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# Gastrointestinal Anastomosis leakage Risk Factors after Cancer Surgery: is Transfusion an Independent Risk Factor for Anastomosis Leakage?

Mohammad Amin Shahrbaf (MD)

[1]*Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

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**ABSTRACT**

Gastrointestinal (GI) anastomosis is a usual procedure in the context of GI cancer surgeries. Performing an anastomosis may be complicated by infection, bleeding, anastomotic stricture, and anastomotic leakage. Anastomosis leakage is one of the devastating complications after performing an anastomosis which can be associated with several preoperative, intraoperative, and postoperative risk factors. Gender, body mass index, chemoradiotherapy, and underlying disease are preoperative risk factors for anastomosis leakage. In addition, surgical technique, operation time, tumor characteristics, blood loss, and blood transfusion are intraoperative risk factors. Diverting stoma and intestinal microbiota are assumed as post-operative risk factors for anastomosis leakage. In this comprehensive review, we aimed to describe risk factors of anastomosis leakage, especially blood transfusion. Blood transfusion can affect anastomotic healing by interfering with microcirculation, anastomotic healing phases, and the inflammatory phase of anastomosis healing. Compromised microcirculation caused by transfusion is one of the possible mechanisms for the failure of the anastomoses.

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## Introduction

Gastrointestinal (GI) tract anastomosis is a crucial procedure usually performed after GI cancer treatment to rebuild the GI tract (1-3). GI anastomosis can be conducted by several techniques, including hand-sewn, staple line, single layer, and double-layer reconstruction (4). Making an anastomosis can be complicated by some risk factors, including anemia, underlying disease, malnutrition, alcohol abuse, immunosuppressants, and anatomical location of the anastomosis (5, 6). In addition, this procedure is associated with significant blood loss and high blood transfusion rates (7-9).

Anastomotic leakage is one of the GI surgery's major complications, which can cause several morbidities and is associated with the increment of costs and hospitalization (10-12). It was shown that this complication could be associated with blood transfusion. This study aimed to investigate the possible effect of blood transfusion on anastomosis leakage development after GI surgeries.

## Literature review

### *1. GI Anastomosis: overview, healing pathophysiology, complications*

GI anastomosis is a common procedure in GI surgery (13). A GI anastomosis becomes cru-

***Corresponding author:** Mohammad Amin Shahrbaf, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
***E-mail:** aminshahrbaf41@gmail.com*
***Tel:** 989189104127*

cial when a part of the GI tract is excised due to a benign or a malignant lesion, and GI continuity needs to be restored (14). GI anastomoses can be conducted in several situations of the surgical practice; for instance, ileocolic anastomosis is usually established after right hemicolectomy in the elective setting (15, 16); in addition, anastomosis can be used for Crohn's disease surgery (17, 18), or in the emergency setting after major trauma (19). Moreover, it is common in the treatment setting of rectal cancers (20-22).

The process of anastomotic healing is classified into three phases, including 1) hemostasis or inflammatory phase, which involves vasoconstriction, blood coagulation, and inflammatory mediators, 2) proliferative phase, and 3) remodeling phase (23, 24). However, the healing process can be complicated by bleeding (25), surgical infections (26), anastomotic stricture (27), and anastomosis leakage, which are fatal complications (28).

Anastomotic leakage is a crucial and potentially lethal complication that can occur after GI surgeries (29). Anastomotic leakage rate after GI anastomosis is extensively reported between 2 and 23 % (30). The increment in the rate of morbidity and mortality and long-term outcomes are associated with anastomotic dehiscence (31). Some studies observed that the morbidity and mortality rates after GI anastomosis is 20-30% and 7-12%, respectively (32). Anastomosis leakage risk factors are classified into three groups: pre-, intra-, and post-operative risk factors (33).

