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Evaluating the predictive values of inflammatory markers from blood test for anastomosis leak after gastroesophageal surgery

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ABSTRACT

Background and Objective: Anastomotic leak is one of the most dangerous complications of gastrointestinal surgery, leading to significant morbidity and mortality. Early detection of leaks is crucial for reducing mortality, hospital stay duration, and postoperative complications. This study was designed to identify a suitable prognostic factor.

Materials and Methods: This cross-sectional study included fifteen patients selected for gastric and esophagogastric cancer surgery between April 2020 and April 2023. They underwent gastrectomy and primary anastomosis. Demographic information was collected. Complete Blood Count (CBC) and inflammatory markers were recorded preoperatively and on the third day postoperatively. Data analysis was divided into descriptive and inferential statistics. All data were analyzed using Statistical Package for Social Sciences (SPSS) version 24 statistical software, with a significance level of 0.05 for all tests considered.

Results: Three cases of anastomotic leakage post-surgery were reported. Significant statistical differences were observed between the two groups with and without anastomotic leakage in terms of Neutrophil to Lymphocyte Ratio (NLR) (2.67 ± 1.14 *vs.* 1.94 ± 1.06) and Systemic Inflammation Response Index (SIRI) (1.36 ± 1.02 *vs.* 0.87 ± 0.52) preoperatively ($p<0.05$). Additionally, on the third day post-surgery, significant statistical differences were found between the two groups in terms of leukocyte count (13.54 ± 2.89 *vs.* 9.47 ± 2.17), lymphocyte count (1.88 ± 1.10 *vs.* 2.95 ± 1.22), neutrophil count (9.14 ± 1.77 *vs.* 7.25 ± 1.08), CRP levels (54.12 ± 4.57 *vs.* 28.44 ± 2.13), NLR (4.86 ± 1.74 *vs.* 1.45 ± 0.94), and SIRI (3.88 ± 1.50 *vs.* 1.36 ± 0.78) ($p<0.05$). There were no significant differences in Platelet to Lymphocyte Ratio (PLR), Lymphocyte to Monocyte Ratio (LMR), and platelet count between the two groups preoperatively and on the third day postoperatively.

Conclusion: C-Reactive Protein (CRP) levels, leukocyte and neutrophil counts, as well as NLR and SIRI ratios on the third day post-surgery, have predictive value for anastomotic leakage.

Keywords: gastric cancer, esophageal cancer, anastomosis leak, Neutrophil to Lymphocyte Ratio (NLR)

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INTRODUCTION

Gastric cancer is among the most common malignancies globally, and radical surgery is the potential primary treatment choice. Risk classification based on preoperative factors is crucial for predicting long-term outcomes and determining the need for adjunctive therapy [1]. Anastomotic Leakage (AL) is one of the most dreadful postoperative complications in the gastrointestinal system, leading to significant complications and mortality, aiding in local tumor recurrence. Quality of life is often affected by poor functional outcomes with a high rate of permanent stoma formation. The incidence ranges from 1% to 30% [2]. Risk factors include patient-specific factors such as male gender, older age, poor nutritional status, advanced tumor stage, and technical factors like local ischemia, anastomotic tension, local sepsis, and distal obstruction [3].

Implementing Enhanced Recovery After Surgery (ERAS) protocols for patients undergoing gastric cancer surgery allows for early postoperative nutritional intake within 1 day of surgery, with patients typically being discharged between days 6 and days 12. AL may occur after discharge, raising the risk of delayed diagnosis. Hence, early suspicion of AL to exclude patients from early postoperative oral intake is crucial as it can prevent disease exacerbation towards sepsis, multi-organ failure, or death. Additionally, timely diagnosis of AL can optimize its treatment and potentially have a beneficial impact on quality of life, disease-free survival, and overall survival [4].

A high preoperative negative predictive value is associated with leakage due to peritonitis or mediastinitis, leading to the development of Systemic Inflammatory Response Syndrome (SIRS) and sepsis. Often, the contents discharged through anastomotic leakage do not immediately exit the drain tube and create localized accumulation. Given that reducing the number of drain tubes leads to decreased hospitalization, the need for predictive markers of fistula formation is increased to ensure the appropriate use of drain tubes in high-risk patients [5]. Early detection of leakage is essential to reduce mortality, hospitalization duration, postoperative complications, tumor recurrence, and costs. Clinical presentation may vary widely, but surgical intervention is often necessary, ranging from benign symptoms to signs of peritonitis and septic shock. CT scans, endoscopy, biomarkers, and analysis of drain secretions are the most commonly used tools for diagnosing anastomotic leakage in clinical practice [3].

