

## STUDYING RISK FACTORS FOR ANASTOMOSIS LEAKAGE FOLLOWING TOTAL AND SUBTOTAL GASTRECTOMY FOR GASTRIC CANCER

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### ABSTRACT

**Background:** Despite the significant improvement in surgical techniques, anastomotic leakage(AL) remains one of the most consequences that associated with high rates of morbidity and mortality. **Objective:** The aim of this study is to evaluate risk factors for ALs following gastric surgery. **Materials and Methods:** A prospective comparative study was conducted for the period two years (2020 - 2022) at Tishreen University Hospital in Lattakia-Syria. The study included 95 patients who underwent gastrectomy for stomach cancer. **Results:** Males represented 56.84 % of the patients and females 43.16%, with mean age 60 years. Tumors were most commonly located in the lower part of stomach (48.42%) followed by middle (34.74%) and upper parts (16.84%). Tumors stage III constitutes up approximately two-third of patients. Sub-total gastrectomy was applied in 72 patients (75.8%) and total gastrectomy in 23 patients (24.2%), with combined resection of other organs in 7 cases (7.37%). The rate of ALs was 13.68%. Male gender (p: 0.02), location of tumor (p: 0.008), complete resection of tumor (p: 0.04), combined resection of other organs (p: 0.0005), duration of surgery longer than 4 hours(p:0.02), blood loss during surgery more than 200 ml(p:0.01), serum level of albumin lower than 3.5 mg/dL (p: 0.01), and advanced stage of tumor(p:0.02) were risk factors for ALs after gastric resection. ALs were managed either by conservative management (69.23%) or surgically (30.77%), and mortality rate was 23.08% among patients with ALs. **Conclusion:** Anastomotic leakage represents a considerable risk for patient who underwent digestive surgery, with presence of many risk factors for development AL, so that we emphasize the importance of early detection of risk factors and taking preventive measures to improve final outcome.

**KEYWORDS:** Anastomotic leakage AL, stomach cancer, risk factors.

### INTRODUCTION

Gastric cancer represents one of the most common cancers worldwide with the fifth incidence and the third leading cause of cancer deaths.<sup>[1]</sup> According to the World Health Organization(WHO) estimation in 2018, gastric cancer accounted for 783.000 deaths worldwide.<sup>[2]</sup> It affects older persons, with occurrence fewer than 2% of cases in persons younger than 35 years. Rates of gastric cancer are about twice as high in men as in women.<sup>[3,4]</sup>

Pathogenesis of gastric cancer is more likely multifactorial, and many risk factors are identified to be associated with the development of cancer. Factors that contribute to gastric carcinogenesis include: H. pylori infection, diet, lifestyle, genetic, and socioeconomic factors.<sup>[5]</sup> Most patients with gastric cancer are symptomatic. Persistent abdominal pain and weight loss represent the most frequent symptoms at diagnosis, with

presence a history of gastric ulcer in approximately quarter of the patients.<sup>[6]</sup> Gastric cancers have been classified in a number of ways that include: anatomic location, extent of disease, histomorphologic appearance, and molecular subtypes. There are different gastric malignancies regarding histological findings: adenocarcinoma (90-95%), lymphoma (1-5%), gastrointestinal stromal tumors (2%), and others (1%).<sup>[7,8]</sup>

Diagnosis may be suspected in patients with previous clinical manifestations, characteristic findings of upper endoscopy or radiographic imaging, and histological examination is required to establish the diagnosis. Staging of tumors is considered essential to initiate the most appropriate management and predict outcome.<sup>[9]</sup> Complete surgical resection with extended lymph nodes dissection is the principal therapy for non-metastatic gastric cancer with best chance for long term survival,

while neoadjuvant and adjuvant chemotherapies, as well as chemoradiation can improve outcome.<sup>[10]</sup> Gastrectomy may be associated with high rate of anastomotic leak(AL), with incidence of ALs ranges from 2 to 14.6 percent in esophagojejunal anastomosis, and 2 to 5 percent from duodenal stump. AL was associated with high morbidity, mortality, and contribute to the rise in health care costs. Early detection of the risk factors that associated with ALs might decrease the occurrence and improve final outcome.<sup>[11,12]</sup> Therefore, the objective of the study was to investigate risk factors for development of ALs following gastrectomy during first month of surgery.

## PATIENTS AND METHODS

### Study Population

After approval by local research ethics committee, a prospective comparative study was conducted in a group of patients attending Department of General Surgery at Tishreen University Hospital in Lattakia-Syria during two-year period (January 2020 -January 2022).

**Inclusion Criteria were as follows:** patients with gastric cancers who underwent total or subtotal gastrectomy.

**Exclusion Criteria:** Patients with one of the following: benign tumors of stomach, operations without resection of pylorus region, emergency surgery for complicated gastric cancers, patients who received only palliative therapy, and patients who received chemotherapy before surgery.