## *2. Risk factors of GI anastomosis*

### *2.1. Preoperative risk factors*

#### *2.1.1. Gender*

The role of gender in the rectum's anastomosis leakage is well-known (34). Males have a narrow pelvis, making it difficult to make an anastomosis in rectal operations (35). In addition, in an animal study conducted by Kjaer et al., collagen concentration in the wound site of colonic anastomosis was lower in the males than in females (36). Moreover, Ba et al. showed that androgens can affect the intestinal endothelial function and may have effects on the healing after GI anastomosis (37).

#### *2.1.2. Body mass index*

Body mass index (BMI) and visceral fat tissue can increase the risk of anastomosis leakage (38). Yamamoto et al. concluded that BMI might be a potential risk factor for the emersion of leakage after rectal anastomosis (39). Moreover, in another study, the BMI was assumed as one of the anastomosis leakage predictors (40). Furthermore, in an observational study conducted by Sparreboom et al., the BMI directly relates to the occurrence of late anastomosis leakage (41). In contrast, one study in 2015 suggested that BMI does not affect the occurrence of anastomosis leakage (42). It seems that more studies are needed to confirm the effect of BMI as a risk factor for the development of anastomosis leakage.

#### *2.1.3. Chemoradiotherapy*

Preoperative chemotherapy and radiotherapy, which consider before the surgical operation of GI cancers, especially rectal cancers, may be effective in developing anastomosis leakage (43). In the study of Li et al., which conducted 550 patients with rectal cancer, the incidence of anastomosis leakage was associated directly with chemoradiotherapy (44).

In addition, another study by Koyama et al. reported that preoperative chemotherapy is significantly associated with anastomosis leakage in rectal cancer patients (45). The effect of radiotherapy on the intact intestinal tissue and the antiangiogenic effect of chemotherapy agents are possible mechanisms for anastomosis leakage development (46).

However, some other studies conflict with previous results. Hu et al. concluded that neoadjuvant therapy is not associated with the incidence of postoperative leakage after rectal cancer (47). It is better to conduct more prospective studies to explore perioperative chemoradiotherapy's impact on the incidence of anastomosis leakage.

#### *2.1.4. Medications*

Different medications can impress the anastomosis healing either in the preoperative or postoperative period. Iversen et al suggested that changing in clinical practice including exclusion of perioperative nonsteroidal anti-inflammatory drugs consumption can significantly reduce the rate of anastomotic leakage after colorectal resections (48). In contrast, Saleh et al. concluded that there is not a significant association between perioperative use of ketorolac and anastomotic leakage after colorectal surgery (49).

In terms of corticosteroid treatment before GI surgery, Eriksen et al reported a leakage rate of 6.77% in the corticosteroid group compared to 3.26% in the non-corticosteroid group after lower gastrointestinal surgery (50). In addition, in the study of Trésallet et al. the incidence of postoperative complications such as anastomosis leakage was higher in the patient who underwent systemic steroid therapy (51). Although, Kumano et al reported lower rate of anastomosis leakage after esophageal resection in patients treated with corticosteroids (52).

NSAIDs can affect the rate of anastomosis leakage after the operation. In the animal study of Ji et al., the rate of anastomosis leakage was higher in the case of non-steroidal anti-inflammatory drugs (NSAIDs) postoperative consumption (53). In addition, Fjederholt et al observed the association between the postoperative use of ketorolac and other NSAIDs with the risk of anastomotic leakage after gastro-esophageal-junction cancers surgery in a historical cohort (54). Furthermore, Huang et al demonstrated a strong relationship between NSAIDs and anastomotic leakage after colorectal surgery (55).

#### *2.1.5. Habitual factors*

Smoking and alcohol consumption can be associated with anastomosis leakage (56). In the study of Kwak et al., the risk of leakage was increased in smokers (57). Moreover, Van Daele et al. reported that smoking is a preventable risk factor for anastomosis leakage (58). Besides, Sørensen et al reported alcohol consumption and smoking as predictive risk factors for anastomosis leakage (59). Micro ischemia caused by smoking and poor nutritional status in the case of alcohol consumption may be responsible for anastomosis leakage (60).