Currently, there is no specific marker for early detection of leakage after surgery. It is well known that a systemic inflammatory response following surgery, which is indicated by higher levels of the acute-phase protein CRP on the third and fourth days post-surgery, may be strongly associated with the occurrence of septic complications related to intra-abdominal leakage [6]. Recently, the Neutrophil-to-Lymphocyte Ratio (NLR) has been used as a simple clinical indicator of the inflammatory response. Additionally, some reports have been published to evaluate the role of preoperative NLR in the peripheral blood of patients with malignant diseases. NLR has also been assessed as a predictor of major post-abdominal surgical complications. However, the predictive role of preoperative NLR in anticipating early intra-abdominal complications after surgery in patients is still unclear and requires further evaluation [7, 8]. The Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Lymphocyte-to-Monocyte Ratio (LMR) are considered biological markers related to the immune response, calculated from the numbers of neutrophils, lymphocytes, platelets, and monocytes and are used. Furthermore, the Systemic Immune-Inflammatory Index (SIRI) (neutrophil x platelet/lymphocyte), derived from the numbers of neutrophils, platelets, and lymphocytes, has also been investigated [9]. Gohil and colleagues reported that preoperative NLR values were associated with increased hospital stay after colorectal surgery [10]. In another study, the results showed that preoperative NLR values greater than or equal to 2.3 were significantly associated with major postoperative complications. However, no correlation was found between preoperative NLR and the type of complications, although a tendency towards anastomotic leakage was observed [11]. Due to insufficient evidence in this area and the importance of managing anastomotic leakage, the aim of the present study is to assess the predictive value of CBC indices in diagnosing anastomotic leakage in patients who have undergone surgery at Imam Khomeini Hospital in Sari [12-15].

MATERIAL AND METHOD

This study was conducted at Imam Khomeini Hospital in Sari after obtaining approval from the Ethics Committee with the code IR.MAZUMS.IMAMHOSPITAL.REC.1402.17896. The patients who were hospitalized with a diagnosis of gastric or esophageal cancer and underwent surgical treatment, as well as those who had completed chemotherapy preoperatively, radiotherapy, or both, were included in this study.

Using the hospital's Health Information System (HIS), a list of all patients diagnosed with gastric and esophageal cancer admitted to the hospital between April 2020 and April 2023 was extracted for the study period. Medical records of patients undergoing surgery were reviewed, and among them, the records of patients who had undergone any preoperative treatments such as preoperative radiation, peripheral blood count, etc., were separated. After obtaining written consent from the patients or their legal guardian/representative, they were included in the study, and the necessary information was collected from their records, supplemented by telephone or in-person interviews as needed for statistical analysis.

A questionnaire comprising demographic information (age, gender, diagnosis, type of surgery, type of anastomosis, complications including death, bleeding, leakage, reoperation) was designed. CBC results before and on the third day after surgery were extracted from the records. The lymphocyte, monocyte, neutrophil, and platelet counts were reported as percentages, and the NLR, LMR, and PLR ratios, as well as SIRI values, were calculated.

All data and patients' demographic information were entered into Excel software after collection. Data analysis was performed in two parts: descriptive statistics and inferential statistics. Descriptive statistics included frequency, percentage, and related charts for qualitative data, while quantitative data presented mean, median, variance, standard deviation, and relevant charts. All data were imported into the statistical software SPSS version 22 for analysis, with a significance level of 0.05 considered for all tests.

RESULTS

Based on the information extracted from the patients' records from April 2020 to April 2023, a total of 15 patients were included in the study. Out of these, 9 were male (60%) and 6 were female (40%). The average age of individuals in this study was 54.9 years. The average BMI of participants in the study was 30.4. Among these individuals, 2 cases (13.3%) were related to esophageal cancer and 13 cases (86.7%) were related to gastric cancers. Among individuals with stomach cancer, 8 cases had tumors in the distal stomach and 5 cases had tumors in the proximal stomach.

In total, 2 cases (13.3%) underwent esophagectomy. Additionally, 7 cases (46.7%) underwent subtotal gastrectomy and 6 cases (40%) underwent total gastrectomy (Figure 1).