Complete medical history together with the physical examination were done. The following laboratory investigations were done for all cases including: complete blood count CBC, serum albumin, aminotransferase, and serum tumor markers CEA and CA 19-9. Upper endoscopy was done in all patients and biopsies were taken for histopathological examination, with performing CT -scan chest, abdomen and pelvis. Patients with low albumin or hemoglobin levels were optimized preoperatively. All patients underwent open surgery under general anesthesia with subtotal or total gastrectomy depending on tumor location and histopathological findings. Tumors were divided into

three groups according to the location: upper part (below the esophagogastric junction 2 cm until body of the stomach, middle (region of body), and lower part (region of antrum and pylorus). Reconstruction was performed using Roux-en-Y or Billroth II, and anastomose was checked by using methylene blue test. Patients were maintained on intravenous fluids and are not given anything by mouth(NPO), with gradual early postoperative enteral feeding. Occurrence of ALs was suspected in patients with abdominal pain, fever>38.5, and neutrophilia (>85%) during the first week of surgery with abnormally drained gastrointestinal contents. AL was confirmed by abdominal CT scan, with giving gastrografin swallowing to evaluate leak of anastomosis. The Clavien-Dindo classification was used for assessment the severity of leakage and the associated risk factors for ALs.<sup>[13]</sup>

**Ethical consideration:** All patients were provided a complete and clear informed consent after discussion about the study. This study was performed in accordance with the Declaration of Helsinki.

### Statistical Analysis

Statistical analysis was performed by using IBM SPSS version20. Basic Descriptive statistics included means, standard deviations(SD), median, Frequency and percentages. Independent t student test was used to compare 2 independent groups. All the tests were considered significant at a 5% type I error rate( $p<0.05$ ),  $\beta$ :20%, and power of the study:80%.

## RESULTS

The study included a group of 95 patients (54 males, 41 females) with mean age 60 years who underwent surgical management of gastric tumors. The common site of tumors occurrence was the lower part of the stomach (48.42%), followed by middle part (34.74%) and upper part (16.84%). Among these, 3 patients (3.16%) were diagnosed with stage I, 32 patients (33.68%) with stage II, and 60 patients (63.16%) with stage III gastric tumors. 51(53.68%) of the participants had preoperative serum albumin levels lower than 3.5 mg/dL, and 44(46.32%) had albumin levels greater than 3.5 mg/ dL.

**Table 1: Demographic characteristics of the study population.**

Variable	Result
<b>Sex</b>	
Male	54(56.84)
Female	41(43.16%)
<b>Location of tumors</b>	
Upper part	16(16.84%)
Middle part	33(34.74%)
Lower part	46(48.42%)
<b>Stage of tumor</b>	
I	3(3.16%)
II	32(33.68%)
III	60(63.16%)

<b>Albumin(mg/dL)</b>	
<3.5	51(53.68%)
>3.5	44(46.32%)

As shown in table (2), The extent of resection was total in 23 patients (24.2%), subtotal in 72 patients (75.8%), and 7 patients (7.37%) underwent gastrectomy combined with resection of invaded organs, while the other 88 patients (92.63%) underwent gastrectomy alone.

Operative time was shorter than 4 hours' in 34 patients (35.79%), and longer than 4 hours' in 61 patients (64.21%). Intraoperative blood loss was less than 200 ml in 51 cases (53.68%), and more than 200 ml in 44(46.32%).

**Table 2: Distribution of the study population according to the surgical characteristics.**

Variable	Result
<b>Type of surgical resection</b>	
Complete	23(24.2%)
Incomplete	72(75.8%)
<b>Combined resection of other organs</b>	
Present	7(7.37%)
Absent	88(92.63%)
<b>Duration of surgery (hours)</b>	
<4	34(35.79%)
>4	61(64.21%)
<b>Estimated blood loss(ml)</b>	
<200	51(53.68%)
>200	44(46.32%)

ALs developed in 13 patients (13.68%) after surgery. In total resection, ALs involved duodenal stump in six cases (6.3%) and esophagojejunal anastomosis in three cases (13.01%), whereas in sub-total resection ALs included gastrojejuna anastomosis in two cases (2.7%), and jejuno-jejunal anastomosis in two cases (2.11%). The percentage of males was significantly higher in the leakage group than females (20.3% vs 4.8%, p: 0.02). Patients with cancer in the upper part of stomach were more likely to develop AL (37.5%) versus 10.8% in middle part and 6% in lower part, p:0.008. Patients who

had AL are more likely to have albumin level <3.5 mg/dL (21% vs 4.5%, p:0.01), and blood loss of >200 ml (23% vs 6%, p:0.01). AL was significantly more frequent in patients with tumors grade III (20%), followed by grade II (3%), without any case in tumors grade I, p: 0.02. ALs were significantly more frequent in patients who underwent complete surgical resection (26% vs 9.7%, p: 0.04), with combined resection of other organs (57% vs 10%, p:0.0005), and prolonged operative duration>4 hours (20% vs 3%, p: 0.02).

