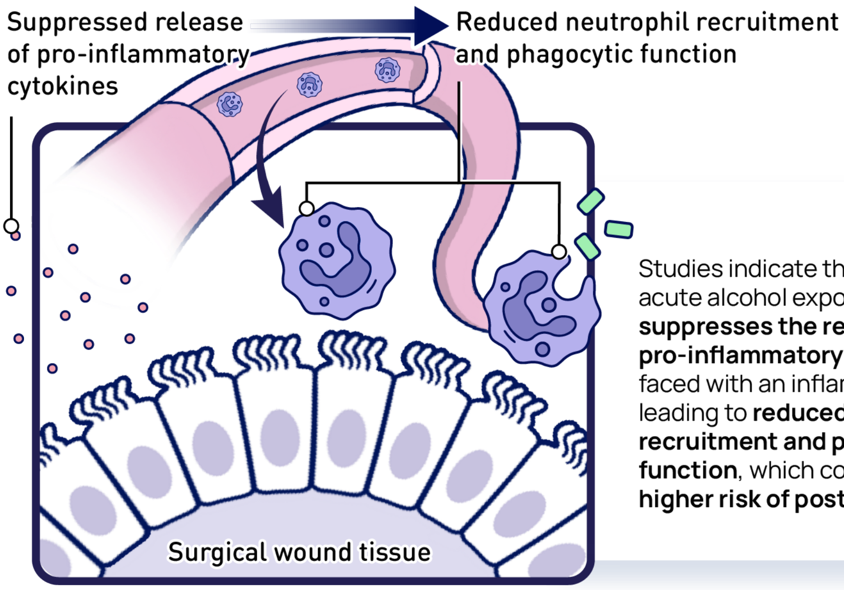
Furthermore, alcohol abuse can lead to nutritional deficiencies, particularly in essential nutrients like vitamin C, which is crucial for collagen synthesis and tissue repair.



Research has demonstrated that alcohol exposure hampers the healing process of wounds and increases the likelihood of infection.

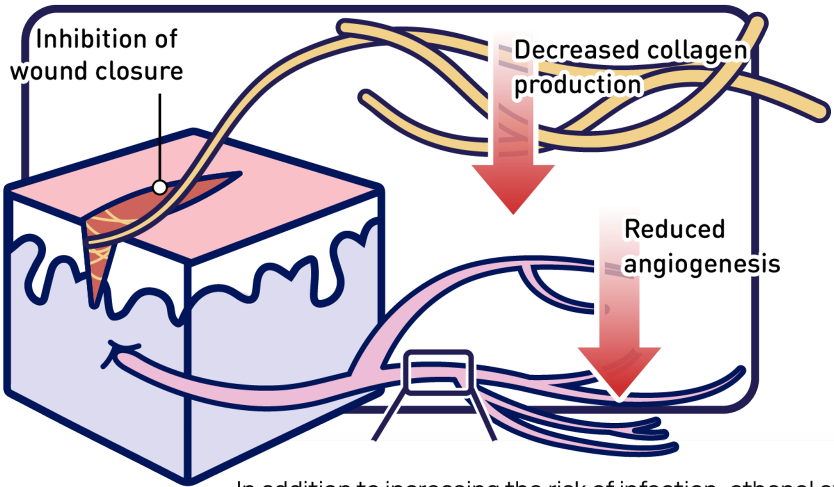
Alcohol exposure weakens the body's defense mechanisms, making individuals more susceptible to infections at the site of the surgical wound.

The effects of alcohol on the body's ability to defend itself are strongly influenced by factors such as the **duration** and **amount** of alcohol consumed, as well as the **timing of exposure** and **withdrawal** from alcohol.



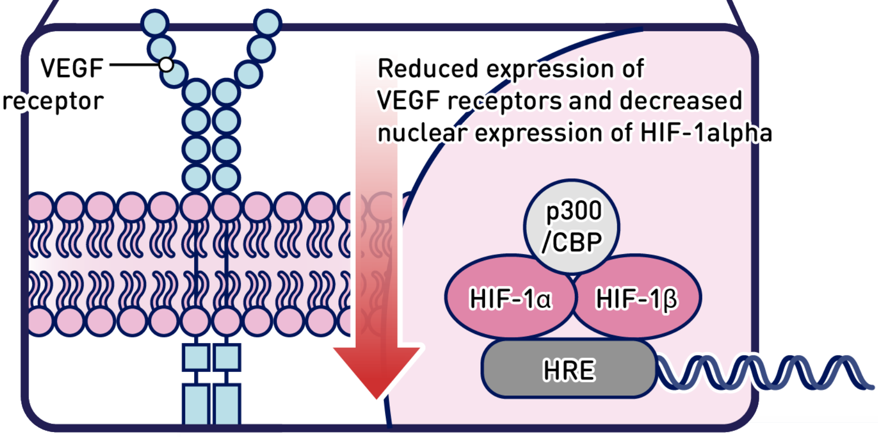
Studies indicate that short-term acute alcohol exposure generally **suppresses the release of pro-inflammatory cytokines** when faced with an inflammatory challenge, leading to **reduced neutrophil recruitment and phagocytic function**, which correlates with a **higher risk of post-injury infection.**

Fig 2. Pathophysiology of alcohol consumption and impaired wound healing



In addition to increasing the risk of infection, ethanol exposure also **affects the proliferative phase of wound healing.** Animal studies have shown that a single dose of alcohol, resulting in blood alcohol levels just above the legal limit in most states in the US, **disrupts various aspects of healing,** including **re-epithelialization, angiogenesis** (formation of new blood vessels)**, collagen production,** and **wound closure.**

Acute ethanol exposure also influences connective tissue restoration by **decreasing collagen production** and **altering the balance of proteases at the wound site**.



The most significant impact is observed in wound angiogenesis, which can be reduced by up to 61% after a single exposure to ethanol. This decrease in angiogenesis is associated with **reduced expression of VEGF receptors** and **decreased nuclear expression of HIF-1alpha** in endothelial cells.

Alcohol exposure leads to **decreased vascularity**, **increased hypoxia**, and **oxidative stress** in the wound area.

Study name	Design	Odds Ratio (OR)	Sample size	Conclusion
Mäkelä et al. (2003)	Early study	**OR** = 6.19; 95% CI: 2.39-15.99; P = 0.001	N/A	Alcohol consumption is associated with increased risk for AL.
Nickelsen et al. (2005)	Subsequent study	**Heavy alcohol consumption: OR** = 2.48; 95% CI: 1.07-5.77. **No/ low alcohol consumption: OR** = 0.81; 95% CI: 0.50-1.31	N/A	Heavy alcohol consumption is associated with increased risk for AL.
Jannasch et al. (2015)	Prospective study	**OR** = 1.628; 95% CI: 1.233-2.150, P = 0.001	N/A	Alcohol history is associated with increased risk for AL.
McDermott et al. (2015)	Systematic review	**OR** = 7.18; 95% CI: 1.2-43	N/A	Heavy alcohol intake is associated with increased risk for AL.
Bertelsen et al. (2010)	Investigation of risk factors	**OR** = 1.37; 95% CI: 0.51-3.67	154 patients	No significant association between alcohol consumption and AL.

Table 3. Summary of findings for alcohol consumption as a risk factor

Obesity

It is well-established that obesity is a risk factor for numerous health conditions, and also adds risk in the surgical setting (30). In the context of colorectal surgery, obesity has been cited as a risk factor, particularly for left-sided anastomotic leaks (30). Risk for other postoperative complications is also elevated for obese patients, including wound dehiscence and incisional site herniation (30). Early reviews of the literature found strong evidence for a link between obesity and anastomotic leaks. Retrospective analyses demonstrated that obesity was a strong risk factor for leaks in those with low-level anastomosis; in some cases, a two-fold increased risk over non-obese patients (31). In one retrospective review, Benoist et al. found a weakly significant difference in leak rates between obese and nonobese patients (P = 0.05) (32). Other studies have found increased odds ratios for risk of anastomotic leak in obese patients, ranging from 1.5 to 2.32, depending on BMI (33). However, in multivariate analyses, these results were found not to be significant, despite other groups finding significant results using similar statistical methods (OR = 9; P= 0.016) (34).

Other studies have found less evidence that it is obesity itself conferring risk, and rather, that low-level rectal anastomosis is the major risk factor (35). Through retrospective reviews of patient records, several research groups have found no significant association between obesity and AL (20,36,37). It is important to note that a number of these early publications did not provide full descriptions of their study populations and/or data, including incomplete research definitions of 'obesity,' and proportion of overweight/obese patients in study cohorts.

More recent work has presented a similarly inconclusive picture of the exact impact of obesity on anastomotic leak risk. In 2013, a retrospective analysis carried out by Kang et al. (n = 72,055 patients) did not find a higher incidence of obesity or diabetes mellitus in those who suffered a leak (38). Another retrospective study from Piecuch et al. (2015) also did not find a significant relationship between leak and BMI based on logistic regression (OR = 0.58; 95% CI 0.22-1.53; P = 0.27) (39). In a large meta-analysis, based on thirty-one studies and 32,953 patients, those with obesity were found to have a significant increase in risk for AL (Western study group: OR = 1.57, 95% CI 1.01-2.44; Asian study group: OR=1.58, 95% CI 1.07-2.32) (40). Importantly, this increase was only found to be clinically significant in rectal anastomotic subgroups, agreeing with previous findings.

Obesity is associated with various parameters that may themselves better predict a patient's risk for AL, rather than BMI. In 2020, Chen et al. investigated such parameters, in 589 rectal cancer patients who underwent anterior resection of the rectum (41). Results found that sex, neoadjuvant chemotherapy, operation time, and anastomosis level from the anal verge were all risk factors ($P < 0.05$). The level of serum triglycerides was found to be an independent risk factor for AL (OR = 2.95; P = 0.024), however other obesity-associated parameters were not (including BMI; visceral, subcutaneous, and total fat area; and serum cholesterol ($P > 0.05$)).

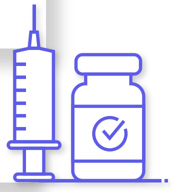
Overall, results remain mixed regarding obesity and risk for anastomotic leak. While in some cases high BMI (greater than 30kg/m2) has been identified as an independent risk factor for AL, in other cases, this has not been the case (as described above) (5,42–44). It does appear that particularly for very low rectal anastomoses, obesity increases the likelihood of a leak (potentially due to tension at the anastomotic site) (5). In other cases, it appears that factors commonly associated with obesity may be driving the relationship between high BMI and AL (31, 42). Regardless, controlled weight loss should be encouraged by clinical teams for any obese patient, including healthy lifestyle choices that decrease overall risk for postoperative complications and a range of health issues known to be associated with obesity.