Among the patients examined, 3 cases of anastomotic leakage (20%) were reported after surgery, with 1 case (6.7%) in the esophageal cancer group and 2 cases (13.7%) in the gastric cancer group. The statistical difference between the two groups with and without leakage was not significant (Table 1). Additionally, the average occurrence of anastomotic leakage was found to be 6.2 days.

Based on the data from CBC tests and CRP inflammatory markers before surgery, statistically significant differences were not observed between the two groups with and without anastomotic leakage in terms of variables such as the number of leukocytes, lymphocytes, neutrophils, platelets, and levels of CRP, PLR, and LMR in the preoperative CBC and inflammatory marker tests. However, significant differences were observed between the two groups with and without anastomotic leakage in terms of the variables NLR (2.67 ± 1.14 *vs.* 1.94 ± 1.06) and SIRI (1.36 ± 1.02 *vs.* 0.87 ± 0.52) ($p<0.05$) (Table 2).

Based on the data from CBC tests and CRP inflammatory markers on the third day after surgery, significant statistical differences were present between the two groups with and without anastomotic leakage in terms of variables such as the number of leukocytes (13.54 ± 2.89 *vs.* 9.47 ± 2.17), lymphocytes (1.88 ± 1.10 *vs.* 2.95 ± 1.22), neutrophils (9.14 ± 1.77 *vs.* 7.25 ± 1.08), CRP levels (54.12 ± 4.57 *vs.* 28.44 ± 2.13), NLR (4.86 ± 1.74 *vs.* 1.45 ± 0.94), and SIRI (3.88 ± 1.50 *vs.* 1.36 ± 0.78) ($p<0.05$). There were no statistically significant differences between the two groups in terms of PLR, LMR, and the number of platelets on the third day post-surgery (Table 3).

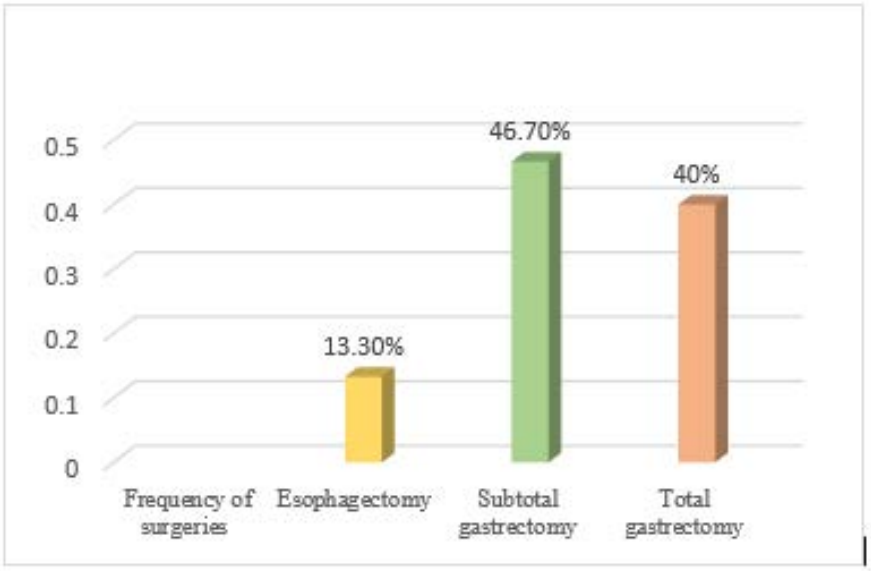

Fig. 1. Frequency of facial surgeries among patients with gastroesophageal cancers

Tab. 1. Frequency of facial surgeries among patients with gastroesophageal cancers

	With anastomotic leakage n=3 (%)	Without anastomotic leakage n=12 (%)	p-Value
Stomach Cancer	2 (66.7%)	11 (91.7%)	0.88
Biliary Tract Cancer	1 (33.3%)	1 (8.3%)	1

Tab. 2. CBC indices and inflammatory markers before surgery in two groups with and without anastomotic leakage