#### *2.1.6. Diabetes mellitus*

Hyperglycemia and a high level of HbA1c in diabetic patients are associated with a high rate of complications following GI surgeries, especially anastomosis leakage (61, 62). Diabetic angiopathy is the possible reason for the higher rate of anastomosis leakage in diabetic patients. In addition, the risk of anastomosis leakage has a positive correlation with the glucose level (63).

#### *2.1.7. Nutritional status*

Poor nutritional status in the preoperative period is correlated with the development of postoperative anastomosis leakage (64). Telem et al. suggested that low levels of albumin (<3.5 gr/dl) is associated with the development of anastomosis leakage (32). In addition, in the study of Kingham et al., nutritional status was one of the predictive factors in the development of anastomosis leakage (65).

### *2.2. Intraoperative risk factors*

#### *2.2.1. Surgical technique*

There are several techniques for making a GI anastomosis (66). The two most commonly used techniques are hand-sewn and stapled anastomosis (14). However, some studies suggest no differences between outcomes and complications of these two techniques (67). In a systematic review conducted by Lustosa et al., the rate of anastomosis leak in the stapled technique and hand-sewn technique was 13% vs. 13.4%, respectively (68). In contrast, in the study of Choy et al., the leakage rate was fewer in the stapling technique (69). Moreover, in the study of Jurowich et al., the stapled technique had fewer minor complications than the hand-sewn technique (70). It seemed that evidence is insufficient to demonstrate the superiority of surgical technique in GI anastomosis complications.

#### *2.2.2. Operation time*

The operation time is one of the interfering factors that affect the anastomosis leakage (71). Two studies showed that the operation time is directly associated with the rate of anastomosis leakage (72,73).

#### *2.2.3. Tumor features*

Tumor measurement is a recognized risk factor for anastomosis leakage after gastrointestinal resection (74). In fact, large diameters (tumor size > 5 cm) and advanced stage tumors are more susceptible for developing the leakage after the GI resection (75,76).

#### *2.2.4. Blood loss*

Intra-operative blood loss, even in low volume (<100 ml), is one of the important predictors for anastomosis leakage (77, 78). Goense et al. suggested that blood loss of more than 250 mL is associated with a high risk of anastomosis leakage (79). Furthermore, severe blood loss causes hypovolemia and anemia, which can negatively impress the wound healing of the anastomotic site (80,81).

#### *2.2.5. Blood transfusion*

Massive blood transfusion is an independent risk factor of anastomosis leakage (82). Ohwada et al. concluded that whole-blood transfusion increased the risk of anastomotic abscess and impaired anastomotic wound healing process (83). In addition, Shah et al. demonstrated that intraoperative and postoperative blood transfusion is associated with surgical complications after intestinal anastomosis (84). Furthermore, in the study of Boukerrouche, intraoperative blood transfusion was considered a risk factor for anastomotic leak rate after esophageal reconstructive surgery (85). Moreover, the risk of anastomosis leakage is highly associated with the number of units transfused (86).

### *2.3. Postoperative risk factors*

#### *2.3.1. Diverting stoma*

Performing a diverting stoma is one of the

methods for preventing anastomosis leakage (87). However, the results of studies on this issue are inconsistent. In the study of Matthiessen et al., the rate of anastomosis leakage was 10.3% in the defunctioning stoma group compared to 28% in the control group (88). In addition, Peeters et al. supported constructing a defunctioning stoma after total mesorectal excision (89).

Moreover, Hamabe et al. suggested that creating a diverting stoma can significantly reduce the occurrence of anastomosis leakage (90). Although, Shiomi et al. concluded that diverting stoma is not significantly associated with the rate of anastomosis leakage; however, it can be effective in consequence of lower anterior resection surgery for rectal cancer (91). The effect of diverting stoma is doubtful, and further prospective studies are needed to determine its clinical efficacy.

### *2.3.2. Intestinal microbiota*

The intestinal microbiota strongly affects the wound healing process after GI anastomosis (92). van Praagh et al. suggested that Lachnospiraceae bacterial family, which is observed in obese patient, and low microbial diversity is associated with anastomosis leakage (93).