Study name	Design	Odds Ratio (OR)	Sample size	Conclusion
Various, 2023	Literature Review	**OR** = N/A	N/A	Obesity is a risk factor for numerous health conditions, and also adds risk in the surgical setting. Obesity has been cited as a risk factor, particularly for left-sided anastomotic leaks. Risk for other postoperative complications is also elevated for obese patients, including wound dehiscence and incisional site herniation. Early reviews of the literature found strong evidence for a link between obesity and anastomotic leaks.
Benoist et al., 2000	Retrospective Analysis	**OR = 1.5-2.32**	N/A	Obesity was found to be a strong risk factor for leaks in those with low-level anastomosis, with a two-fold increased risk over non-obese patients in some cases.
Various, early publications	Retrospective Analysis	**OR** = N/A	N/A	Some studies found no significant association between obesity and anastomotic leak.
Kang et al., 2013	Retrospective Analysis	**OR** = 7.18; 95% CI: 1.2-43	72,055 patients	No higher incidence of obesity or diabetes mellitus was found in those who suffered a leak.
Piecuch et al., 2015	Retrospective Analysis	**OR** = 0.58	N/A	No significant relationship was found between leak and BMI.

Table 4. Summary of findings for obesity as a risk factor

Medications

	NSAIDs	STEROIDS
Examples	Ibuprofen, Naproxen, Aspirin	Prednisone, Dexamethasone
Mechanism of action	**NSAIDs** work by inhibiting the activity of cyclooxygenase enzymes (COX-1 and COX-2), which are responsible for the production of prostaglandins, substances that mediate inflammation and pain.	**Steroids** work by decreasing the activity of the immune system and reducing the production of substances that trigger inflammatory responses.
Uses	Pain relief, reducing inflammation, fever reduction. Often used for conditions like headaches, arthritis, menstrual cramps, minor injuries.	More severe inflammatory conditions like autoimmune diseases (e.g., lupus, rheumatoid arthritis), asthma, severe allergies, inflammatory bowel diseases.



In addition to substances such as cigarettes and alcohol, certain medications may also play a role in the development of leaks following colorectal surgery. Most research has focused on two classes of prescription medications, and their role in the risk of AL: steroids and anti-inflammatory drugs.

In 2012, a prospective study was carried out by Slieker et al., investigating the risk of AL in 259 patients with left-sided colorectal anastomoses (45). Importantly, patients involved in this study were prescribed corticosteroids either as a long-term medication, or perioperatively for the prevention of postoperative pulmonary complications. Overall, the incidence of AL was 7.3%, with rates significantly higher in those on long-term corticosteroids (50%) or on perioperative steroids (19%). For those with pulmonary comorbidities, the rate of AL was also significantly elevated (22.6%). While this compelling evidence suggests medications can increase rate of anastomotic leaks, the role of underlying pulmonary disease must be considered.

In a 2014 systematic review by Eriksen et al., corticosteroids were found to increase the risk of anastomotic leaks, with an overall AL rate of 6.77% (95% CI: 5.48-9.06) in patients using corticosteroids, compared to 3.26% (95% CI: 2.94-3.58) in those not on the medication (46). This was based on 12 studies, with a total of 9,564 patients. Further evidence supporting a role for corticosteroids in increased risk of AL comes from Jina & Singh (2019), which found an odds ratio of 4.857 ($P < 0.001$) for leaks in patients on corticosteroid therapy, compared to those not using the medication (47).

Conflicting evidence was found in a Danish cohort study by Ostenfeld et al. (2015), which looked at the relationship between AL and preadmission glucocorticoids (48). Of the overall 18,190 patients with colon cancer, 6.5% experienced an AL. Glucocorticoid use as a whole did not lead to an increase in risk of AL (6.9% among those who had never used; OR=1.05; 95% CI: 0.89-1.23). The method of drug administration (oral, inhaled, intestinal-acting) also did not significantly affect the risk of leakage. Similarly, for those with rectal cancer (n = 5,284 patients), glucocorticoid use slightly elevated the risk (14.6% vs 12.8% among never-users; OR 1.36; 95% CI: 1.08-1.72), and results did not significantly differ by route of administration. Based on these results, the authors suggested that a moderate risk may be associated with anastomotic leak (particularly after rectal cancer resection), but absolute risk difference were small and the clinical impact may be limited.

Perioperative use of nonsteroidal anti-inflammatory drugs (NSAIDs) is also associated with a risk of AL. Given that recovery guidelines are increasingly suggesting opioid-sparing medications be used whenever possible following colorectal surgery, post-operative NSAID use is a common occurrence. It is thus important to be aware of the potential impact on risk of AL from this class of medications.

In 2012, a cohort study was completed evaluating the effect of postoperative use of NSAIDs on AL requiring reoperation following colorectal surgery (49). Data for this study was drawn from a prospective clinical database and electronic medical records. Overall, NSAID use (specifically, diclofenac and ibuprofen) was found to be significantly associated with AL rate, compared with controls (12.8% and 8.2% vs. 5.1%; P < 0.001). After multivariate logistic regression analysis, only diclofenac treatment was found to be a risk factor for leakage (OR 7.2; 95% CI: 3.8-13.4, P < 0.001). Based on these results, the authors suggested that medications like diclofenac should be used with caution, but that large-scale, randomized control trials were (at the time) urgently needed to further understand the relationship between NSAIDs and anastomotic leak risk.

While most investigations consider NSAID use broadly, some studies further refine by

> **... certain medications**, even within the same drug class, may put patients at higher risk of post-operative complications than others.

NSAID type, recognizing that different drugs may confer different risk. Modasi et al. (2018) performed a systematic review whereby AL rate was assessed following NSAID use for colonic or rectal anastomoses in the post-operative care period (50). Interestingly, while use of post-operative NSAID was associated with an overall increased risk of AL (OR = 1.58; 95% CI: 1.23-2.03; P = 0.0003), non-selective NSAIDs were associated with increased risk specifically (OR = 1.79; 95% CI: 1.47-2.18; P < 0.00001), while selective NSAIDs were not. In this particular review, the non-selective NSAID, diclofenac, was associated with increased risk of leak (OR = 2.79; 95% CI: 1.96-3.96; P < 0.00001), while ketorolac was not (OR = 1.36; 95% CI: 0.89-2.06; P = 0.16). These results suggest that certain medications, even within the same drug class, may put patients at higher risk of post-operative complications than others.

A further meta-analysis conducted by Huang et al. (2018) found that, across all studies, there was a significantly lower rate of anastomotic dehiscence in patients not taking NSAIDs (pooled OR = 2.00; 95% CI: 1.48-2.71; P < 0.00001) (51). However, when analyses were completed using only randomized control trials, similar dehiscence rates were found between groups (P = 0.17). In subgroup analysis, non-selective NSAIDs were associated with higher risk of leaks (pooled OR = 2.02; 95% CI: 1.62-2.50; $P < 0.00001$), but there was no significant difference in incidence of leaks between patients not taking NSAIDs, and those on selective NSAIDs ($P = 0.05$). Another recent systematic review and meta-analysis by Jamjittrong et al. (2019) found that there was a significant association between NSAID use and anastomotic leakage (OR = 1.73; 95% CI: 1.31-2.29; $P < 0.0001$) (52). Included in this analysis were twenty-four studies with a total of 31,877 patients. Subgroup analyses revealed that non-selective NSAIDs (but not COX-2 selective NSAIDs) were significantly associated with risk of AL. No significant subgroup difference was found between selective and non-selective NSAIDs. Chen et al. (2022) recently examined postsurgical ketorolac administration, and its impact on anastomotic leak rate (53). In this meta-analysis, which included seven studies and 400,822 patients, an increased risk was observed, though this did not stand up to statistical significance (OR = 1.41; 95% CI: 0.81-2.49; $P = 0.23$). Subgroup analyses in case-control and retrospective cohort studies did reveal a significantly increased risk of leak ($P < 0.05$).

...**more evidence** is necessary to continue elucidating the role of NSAIDs as a risk factor for post-operative leaks

Recognizing the many physiological effects that NSAIDs can have, including impacts on wound healing, Hakkarainen et al. (2015) evaluated the relationship between postoperative NSAID administration and anastomotic complications (54). These results, published in a report from Washington State's Surgical Care and Outcomes Assessment Program (SCOAP) found that NSAIDs were associated with a increased risk of leak, which was isolated to nonelective colorectal surgery (12.3% in the NSAID group vs. 8.3% in the non-NSAID group, OR = 1.70; 95% CI: 1.11-2.68). This was after risk adjustment and based on a retrospective cohort study of 13,082 patients undergoing either bariatric or colorectal surgery.

Some work investigating the impact of NSAIDs on AL leak rate has found conflicting results. In 2020, Arron et al. performed a systematic review and meta-analysis (55). In this study, which included a cohort of 10,868 patients, overall anastomotic leak rate was not increased in patients using NSAIDs for postoperative analgesia compared to non-users (RR = 1.23; 95% CI: 0.81-1.86; $P = 0.34$). Even after stratification for low anterior resections, the effect remained non-significant. When further analyses examined non-selective NSAIDs versus COX-2 selective NSAIDs, again, neither drug sub-type was found to significantly increase the risk of AL ($P = 0.19$, $P = 0.26$).

Given that other drugs taken concurrently can bias risk assessment, Rushfeldt et al. (2016) carried out a study specifically investigating risk of AL associated with NSAIDs and steroids used perioperatively (56). Based on a total of 376 patients included in the study, the rate of AL in the cohort was 15.7%. When adjusted for age, sex, and multivariable propensity scores, OR for leak were found to be: 1.07 ($P = 0.92$)

for ketorolac, 1.63 (P = 0.31) for diclofenac, and 0.41 (P = 0.19) for dexamethasone. Regular use of steroids conferred an OR of 7.57 (P = 0.009). Other factors included within the study such as malignancy, use of a vasopressor, and blood transfusions were similarly found to have a significant risk of leaks. As such, the study authors concluded that factors beyond perioperative drugs may be more crucial for surgical teams to consider, given their modest impact on AL risk.

Overall, conclusions about NSAID use and risk of anastomotic leak remain mixed. As outlined in an article by Lee & Fiore Jr. (2021), all evidence points to more benefits from NSAID use as post-operative pain control, than downsides from risk of anastomotic leak (57). Given the unclear association between NSAID use and AL, more evidence is necessary to continue elucidating the role of NSAIDs as a risk factor for post-operative leaks. It is important to note that patients on long-term corticosteroids and/or anti-inflammatory drugs would have been prescribed these medications to treat another pre-existing condition, which could also contribute to the development of conditions favouring post-operative complications, such as an AL.