**Table 3: Distribution of the study population according to presence of ALs and demographic variables.**

Variable	Anastomotic leakage		P value
	Present	Absent	
<b>Sex</b>			0.02
Male	11(20.3%)	43(79.7%)	
Female	2(4.8%)	39(95.2%)	
<b>Location of tumors</b>			0.008
Upper part	6(37.5%)	10(62.5%)	
Middle part	5(10.8%)	41(89.2%)	
Lower part	2(6%)	31(94%)	
<b>Stage of tumor</b>			0.02
I	0(0%)	3(100%)	
II	1(3%)	31(97%)	
III	12(20%)	48(80%)	
<b>Albumin(mg/dL)</b>			0.01
<3.5	11(21%)	40(79%)	
>3.5	2(4.5%)	42(95.5%)	
<b>Type of surgical resection</b>			0.04
Complete	6(26%)	17(74%)	
Incomplete	7(9.7%)	65(90.2%)	
<b>Combined resection of other organs</b>			

Present	4(57%)	3(43%)	0.0005
Absent	9(10%)	79(90%)	
<b>Duration of surgery (hours)</b>			0.02
<4	1(3%)	33(97%)	
>4	12(20%)	49(80%)	
<b>Estimated blood loss(ml)</b>			0.01
<200	3(6%)	48(94%)	
>200	10(23%)	34(77%)	

Majority of ALs cases were developed between the fifth and tenth day, and classified according to the Clavien-Dindo classification into the following groups: mild to moderate cases (9 patients:69.23%) managed by conservative management, and severe cases (4 patients:30.77%) managed surgically. 3 patients (23.08%) with ALs died, and the rate of mortality of the study population was 3.16%.

## DISCUSSION

This prospective comparative study of 95 patients with gastric cancer assessed the prevalence of ALs, as well as risk factors predispose a patient to post-operative ALs. The present study demonstrated the main findings. First, gastric cancer was more frequent in males than females. Second, approximately two-third of the patients were in grade III of tumors classification and lower part was more frequently involved. Third, majority of the patients underwent sub-total gastrectomy without resection of other organs. Finally, there are several identified factors that increased the risk of ALs: male gender, upper location of tumor, complete resection of tumor, combined resection of other organ, duration of surgery longer than 4 hours, blood loss during surgery more than 200 ml, serum level of albumin lower than 3.5 mg/dL, and advanced stage of tumor( $p<0.05$ ). These findings may be explained by the following: delay in diagnosis gastric cancer until advanced stage with spreading tumor cells beyond the primary site to invade other organs, hypoalbuminemia is associated with delayed wound healing and interferes with normal functioning of gastrointestinal tract. In addition to that, there was a surgical difficulty in the upper part of stomach especially implementation of esophagojejunal anastomosis. The high percentage of leakage from duodenal stump might be explained by presence of comorbidities, prolonged operative duration and nutritional status perioperative. The results of current study are consistent with the previous studies.

Kim et al (2015) demonstrated in a study conducted in 3827 patients with gastric cancer who underwent gastrectomy that rate of AL was 1.88%. The predictive factors that associated with ALs were: male sex( $p<0.001$ ), blood transfusion( $p<0.001$ ), location of tumor( $p<0.001$ ), and presence of cardiovascular disease( $p<0.02$ ). There was no significant difference regarding survival between patients who developed ALs and those who didn't( $p<0.07$ ).<sup>[14]</sup>

Ma et al (2021) showed in a study conducted in 525 patients with gastric cancer who underwent radical gastrectomy that post-operative complications including AL developed in 114 patients (21.7%). Age( $p<0.01$ ), presence of comorbidities( $p<0.02$ ), blood loss( $p<0.001$ ), and type of surgery( $p<0.0001$ ) were independent risk factors for post-operative surgery. Blood loss( $p<0.01$ ) and resection type( $p<0.04$ ) represented risk factors for severe complications.<sup>[15]</sup>

By comparison the current study with previous studies, we found that tumor location, resection of other organs, and serum albumin didn't affect the occurrence of ALs in Ma et al study. In addition to that, esophagojejunal anastomosis was more frequent in Kim et al study whereas duodenal stump leakage was more frequent in the current study.

In summary, we emphasize the importance of regular follow up of hematologic parameters represented by hemoglobin and nutritional status and taking preventive management when necessary.

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