In addition, Alam et al. found that Akkermansia muciniphila plays a major role in wound healing by improving the intestinal barrier and preventing anastomosis leakage (94). Moreover, some studies suggested that Enterococcus feacalis can impress on the anastomosis healing and cause leakage by adhering to extracellular cellular matrix proteins and collagens (95). Furthermore, Pseudomonas aeruginosa is known as a contributing factor in the occurrence of anastomosis leakage (96,97).

### *3.Blood transfusion and anastomosis leakage*

Sufficient microcirculation is necessary for anastomosis healing (98). Blood transfusion can affect anastomotic healing by interfering with microcirculation and anastomotic healing phases (99); therefore, compromised microcirculation caused by transfusion is one of the possible mechanisms for the failure of the anastomoses. In addition, the blood rheology changes during the storage process, which can impress the microcirculation and anastomotic healing (99).

Another mechanism for the antagonistic relation between blood transfusion and anastomosis leakage is immunogenic factors which can affect the inflammatory phase of the anastomosis healing (100). In fact, the immunosuppressive effect of the massive transfusion may increase the risk of anastomosis leakage by undermining lymphoblastogenesis and macrophage functions (101, 102).

Moreover, allogeneic leukocytes that have a critical role in the induction of immunosuppression after blood transfusion may decrease the production of interleukin-2, which is an essential factor in the stimulation of anastomosis healing (103). Furthermore, transfusion can reduce the synthesis of collagen that causes an impairment in the anastomotic strength, and can increase the risk of anastomosis leakage (104). The effects of blood transfusion on GI anastomosis are presented in Figure 1. It seems that blood transfusion is an effecting factor for anastomosis leakage. We should consider the administration of blood products during GI surgeries.

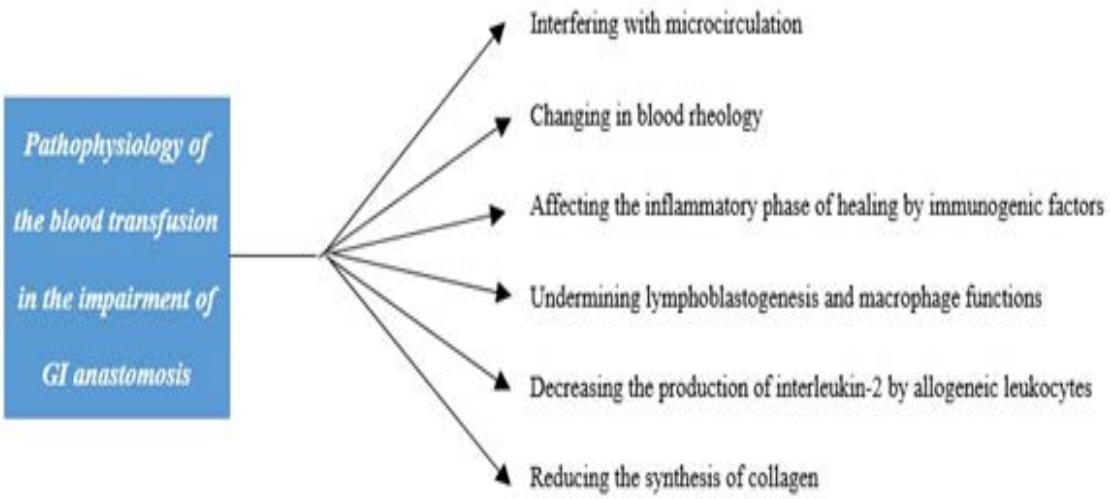


**Figure 1.** Pathophysiology of blood transfusion in the impairment of GI anastomosis

## Conclusion

Anastomosis leakage may be associated with several risk factors including gender, BMI, medications, operation time, surgical technique, blood loss, blood transfusion and etc. Blood transfusion is one of the intraoperative risk factors of anastomosis leakage, which can affect anastomosis healing through impression on microcirculation and immunosuppression.

## Conflict of Interest

There is no conflict of interest.

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