Study name	Design	Odds Ratio (OR)	Sample size
Slieker et al. (2012)	Prospective study	**OR** = 50% (long-term) or 19% (perioperative)	259 patients
Eriksen et al. (2014)	Systematic review	**OR** = 6.77% (95% CI: 5.48-9.06)	9,564 patients across 12 studies
Jina & Singh (2019)	Retrospective Analysis	**OR** = 4.857 (P < 0.001)	N/A
Ostenfeld et al. (2015)	Cohort study	**OR** = 1.05 (95% CI: 0.89-1.23) (colon cancer) or 1.36 (95% CI: 1.08-1.72) (rectal cancer)	18,190 patients (colon cancer), 5,284 patients (rectal cancer)
Klein et al. (2012)	Cohort study	**OR** = 7.2 (95% CI: 3.8-13.4, P < 0.001)	N/A
Modasi et al. (2018)	Systematic review	**OR** = 1.79 (95% CI: 1.47-2.18; P < 0.00001)	N/A

Table 5. Summary of findings for medications as a risk factor

Immunosuppression

When considering preoperative risks for patients undergoing colorectal surgery, immunosuppression is a critical factor that must not be overlooked. Not only is prevalence of immunosuppression for surgical patients nearly double (~5%) that of the average citizen in the United States, but this number is expected to continue to rise as survival outcomes for immunosuppressed patients improve (58,59).

In 2014, Snieder & Davids explored the effects of chemotherapy, radiation, and immunosuppression on the integrity of intestinal anastomosis (60). As discussed above, corticosteroids (which have a significant impact on immunosuppression), are recognized to confer risk for AL in colorectal surgery. Snider & Davids further explored other agents that result in suppression of the immune system, including immunomodulators (e.g. azathioprine and 6-mercaptopurine) and biologic agents (e.g. infliximab). In a retrospective study involving 417 patients with bowel anastomoses for Crohn's disease, there was no significant difference in risk between patients on immunomodulators versus not (10% versus 14%, P = 0.263), though use of corticosteroids was once again found to be a risk factor (P = 0.007) (61). Similarly, in a retrospective analysis of 518 patients undergoing elective laparoscopic bowel resection (142 of which were on preoperative infliximab), no difference was found in the rate of AL between patients on the biologic agent versus not (2.1% with infliximab vs. 1.3% without, P = 0.81) (62).

In addition to corticosteroids, immunomodulators, and biologic agents, long-term immunosuppression in organ transplant recipients has also been considered. Given the chronic nature of these immunosuppression regimen, and the impact this may have on wound healing, studies have been conducted to explore the potential elevation in risk presented for AL. Despite limited clinical data on the use of newer immunosuppressive agents (mTOR inhibitors, such as sirolimus and everolimus), animal studies have investigated the impact on AL. A study in a rat model found that everolimus decreased ileal and colonic anastomotic breaking strength in a dose-dependent manner, up to 73% at the highest dose, 3 mg/kg/24h ($P < 0.05$) (63). When examined histologically, anastomoses of rats treated with the mTOR inhibitor demonstrated signs of decreased anastomotic healing including less collagen deposition and hydroxyproline content. In a follow-up study conducted in the same rat model, no significant changes in anastomotic strength were observed if everolimus administration was withheld in the early postoperative period (first 2-3 postoperative days), suggesting that mTOR inhibitors have the greatest impact on the early, proliferative phase of wound healing (64). Further experimental evidence exists to suggest that other immunosuppressants may slow wound healing (and by extension, increase the risk of AL), including mycophenolate mofetil, cyclosporin A, and tacrolimus (65–67). Other treatments, including recent chemotherapy, antiangiogenic and antimitotic agents, have been suggested to impact AL risk via impaired wound healing, though direct evidence linking these agents and AL in human patients remains lacking (29).

In 2016, Yamamoto et al. conducted a retrospective, multicentre study to identify risk factors for complications following ileocolonic resection for Crohn's disease, focusing specifically on preoperative immunosuppression and biologic therapy (68). Based on data from 231 patients across three countries (Japan, Brazil, Italy), neither immunosuppression nor biologic therapy prior to surgery was found to be significantly associated with complications, including anastomotic leak. That same year, Thomas & Margolin published an article exploring various considerations in the management of anastomotic leaks, including immunosuppression (3). Importantly, they point out the challenges for assessing this risk factor, noting that because colorectal anastomoses are frequently carried out in patients with diseases requiring immunosuppressive therapy (who may also be sicker than the average patient, e.g., IBD), it is difficult to tease apart the role of immunosuppression itself from other patient characteristics that play into AL risk. Though corticosteroids are well-recognized as a risk factor, other immunosuppressive drugs have not been studied extensively enough to provide definitive conclusions. Even for those which have been studied (as discussed above), results have been mixed.

Given this conflicting data in the literature, and often pivotal role immunosuppressive agents play in managing pre-existing conditions patients present to surgeons with, some research has begun to emerge that explores the impact of chronic immunosuppression on outcomes of colorectal surgery. El Hechi et al. (2020) examined the Colectomy-Targeted ACS-NSQIP database for patients who underwent emergent colectomies, dividing patients into those using immunosuppressants (IMS) versus those with no immunosuppression use (NIS) (69). Out of the total 17,707 patients who underwent an emergent colectomy, 15,422 were NIS, and 2,285 were IMS. After patients were propensity-score matched on demographics, comorbidities, preoperative laboratory values, and operative variables, a total of 2,882 patients were included for analyses (1,441 NIS, 1,441 IMS). Though other complications were found to be significantly elevated in patients with immunosuppression, rates of anastomotic leaks were not significantly different between the two groups ($P = 0.13$). Similarly, other wound infections were not significantly elevated in those receiving immunosuppression (superficial, deep, and organ/space surgical site infection: $P = 1$, $P = 0.61$, and $P = 0.41$, respectively).

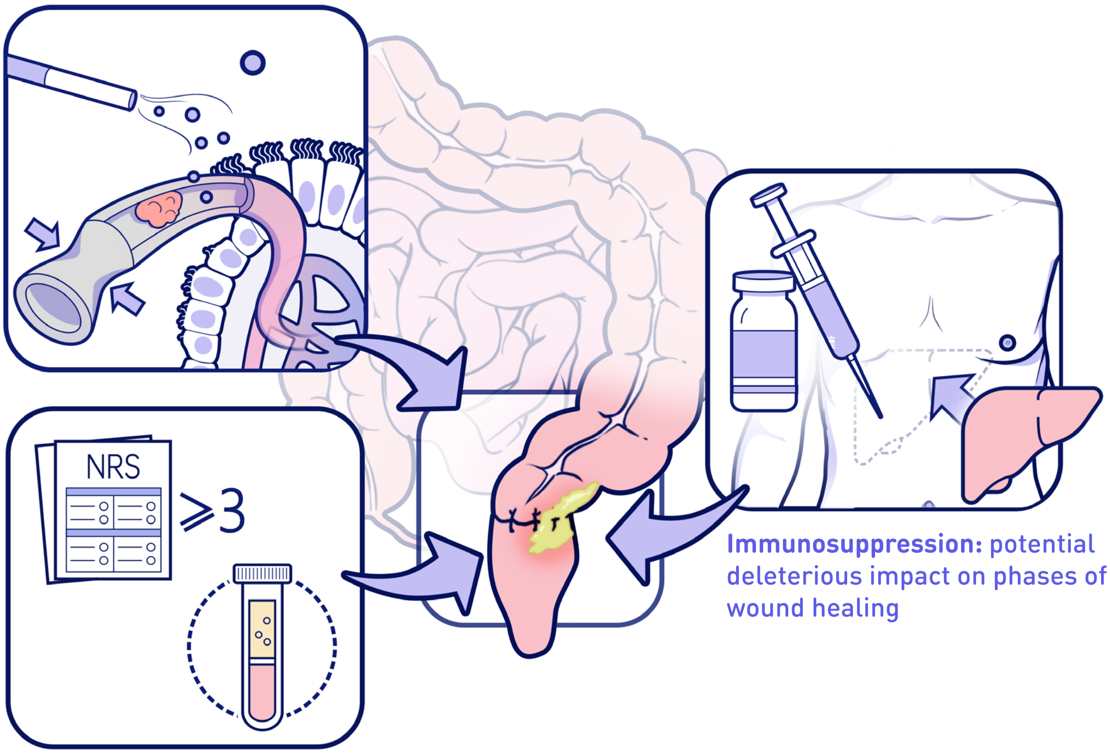


Fig 3. Pathophysiology of certain modifiable risk factors in AL patients

Study name	Design	Sample size	Conclusion
Snieder & Davids (2014)	Prospective study	417 patients	No significant difference in the risk of anastomotic leak (AL) between patients on immunomodulators and those not on immunomodulators. Corticosteroids were found to be a risk factor for AL.
Eriksen et al. (2014)	Retrospective Analysis	518 patients	No difference in the rate of AL between patients on the biologic agent (infliximab) and those not on the biologic agent.
Jina & Singh (2019)	Animal study	N/A	Everolimus (mTOR inhibitor) decreased ileal and colonic anastomotic breaking strength and impaired anastomotic healing.

Study name	Design	Sample size	Conclusion
Yamamoto et al. (2016)	Cohort study	231 patients	Preoperative immunosuppression and biologic therapy were not significantly associated with complications, including anastomotic leak.
El Hechi et al. (2020)	Cohort study	2,882 patients	Rates of anastomotic leaks were not significantly different between patients with immunosuppression and those without. Other wound infections were also not significantly elevated in patients receiving immunosuppression.

Table 6. Summary of findings for immunosuppression as a risk factor

Nutrition and Hypoalbuminemia

Given the impact of nutrition (and malnutrition) on processes throughout the body – including those relevant to postoperative complications (e.g. wound healing), it is not surprising that associations have been found between malnutrition and anastomotic leaks. Alongside nutritional deficits more broadly, specific physiological outcomes such as hypoalbuminemia have been observed as particularly important biomarkers for AL risk.

Research conducted by Kang et al. (2013) found that, within 72,000 rectal resections, preoperative weight loss and malnutrition (OR = 2.81; 95% CI: 2.32-3.40) and fluid and electrolyte disturbances (OR = 1.79; 95% CI: 1.58-2.03), conferred an increased risk for AL (38). Shortly thereafter, Kwag et al. (2014) identified poor nutrition as an independent risk factor for postoperative morbidity, in patients undergoing surgery for colorectal cancer (70). In this study, 352 patients (enrolled prospectively) had nutritional risk screening (NRS) scores calculated on admission, alongside other clinical characteristics (e.g., tumor status, surgical procedure, etc.). Those at nutritional risk (based on NRS score) were significantly more likely to experience postoperative complications, including anastomotic leakage (P = 0.027), as well as wound infection (P = 0.01). A follow-up study carried out by Lee et al. (2018) aimed at further evaluating the association between NRS scores and AL again found significant results (71). Here, retrospective reviews of data from rectal cancer surgeries found that high NRS scores (increased nutritional risk) were an independent risk factor for AL (OR = 2.044; 95% CI: 1.085-3.851).

Albumin remains a gold standard for preoperative markers of nutrition, and thus, is an important parameter to explore when understanding risks for anastomotic leaks. In a prospective observational, quality-improvement study by Sameer M.D. et al. (2018), a cohort of 100 patients undergoing small and large bowel resection was included (72). Uni- and multivariate analyses identified several factors that were significantly associated with AL risk, including serum albumin <= 3.0 gm/dl and serum pre-albumin <= 20mg/dl. This study also found that pre-albumin was a better indicator of AL risk compared to albumin (P = 0.002), suggesting that pre-albumin may be a better marker to use when assessing nutritional status of patients, as it relates to risk for anastomotic leaks. More recent research from Xu & Kong (2019) further clarifies the role of malnutrition-related factors, and how these contribute to elevated risk for anastomotic leakage in the context of surgery for rectal cancer (73). Based on perioperative clinical data from 382 patients, multivariate analysis revealed that low postoperative albumin (P = 0.044) was a significant independent risk factor for postoperative AL. This suggests that monitoring patient albumin levels both prior to and following surgery may be valuable in discerning nutritional status and risk for leakage. Further, in a NSQIP investigation carried out in 2020, subgroup analysis for the 543 patients with available preoperative serum albumin levels revealed that low albumin levels prior to surgery were significant associated with risk for AL (P = 0.023) (22).

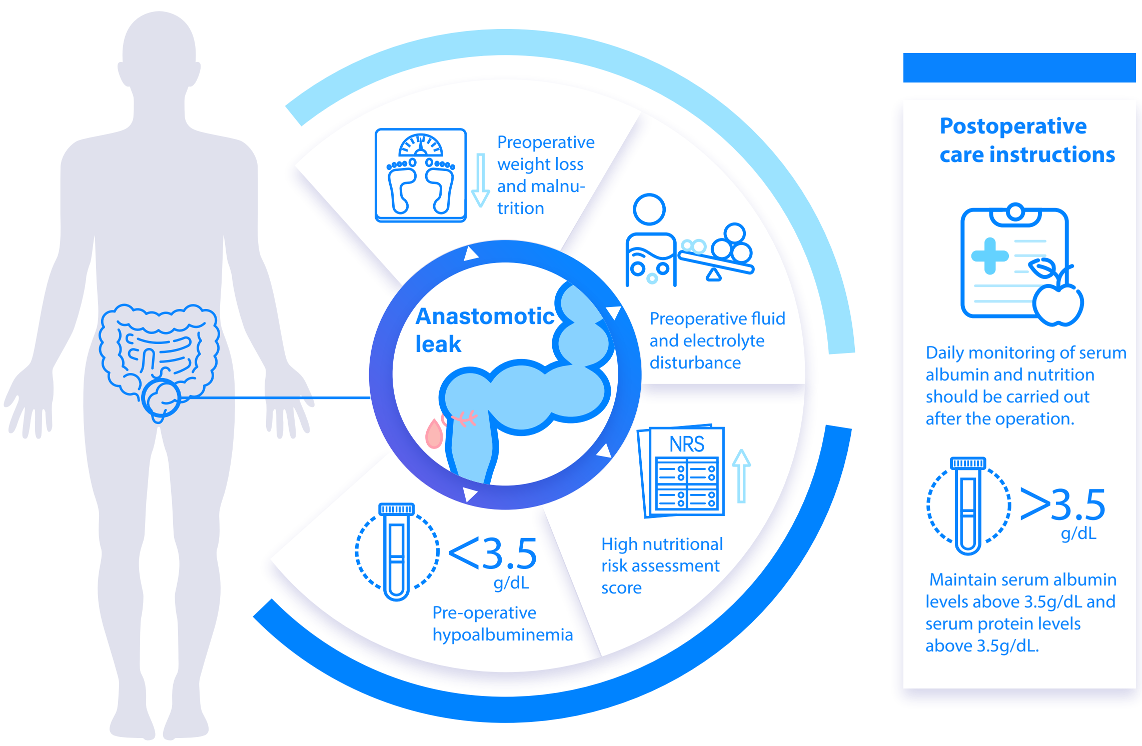


Fig 4. Figure caption

In 2008, a prospective review of patient and operative characteristics that contribute to anastomotic leaks was undertaken, in a cohort of 672 patients (74). Here, several variables were found to be significant risks for AL in colorectal resection, including baseline albumin levels less than 3.5 g/dL (P = 0.04). Other risk factors discussed previously in this article (or to follow) were also identified, such as male sex (P = 0.03) and steroid use at the time of surgery (OR = 3.85; 95% CI: 1.24-11.93; P = 0.02). A subsequent retrospective audit of anastomotic leaks in 1,246 patients (137 of which experienced a leak) also found that albumin levels less than 3.5 g/dL to be an independent risk factor, as were factors including anemia, hypotension, use of inotropes, and blood transfusion (75). These findings were confirmed once again in 2017 by Anandan et al., in a cohort of 112 patients (pre-operative serum albumin <3.5 g/dL significantly associated with leaks; P = 0.0418), and later by Awad et al. (2021) (P = 0.015) (76,77).

Other research has assessed not only the impact of serum albumin on risk for AL, but also how monitoring albumin levels may be beneficial for detecting leaks. Shimura et al. (2018) enrolled 200 colorectal cancer patients undergoing curative laparoscopic surgery, of which 11 cases (5.6%) experienced a leak (78). Here, there was no difference in preoperative serum albumin levels between the leakage group and non-anastomotic leakage group, though postoperative serum albumin levels were significantly lower in those patients with an AL. On multivariate analysis, lower average serum albumin levels on postoperative days 1 and 3 were found to be independent risk factors for anastomotic leakage (OR = 7.53; 95% CI: 1.60-55.80; P = 0.0095). This suggests that daily monitoring of postoperative serum albumin levels may help determine which patients are at greatest risk of developing an anastomotic leak.

> ...lower average serum albumin on **postoperative days 1 and 3** were found to be independent risk factors of anastomotic leakage

Additional work has focused not only on passively assessing the impact of nutritional status (including pre-albumin/albumin), but also evaluating how nutritional interventions may help reduce risk for AL. Tian et al. (2020) assessed whether early enteral nutrition (EEN) could reduce the risk of recurrent leakage in colorectal cancer surgery (79). Here, 12 out of a total of 133 patients experienced recurrent leakage in the EEN group, compared to 28 cases (40%) in patients receiving a standard postoperative nutritional protocol. This suggests that optimizing nutrition in the postoperative period may be beneficial for reducing risk of recurrent leaks.

Overall, the evidence available thus far strongly supports an association between pre-, peri-, and postoperative hypoalbuminemia (a key marker for malnutrition) and the risk of anastomotic leaks following colorectal surgery. Given albumin's key physiological functions, including binding and transport of solutes, platelet inhibition, antithrombosis, and maintenance of colloid pressure, it is well-established that hypoalbuminemia has a deleterious effect on wound healing in colorectal surgery (among other surgical procedures) (80,81). Thus, a focus on both pre- and postoperative nutritional protocols that maintain albumin levels above 3.5 g/dL should be a priority in preventing anastomotic leaks, among other complications.

...the evidence available thus far strongly supports an association between **pre-, peri-, and postoperative hypoalbuminemia**, and the risk of anastomotic leaks following colorectal surgery.

American Society of Anesthesiologist (ASA) Physical Status Classification

The ASA physical status examination is used by anesthesiologists to classify the preoperative physical condition of surgical patients. The scale ranges from 1 (healthy patient) to 5 (patient not likely to survive 24 hours). As might be expected, ASA scores have been found to be associated with risk for anastomotic leakages, with higher ASA scores related to higher risk. Multiple factors are taken into account when assigning an ASA classification level, including smoking status, alcohol consumption, BMI, diabetes mellitus, hypertension, and pulmonary conditions (82). Other factors are also considered for pediatric or obstetric cases. Notably, many of the factors that elevate an ASA grade have also been discussed throughout this article as risk factors for anastomotic leak. Unsurprisingly, research has conclusively shown a strong association between higher ASA scores, and increased risk for AL.

In 2013, Tan et al. (2013) completed a

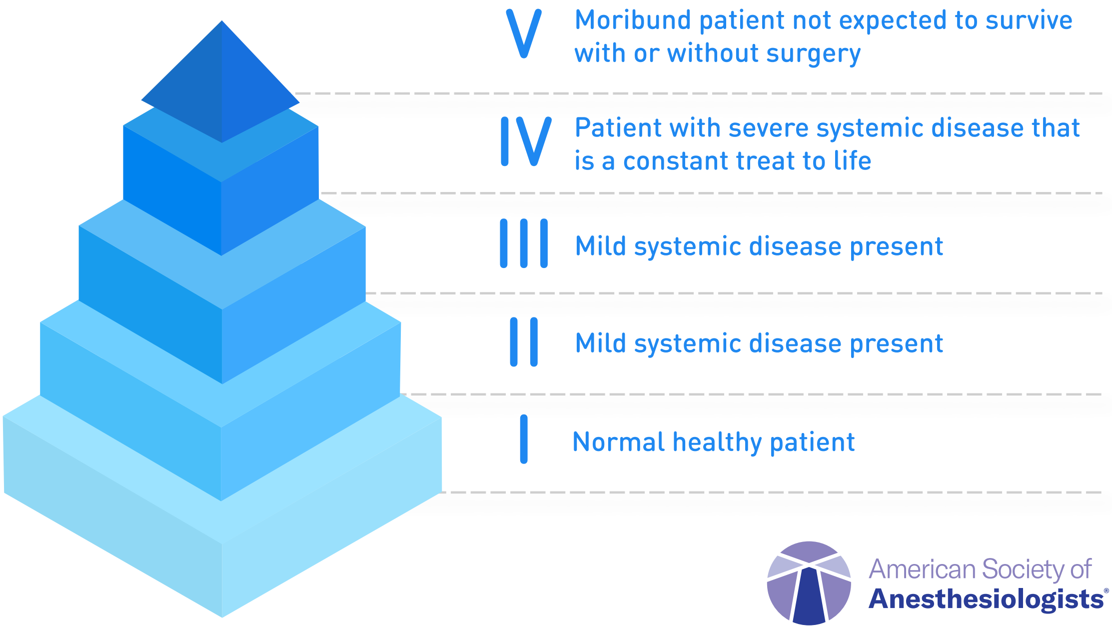


Fig 5. American Society of Anesthesiologist (ASA) Physical Status Classification Score Scale

retrospective study (n = 505 patients), in which a significant association was found between AL and ASA score (OR = 2.99; 95% CI: 1.345-6.670; P = 0.007) (83). Once matched for age, BMI, and Charlson comorbidity index (CCI) on logistic regression, higher ASA scores were independently related to increased risk for leaks (higher ASA scores were independently related to increased risk for leaks, when compared to combined lower ASA scores (ASA I and II) cohort. OR(steroids) = 14.35, P < 0.01; OR(ASA_III v I-II) = 2.02, P = 0.18; OR(ASA_IV vI-II) = 8.45, P = 0.03). In a study by Park et al. (2018), which looked at the influence of ASA score on a range of postoperative complications after laparoscopic colorectal surgery, results demonstrated that rates of complications did indeed increase with ASA scores (84). As with a previous study that found higher ASA scores were a risk factor for AL, ASA scores of 3 or above were an independent risk factor for complications such as leaks (85). Similarly, Jina & Singh (2019) and Kryzauskas et al. (2020) found that ASA grade III or IV conferred a significant risk for anastomotic leaks, with odds ratios of 3.607 and 10.54, respectively (47,86). These findings were based on multivariable analysis performed on data from 900 patients who underwent sigmoid or rectal resection for left-sided colorectal carcinoma. Most recently, Sripathi et al. (2022) provided a comprehensive report that summarized the current agreement regarding a positive association between ASA scores and anastomotic leaks, whereby ASA grades of 3 or above have been shown to be a key risk factor for AL (87–90).

In summary, higher ASA scores have consistently been shown to confer a higher risk for patients experiencing postoperative complications, including anastomotic leaks. Clinical teams should be aware of a patient's ASA grade, and provide careful monitoring for anastomotic leaks for those evaluated at grade III or above.

Mechanical Bowel Preparation and Pre-operative Antibiotics

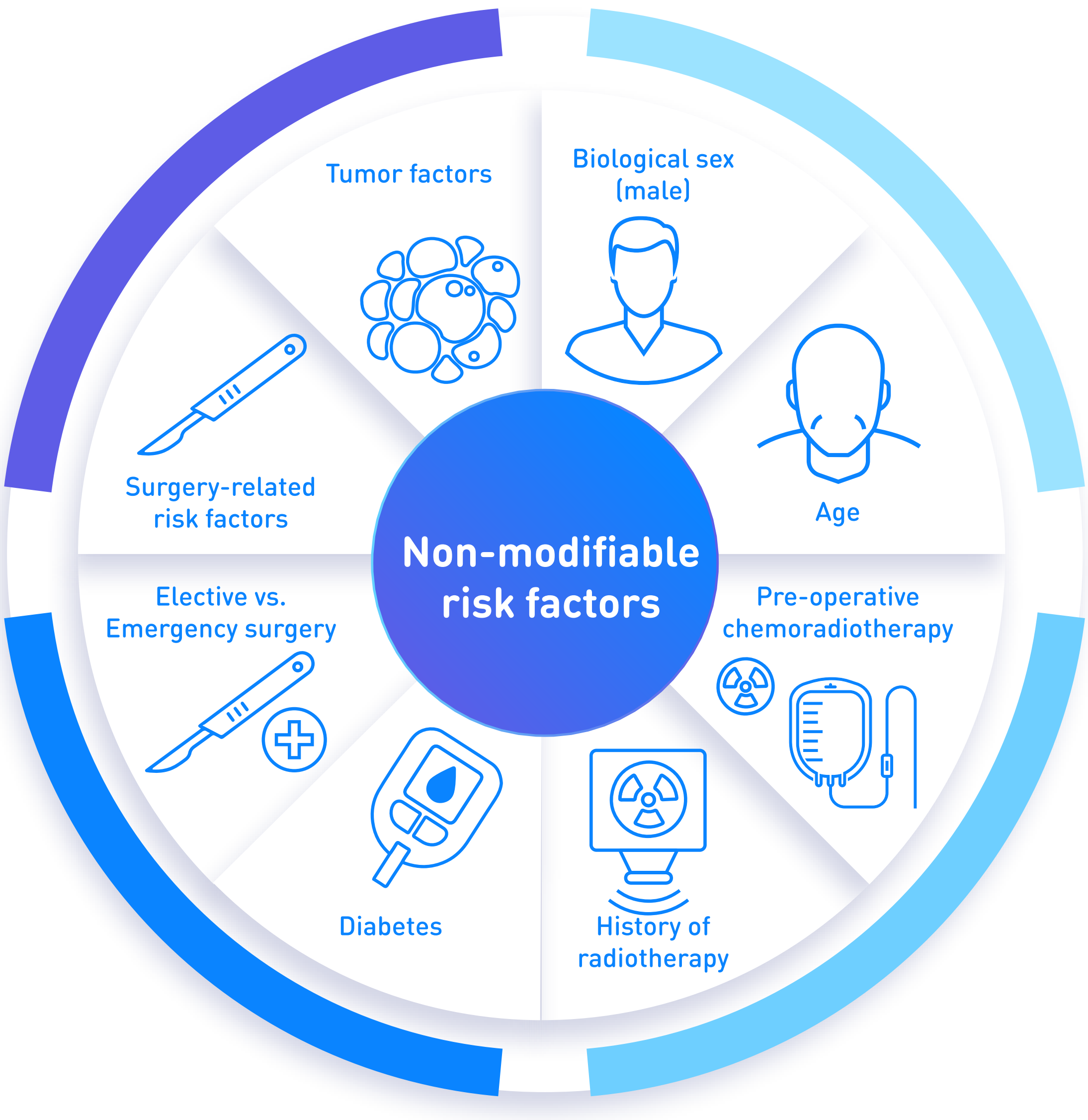
Mechanical bowel preparation (MBP) has traditionally been used to decrease the colon's stool burden, improve visualization during intraoperative endoscopy, and to ease the introduction of stapling devices. MBP is unpleasant for patients and has not been shown, on its own, to reduce rates of AL (29,91). In a study by Contant et al. (2008), a multicentre randomized trial was carried out with 1,431 patients (92). Overall, no significant difference was found in anastomotic leak rate between patients who received mechanical bowel preparation versus those who did not (difference: 0-6%, 95% CI: 1.7%-2.9%, P = 0.69). Additional randomized control trials have similarly found no advantage to including MBP in a patient's preoperative preparation, to reduce risk of AL (93–95). In a systematic review by Güenaga et al. (2011), which involved over 5,000 patients, again, no evidence was found to support MBP, either orally or by enema (96). While one study did find that there was a lower morbidity rate with MBP, no difference in AL rate was found between patients receiving MBP and those who were not (97). There is some variation in the literature regarding the usefulness of MBP, which could be attributable to the lack of standardization of MBP types among surgeons (91). Given all of the currently available evidence, though MBP may be useful for other aspects of surgery (e.g., facilitating endoscopy or stapler insertion), it does not appear to make a meaningful difference in patients' anastomotic leak risk.

> ...only **oral antibiotics** confer any benefit when used alone, and combination with MBP does not provide any additional advantage

Broad spectrum antibiotics are routinely administered intravenously before elective and emergency colorectal surgery (29). The goal of using pre-operative antibiotics is to reduce post-operative infections. Some surgeons in the United States use non-absorbable oral antibiotics, including Tobramycin and Amphotericin B, to perform selective decontamination of the digestive tract (SDD), reducing AL rates from 7.4% to 3.3% (29). According to the American College of Surgeons National Surgical Quality Improvement database (NSQIP), using MBP along with preoperative oral antibiotics lowered the rate of AL from 5.7% to 2.8% (91). Based on these findings, it was concluded that neither oral antibiotics nor MBP alone independently lowers the rate of AL. Later studies using the same NSQIP database demonstrated that only oral antibiotics confer any benefit when used alone, and combination with MBP does not provide any additional advantage (91,98,99).

Non-Modifiable Risk Factors

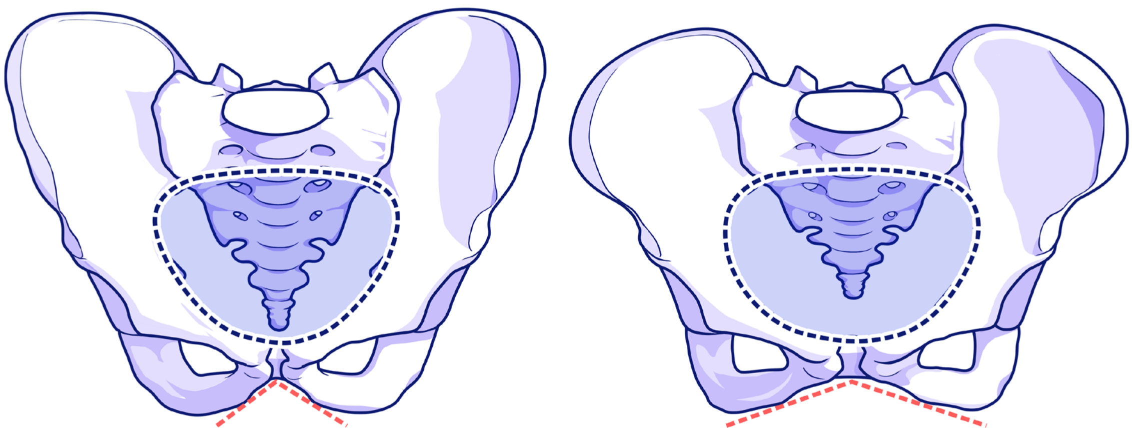
In addition to the modifiable risk factors specified above, several key non-modifiable risk factors also exist for anastomotic leaks. Despite the inability to change/eliminate these factors, they remain important considerations for any surgical team to make note of, potentially warranting additional precautions or care pre-, during, or post-surgery. Further, many of these non-modifiable risk factors may exist in tandem with modifiable risk factors outlined above, potentially even augmenting the likelihood of a patient developing an anastomotic leak. Thus, it is imperative that a patient's pre-operative risk factors be considered holistically, with an awareness about those factors which cannot be modified.



Biological Sex

Several researchers have identified male sex as an independent non-modifiable predictor of AL after colorectal, colocolonic, and rectal anastomoses.(33,100–104). One study by Park et al. analyzed a cohort of 1,609 patients to determine the risk factors associated with AL after laparoscopic rectal cancer excision. The study revealed that biological males had a significantly increased leak rate (8%) compared to biological females (2.8%) (101). Sex differences in AL rates have been explained in part by the anatomical difference between the pelvis of biological males and females (100,103,105–107). The male pelvis is deep and narrow, which may limit visualization during dissection and contribute to a more technically difficult procedure. Conversely, the wider female pelvis permits better visualization, a more accurate dissection, and less trauma to the rectal stump created by retraction. For this reason, significant differences in AL rates between the sexes typically become more apparent with lower anastomoses.

It has also been noted that sex-specific differences exist in intestinal microcirculation, associated with hormonal differences in males and females (108). Specifically, elevated 17β-estradiol (E2) levels and low androgen-to-estrogen ratios in biological females improves endothelial function in the small intestine, allowing better perfusion and microcirculation. It has also been proposed that the pathway for collagen metabolism and tissue repair varies greatly between the two sexes, further supporting the observed discrepancy in male versus female AL rates (109). Female hormones, including estrogen, have been linked to improved collagen deposition, which has proved in experimental models to be an important factor in anastomotic healing (cite Agren et al.).



Male pelvis
- Deep and narrow
- Limits visualization
- More technically difficult procedure

Female pelvis
- Wider
- Permits better visualization
- Less technically difficult procedure

Fig 6. Anatomical difference between the pelvis of biological males and females

Improved intestinal microcirculation and perfusion in biological females related to hormonal differences: a) elevated 17-beta estradiol b) low androgen to estrogen ratios
Improved collagen deposition in biological females due to high estrogen levels

Table 2. Additional sex-specific differences that may impact the development of AL

Age

Many research articles have reported conflicting evidence regarding the impact of age on AL after colorectal resection. While some research indicates that older age may serve as a protective factor for AL, others have reported higher risk of AL and associated mortality in geriatric patients. In other studies, no significant correlation between age and the risk of AL has been observed.

In one investigation, data was derived from the Dutch ColoRectal Audit (DCRA) national registry, investigating the effect of age on AL in 45,488 patients who had undergone primary colorectal cancer resection with construction of a primary anastomosis between 2011 and 2016 (110). Multivariate analyses showed that age was protective for AL after colorectal cancer resection, and that the incidence of AL was lower in older patients. A separate study analyzing 17,518 patients from the 2013 American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database showed very similar results to that observed in the DCRA national registry (Parthasarathy et al.). Here, the average age of patients developing AL was significantly lower than the average age of those without leakage, even upon excluding potential confounders (e.g., inflammatory bowel disease, chronic steroid medication). Further, another study analyzing 9,333 patients from the Danish Colorectal Cancer Group database between May 2001 and December 2009 also revealed that older age was correlated with a lower risk of AL (104). Finally, a more recent study published in 2022, using data from 156,545 patients acquired from the Korean Health Insurance Review and Assessment Service, also reported a lower incidence of AL with older patients (111). Smaller studies, including one conducted in 2021 with 1,900 patients, also demonstrated that age appeared to be a protective factor against AL (112).

Given that older age can increase the risk of complication during surgery and recovery, the lower AL rate observed in the above studies can be explained by the following (110,111):

- Selection bias: The fittest patients may have been chosen during the preoperative patient selection process.
- Surgeons are usually motivated to err on the side of caution when managing geriatric patients due to the higher reported incidences

of postoperative morbidity and mortality associated with this patient group. Therefore, a surgeon may decide to perform a permanent ostomy instead of a primary anastomosis when managing a higher-risk older patient, but not a younger patient with a similar risk profile

- Survivor bias/healthy survivor effect: This describes the phenomenon whereby patients that made it to a specific age (i.e., fitter patients) are chosen while others (i.e., unhealthy patients) who passed away before this age are not.

Standing in contrast to the above-mentioned studies supporting a protective effect of age against AL, other research suggests that older age may in fact be a risk factor. As an example, one study analyzing data from 1,391 patients reported a higher incidence of leaks in those patients who were above 60 years of age (113). Similarly, smaller studies have concluded that advanced age (>60 years) was a major risk factor for AL (109,114).

Thus, although age is included as a risk factor for AL in several publications, at this time, conclusive statistical data is lacking to fully support this. For this reason, the effect of age on AL after colorectal surgery remains unclear.

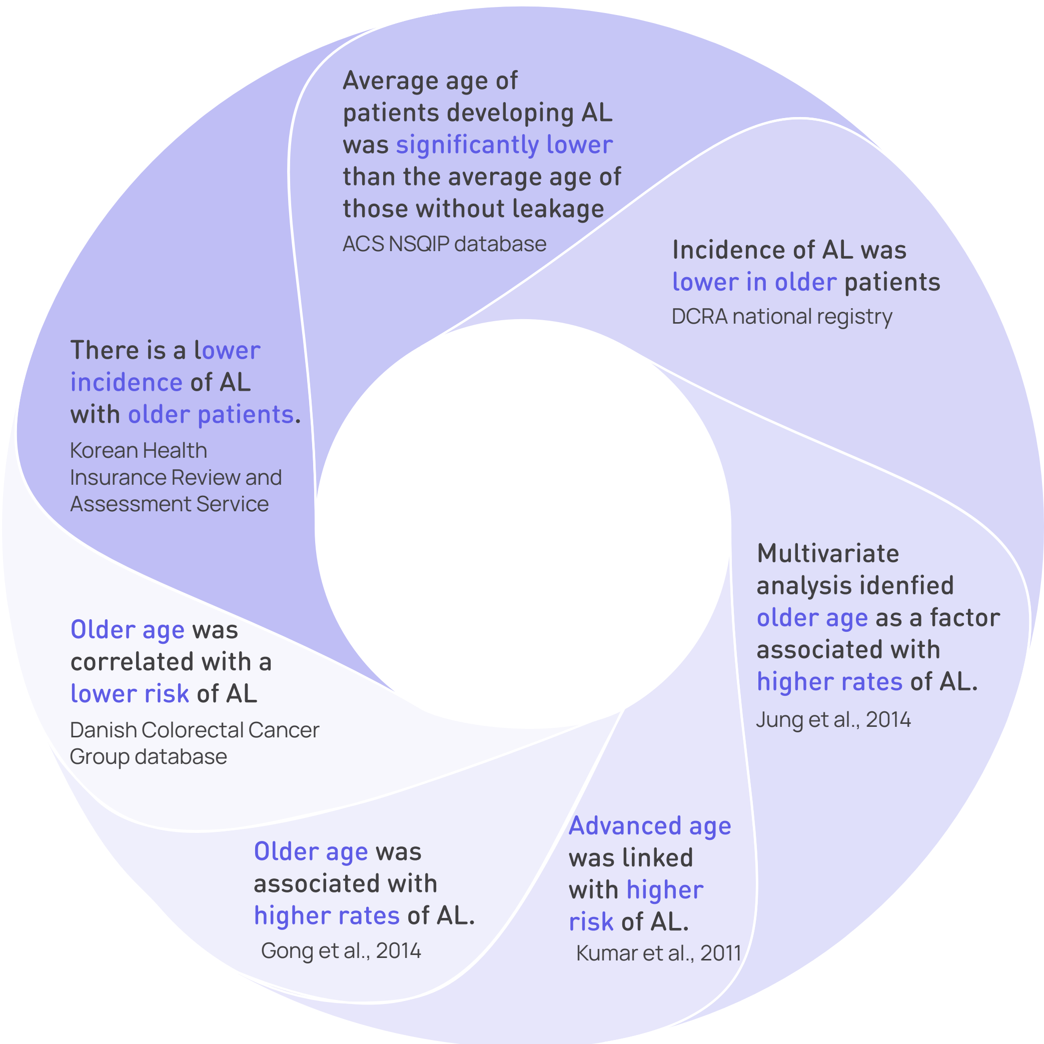


Fig 7. Summary of studies on the relationship between age and risk of AL

Preoperative chemoradiotherapy

Preoperative radiotherapy with or without chemotherapy (preop-R(C)T) is commonly utilized to downsize locally advanced rectal tumours prior to total mesorectal excision (TME) (5,18,29). It is widely accepted that this form of combined treatment can improve long-term oncological outcomes and reduce the rate of local recurrence (115). Contradictory evidence exists regarding the association between preop-R(C)T and AL (5,18,29).

Several retrospective studies revealed that preop-R(C)T is associated with an increased risk of anastomotic leakage. A retrospective analysis of 1,609 patients with rectal cancer who underwent laparoscopic surgery reported that preoperative chemoradiation (HR = 6.284; 95% CI: 2.829–13.961; P < 0.001) was significantly associated with AL (101). Multivariate analysis conducted on 6,833 patients similarly revealed that preoperative radiotherapy is an independent risk factor for AL after elective anterior resection (Matthiessen et al.). This study showed that patients who received preoperative radiation had a 22% higher incidence of leak with 94% of the patients receiving short course radiotherapy (5 x 5 Gy) and 6% receiving long course radiotherapy (50 Gy or 43 Gy) (33). Another retrospective study consisting of 1,958 patients undergoing anterior resection reported that patients receiving radiotherapy had more than double the risk of suffering from an AL compared with patients who did not receive radiotherapy (103). Additionally, a retrospective analysis of 1,278 patients was conducted to compare the AL rates in patients within the following time periods: 1994-2000 and 2001-2006. The study showed that the increased frequency of preop-RCT in 2001-2006 may have led to a 5-fold increase in the incidence of AL. Lastly, a retrospective study of 2,035 patients who underwent LAR showed that preop-RCT using 50.4 Gy as a total radiotherapy dose and 5-fluorouracil/capecitabine for 5 weeks significantly increased the risk for contained leakage by 2.80 times but not free leakage (116). Similarly, a randomized controlled trial on 318 patients revealed a significantly higher AL rate in patients that received preop-RCT (117). The study highlighted that patients receiving radiotherapy treatment with chemotherapy (5-fluorouracil alone or combined with oxaliplatin) had a significantly higher rate of AL than patients who received chemotherapy alone.

Results in experimental settings have revealed similar findings to observations from studies in patients. A study completed in 2008 by Franca et al. showed that preoperative radiotherapy in rats impairs local intestinal microcirculation and fibroblast function, resulting in poorer healing and increased fibrosis (118). Furthermore, it has been hypothesized that preop-RCT leads to changes in the composition of the gut microbiome. This, in turn, may result in impaired healing due to increased levels of collagenase-inducing pathogens (119). For this reason, it is recommended that anastomoses following preop-RCT be protected via a diverting stoma to reduce the risk of AL.

Belallaetal. (2016) included 327 patients receiving elective anterior resection for rectal carcinoma in a retrospective study evaluating the role of preoperative radiotherapy in anastomotic leak risk (120). Here, patients receiving preoperative cobalt therapy (especially those who had a low anterior resection) were at significantly higher

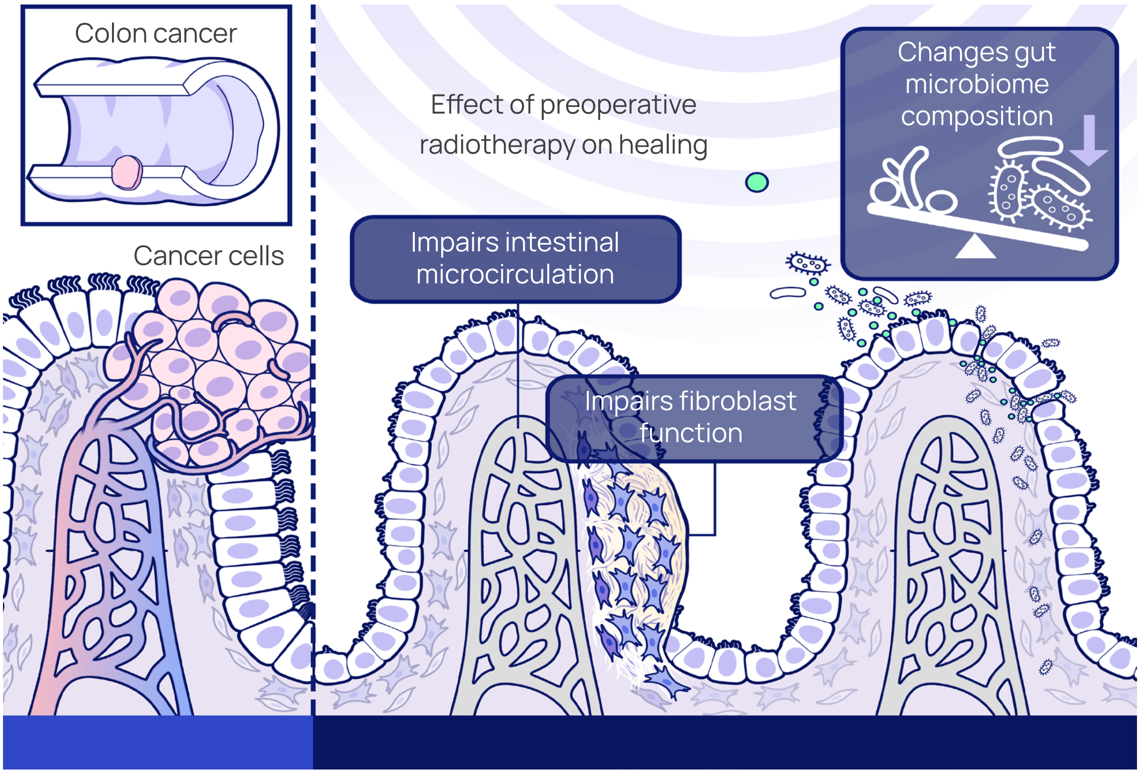


Fig 8. **Summary of studies on the relationship between age and risk of AL**

risk of AL than those not receiving radiotherapy (P = 0.015). Patients treated with intensity modulated radiation therapy (IMRT) were not found to be at increased risk, for either anterior resection or low anterior resection. Another study by Qin et al. (2019) investigated the potential for radiation-induced injury left on surgical margins of anterior resection to pose increased risk for AL (121). In 161 patients undergoing anterior resection with or without neoadjuvant radiation, AL was associated with increased histopathological scores (P = 0.003) and decreased microvessel density (P = 0.004) on the proximal margin, for those with nCRT.

Not all evidence has supported an association between preop-R(C)T and increased risk of AL. For instance, a prospective randomized trial (Dutch TME-trial) of 1,414 patients reported a nonsignificant difference in the incidence of AL after TME in patients that received five doses of 5 Gy preop-RT and those that did not (122). Additionally, a randomized Finnish rectal cancer trial analyzing a smaller patient cohort (278 patients) reported similar findings to the Dutch TME-trial (123). Another multicentre randomized trial of 1,350 patients conducted in 80 centres showed that the AL rates at 1 month were similar in patients that received short-course preoperative radiotherapy (25 Gy in five fractions) and those that received selective postoperative chemoradiotherapy (45 Gy in 25 fractions with concurrent 5-fluorouracil) (124). These results were further substantiated by two meta-analyses, which both revealed that long-course and short-course preoperative radiotherapy had similar AL rates (125,126). Additional work has highlighted that the time of resection following preop-R(C)T had no influence on AL rate (125,127–129). In short, there continue to be mixed findings surrounding the effects of preop-R(C)T on AL, and thus, more research is necessary to clarify its full impact on risk.

Study name	Design	Sample size	Conclusion
Park et al. (2013)	Retrospective analysis	1,609 patients	Preoperative chemoradiation was significantly associated with AL
Matthiessen et al. (2014)	Multivariate analysis	6,833 patients	Preoperative radiotherapy is an independent risk factor for AL after elective anterior resection. Patients who received preoperative radiation had a 22% higher incidence of leak.
Eriksen et al. (2005)	Retrospective analysis	1,958 patients	Patients receiving radiotherapy had more than double the risk of suffering from an AL compared with patients who did not receive radiotherapy.
Yamamoto et al. (2016)	Retrospective analysis	1,278 patients	Increased frequency of preop-RCT in 2001-2006 may have led to a 5-fold increase in the incidence of AL.
Park et al. (2018)	Retrospective analysis	2,035 patients	Preop-RCT using 50.4 Gy as a total radiotherapy dose and 5-fluorouracil/capecitabine for 5 weeks significantly increased the risk for contained leakage by 2.80 times but not free leakage.
Qin et al. (2016)	Randomized controlled trial	318 patients	Significantly higher AL rate in patients that received preop-RCT. Patients receiving radiotherapy treatment with chemotherapy had a significantly higher AL than patients who received chemotherapy alone.
Franca et al. (2008)	Experimental study in rats	N/A	Preoperative radiotherapy impairs local intestinal microcirculation and fibroblast function, resulting in poorer healing and increased fibrosis.

Study name	Design	Sample size	Conclusion
Belalla et al. (2016)	Retrospective study	327 patients	Patients receiving preoperative cobalt therapy (especially those who had a low anterior resection) were at significantly higher risk of AL than those not receiving radiotherapy. Patients treated with IMRT were not found to be at increased risk.
Qin et al. (2019)	Retrospective study	161 patients	AL was associated with increased histopathological scores and decreased microvessel density on the proximal margin, for those with nCRT.
Qin et al. (2019)	Prospective randomized trial	1,414 patients	Nonsignificant difference in the incidence of AL after TME in patients that received five doses of 5 Gy preop-RT and those that did not.
Salmenkylä et al. (2012)	Randomized trial	278 patients	No significant difference in the incidence of AL after TME in patients that received preop-RT and those that did not.
Sebag-Montefiore et al. (2009)	Randomized trial	1,350 patients	The AL rates at 1 month were similar in patients that received short-course preoperative radiotherapy and those that received selective postoperative chemoradiotherapy.
Hu et al. (2017) Ma et al. (2017)	Meta-analyses	1,350 patients	Long-course and short-course preoperative radiotherapy had similar AL rates.

Table 6. Summary of findings for preoperative chemoradiotherapy as a risk factor

Historical Radiotherapy

For patients who may have been previously treated with radiotherapy – for instance, for a past cancer, research again points to an increased risk of AL. Buscail et al. (2015) assessed 1,066 patients previously treated by high-dose radiotherapy for prostate cancer (130). Multivariate analysis showed that external-beam radiotherapy for prostate cancer was an independent risk factor for anastomotic leakage (OR = 5.12; 95% CI 1.45-18.08; P = 0.011).

In patients who may be undergoing bowel anastomosis for chronic radiation enteritis, AL rates are very high – as much as 36%, with associated mortalities reaching 21% (29,131). Thus, whether patients are being treated with neoadjuvant radiotherapy, or have a history of receiving radiotherapy, care should be taken in preoperative discussions and in postoperative follow-up, concerning risk for AL.

Diabetes

Diabetes mellitus (DM) is a common, chronic medical condition that physicians must be aware of in their patients, due to the significant risks both Type I and Type II DM present for a variety of health conditions. In the context of colorectal surgery, this is no different. Importantly, surgical teams must recognize that the impact of DM depends on many factors, including Type (I or II), blood sugar control, years with DM, comorbid conditions, and any pre-existing damage sustained from high blood sugar. Below, considerations for patients with diabetes undergoing colorectal surgery are outlined. Patients with pre-diabetes should also be carefully assessed and considered to be at similar risks as their diabetic counterparts.

It is often assumed that DM results in a higher incidence of postoperative complications, including AL. Since DM is associated with several chronic diseases such as obesity and hypertension, it is often difficult to infer the magnitude of association between the two variables. To account for multimorbidity, studies need to be sufficiently powered to properly assess the relationship between AL and DM, and adequately control for these (and other) confounding variables (3).

A large number of studies have found diabetes to be a significant risk factor for AL. In a 2017 study using the ACS-NSQIP database to analyze 10,392 elderly patients, DM was found to be an independent predictor of AL (OR = 1.229; 95% CI: 0.948–1.593; P = 0.120) (132). Similarly, a study by Parthasarathy et al. also using the ACS-NSQIP database (n = 17,518 patients with a colorectal resection) found DM to be a significant predictor of AL (OR = 1.252; 95% CI: 1.016–1.543; P = 0.035) irrespective of treatment modality used to control blood sugar (oral agents or insulin) (14). Multivariate analysis conducted by Volk et al. (2017) on retrospective data from 463 patients found diabetes to be a predictor of AL (OR = 4.258; 95% CI: 0.973–18.630; P = 0.05) (133). However, this same study did not find DM to be a significant predictor for mortality in patients undergoing colonic surgery with an ileocolonic anastomosis. A larger retrospective analysis of colorectal patients (n = 738) who underwent anterior resection found, through multivariate logistic regression analysis that DM is a risk factor for AL (p = 0.027; OR = 2.906; 95% CI: 1.130–7.475; P = 0.027) (134). Finally, a meta-analysis by Lin et al. (2015) included 4908 patients, 13% of which were diagnosed with diabetes (135). The pooled odds ratio calculated using a fixed-effects model was 1.661 (95% CI: 1.266-2.178). Adjustments made to control for obesity and/or BMI still revealed a dramatically increased risk of AL, demonstrating that DM is associated with an increased risk of AL irrespective of body weight.

One of the earliest studies, carried out be Manson et al. (1976), found several factors to play a role in anastomotic complications, including diabetes (136). A later study, conducted in 1997 by Vignali et al., found DM to be significantly related to the occurrence of AL (35). This was based on a review of 1,014 patients who underwent stapled anastomoses to the rectum or anal canal for colorectal cancer or benign disease. In 2012, Ziegler et al. conducted a study to determine the risk factors in diabetic patients associated with increased postcolectomy mortality and anastomotic leak (137). Interestingly, multivariate analysis showed that the risk of AL for patients with and without diabetes increased only for those with preoperative steroid use

(P < 0.05). In this study, which included 5,123 patients, mortality was not associated with hyperglycemia. However, it should be noted that the presence of an anastomotic leak, should it have occurred, was associated with increased mortality in diabetic patients (26.3% vs 4.5%, P < 0.001) compared with nondiabetic patients (6.0% vs 2.5%, P < 0.05).

A more recent meta-analysis by Tan et al. (2021) further assessed the impact of diabetes on postoperative complications following colorectal surgery (6). Based on fifty-five studies (n = 666, 886 patients: 93,173 with diabetes), anastomotic leaks were found to be significantly higher in patients with diabetes (OR 2.407; 95% CI: 1.837–3.155; P < 0.001). A number of other postoperative complications (septicemia, intra-abdominal infections, mechanical failure of wound healing comprising wound dehiscence and disruption, pulmonary complications, reoperation, and 30-day mortality) were not significantly elevated in those with diabetes. Another meta-analysis by Wong et al. (2021) was the first to investigate the association between preoperative HbA1c levels and postoperative complications in major abdominal surgery (138). From twelve studies overall, totalling 25,036 patients, high HbA1c levels were associated with a greater risk of AL (OR = 2.80; 95% CI: 1.63-4.83; P < 0.001). The authors concluded that HbA1c levels between 6%-7% (or above) is associated with a higher risk of AL.

It is important to note that, like every other risk factor, not every patient with diabetes will have the same likelihood of AL. Surgical teams should consider the length of time a patient has had diabetes, any complications from the disease, how well blood sugar is regulated, medications used to manage the disease, and so on. For patients with diabetes complicated by many significant health outcomes, such as cardiovascular changes which may impact wound healing, particular care should be given during the postoperative window.

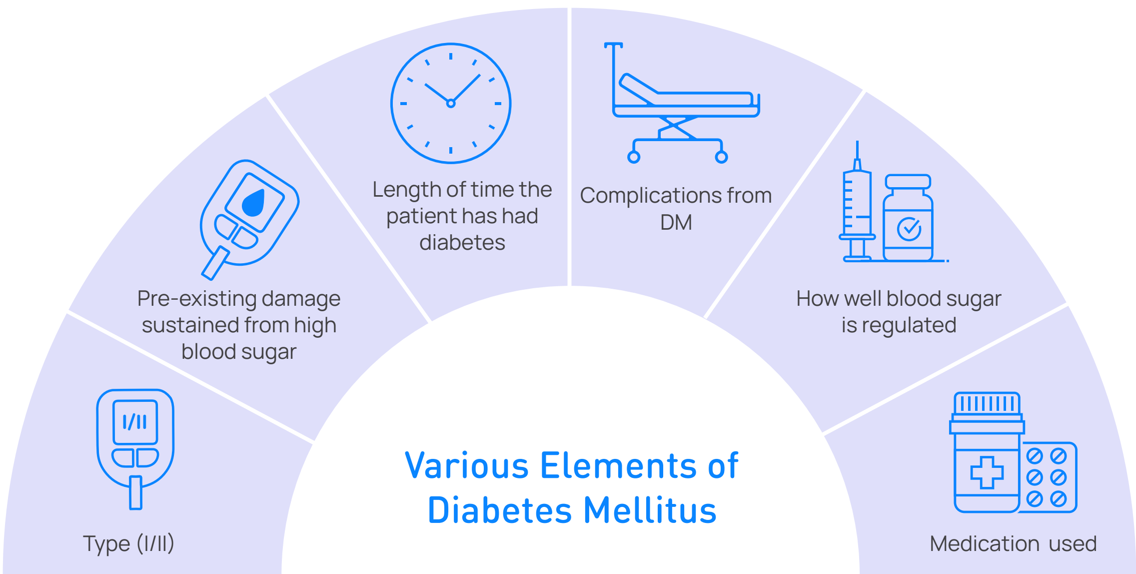


Fig 9. Multi-factorial elements of diabetes mellitus (DM) that may impact risk of AL

Tumor Factors

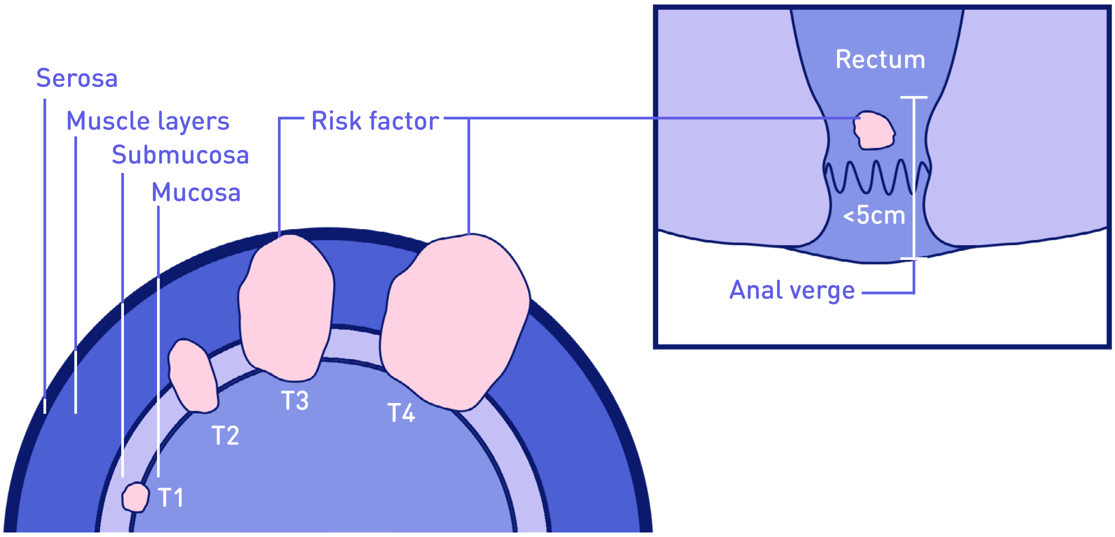


Fig 10. Colorectal tumor staging and distance from the anal verge. T3/T4 stage tumors and tumors within 5 cm from the anal verge have been identified as risk factors for AL.

It is important to acknowledge that factors related to a patient's tumor may play a role in anastomotic leak rates. For instance, for patients with left-sided colorectal cancer surgery, T3/T4 stage tumors have been identified as a risk factor for AL (OR = 2.25; P = 0.017) (86). A nationwide retrospective study (n = 5,398 patients; 552 in group AL and 4,846 in no AL) completed in Italy by Degiuli et al. (2021) also found that tumour stage (P < 0.001) and location (P = 0.004) were independent risk factors for AL (140). Risk of AL was increased for those with advanced cancer (clinical and pathological T3-T4 staging) with metastatic nodes. The authors suggested that the technical complexity of the case itself may help explain the increased risk of leaks in such patients. Distance from the anal verge was also found to be a significant independent risk factor (P = 0.042), consistent with prior literature. For instance, work from Rullier et al. in the 1990s reported 6.5-fold increased risk for leaks in anastomoses located less than 5 cm from the anal verge (31). Similarly, Vignali et al. observed a 7-fold increased risk for AL after low rectal stapling (35).

More recent evidence has also found not only an increased risk for AL in those with lower anastomoses, but also an association between AL and cancer recurrence. In a study conducted by Koedam et al. (2022), oncological outcomes were explored for patients with and without anastomotic leaks, following colon or rectal cancer surgery (141). Findings differed for colon cancer versus rectal cancer. In the former case, AL was not associated with increased local recurrence or decreased disease-free survival. However, patients with AL following rectal cancer surgery were found to have an increase in local recurrences (hazard ratio (HR) = 2.96; 95% CI: 1.38-6.34; P = 0.005) and decreased disease-free survival (HR = 1.67; 95% CI: 1.16-

2.41; P = 0.006). While the exact mechanism behind leakage and cancer recurrence is still under debate, it does suggest that AL may help predict which rectal cancer patients may be at higher risk for recurrence, and thus should be followed more closely. Several hypotheses have been put forward to explain this observation, such as cancer cells spilling into the peritoneal cavity, with natural inflammation from surgical trauma enhancing tumor cell adherence to tissue, and subsequent growth (142,143). In a rat model, local inflammation at the site of leakage upregulated the expression of tumor adhesion receptors, suggesting that a similar process might take place in humans (144). More research is required to better understand the link between AL and cancer recurrence.

To summarize, tumor factors appear to have a strong association to AL, particularly for those with advanced/metastatic tumors, and for anastomoses located close to the anal verge. Given that these patient factors will be known in advance of surgery, particular care should be taken during the postoperative period to ensure those at increased risk are appropriately monitored for anastomotic leaks.

...tumor factors appear to have a **strong association to AL**, particularly for those with advanced/ metastatic tumors, and for anastomoses located close to the anal verge

Mitigating Risk and Monitoring Recovery:

Conclusions on Preoperative Risks, and Technological Advancements in Early Leak Detection

As with any significant surgical procedure, colorectal surgery comes with the risk for complications, with risk likelihoods that may be reduced or augmented by preoperative factors – both modifiable, and non-modifiable. This article has described current evidence for the major preoperative risk factors that surgical teams should be aware of when considering surgical risk for anastomotic leaks. Importantly, not only should these risks be considered and communicated to patients during preoperative discussions, but where possible, should be mitigated. Lifestyle modifications and medical management may both have a significant role to play in reducing risk of AL.

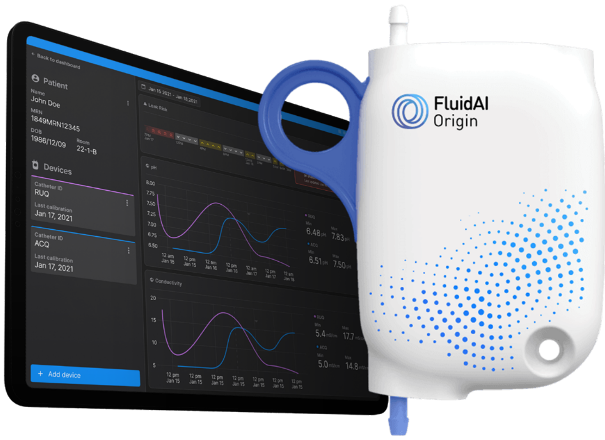


Fig 11. **The Steam™ Platform from FluidAI consists of the Delta™ Tablet and the Origin™ Device**

Along with mitigating risk wherever possible, it is important to recognize that anastomotic leaks will remain a possibility, and thus careful monitoring during the recovery period is essential. To address the reality of AL – and importance of detecting leaks as soon as possible – FluidAI (formerly *NERv Technology Inc.) has developed the Stream™ Platform, a novel technology with real-time monitoring for AL. Using the predictive power of pH and electrical conductivity of drainage fluid, the Stream™ Platform enables medical practitioners to non-invasively detect leaks far earlier than traditional approaches allow. Importantly, this will reduce the significant morbidity, mortality, and healthcare system costs associated with AL.

This technology, and its power in detecting anastomotic leaks, will continue to be explored in additional articles, the next of which will review perioperative risk factors associated with anastomotic leaks.

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