	With Anastomotic Leakage	Without Anastomotic Leakage	p-Value
× 10^3/µL Count of leukocytes	8.06 ± 4.09	7.86 ± 2.58	0.31
× 10^3/µL Count of neutrophils	5.26 ± 2.14	4.13 ± 1.89	0.40
× 10^3/µL Count of lymphocytes	2.58 ± 1.30	2.08 ± 1.14	0.31
× 10^3/µL Count of platelets	288.4 ± 124.34	267.1 ± 110.15	0.15
NLR	2.67 ± 1.14	1.94 ± 1.06	<0.05
PLR	110 ± 44	117 ± 32	0.40
LMR	4.23 ± 1.79	5.36 ± 2.17	0.40
SIRI	1.36 ± 1.02	0.87 ± 0.52	<0.05
CRP	4.12 ± 1.80	3.64 ± 1.77	0.40

Tab. 3. CBC indices and inflammatory markers on the third day post-surgery between two groups with and without anastomotic leak

	With anastomotic leakage	Without anastomotic leakage	p-Value
× 10^3/µL Count of leukocytes	13.54 ± 2.89	9.47 ± 2.17	<0.05
× 10^3/µL Count of neutrophils	9.14 ± 1.77	7.25 ± 1.08	<0.05
× 10^3/µL Count of lymphocytes	1.88 ± 1.10	2.95 ± 1.22	<0.05
× 10^3/µL Count of platelets	236.4 ± 114.33	244.1 ± 108.20	0.31
NLR	4.86 ± 1.74	1.45 ± 0.94	<0.05
PLR	88 ± 35	82 ± 15	0.50
LMR	3.12 ± 1.05	4.28 ± 1.35	0.50
SIRI	3.88 ± 1.50	1.36 ± 0.78	<0.05
CRP	54.12 ± 4.57	28.44 ± 2.13	<0.001

The results of this study indicate that on the third day after surgery, levels of CRP, leukocyte count, neutrophils, as well as the NLR and SIRI ratios serve as predictive values for anastomotic leakage. Within 3 days after surgery, the numbers of leukocytes, neutrophils, and lymphocytes in the blood increase. However, the counts of leukocytes and neutrophils in the anastomotic leak group were higher than in the non-leak group, while the number of lymphocytes in the non-leak group was higher, indicating an increase in the percentage of neutrophils during anastomotic leakage and a decrease in lymphocytes during the course of anastomotic leakage post-surgery. This also led to an increase in NLR and SIRI indices on the third day after surgery in the leak group.

CRP levels increased in both groups after surgery. However, the increase in CRP levels in the anastomotic leak group was higher than in the non-leak group, which was statistically significant and indicates the predictive value of CRP for anastomotic leakage. Platelet levels decreased in both groups after surgery. The decrease in platelets in the anastomotic leak group was higher, indicating the intensity of inflammation in the leak group. However, there

was no significant difference in platelet numbers on the third day after surgery between the two groups, and also the PLR values did not show statistical significance between the two groups. During this study, within 30 days after surgery, no mortality was reported.

DISCUSSION AND CONCLUSION

Neutrophil-to-Lymphocyte Ratio (NLR) is a common index of systemic inflammatory status, calculated easily from the absolute numbers of neutrophils and lymphocytes obtained from a complete blood count. Recently, NLR has been recognized as a simple and readily calculable indicator for systemic inflammatory status in the general population. It has been proven that NLR possesses better predictive properties for systemic inflammation compared to leukocytes or neutrophils alone. Both NLR and SIRI indices can predict the onset of anastomotic fistula and evaluate initial mortality. Our research, after a thorough literature review, indicates the first case outlining the leakage of anastomotic fistula post-gastrectomy for cancer in patients with elevated NLR and SIRI levels before surgery.

The utility of CRP as an inflammatory marker for early detection of AL has been investigated by multiple research groups. In this study, plasma CRP levels tended to increase on the third day post-surgery, with a significantly greater increase observed in the AL group. However, a continuous increase was also noted in patients without leakage. A meta-analysis comprising nearly 7000 patients from 23 studies revealed that from the first day post-surgery to the seventh day, AL patients had significantly higher average CRP levels compared to those without AL ($p<0.001$). CRP proved to be the best predictor for AL on days 4 and days 5 post-surgery, with a cutoff value of 96.8 milligrams per liter and a NPV of 98%. Similar results have been reported by other authors, indicating that a CRP level estimated at 125 milligrams per liter on day 4 post-surgery achieved sensitivity and NPV of 81.8% and 95.8%, respectively. Another study reported that CRP level has good predictive ability for AL on the fifth day post-surgery.

The present study indicates that the preoperative values of NLR and SIRI, along with the values of CRP, leukocyte count, and neutrophils, as well as the NLR and SIRI ratios on the third day after surgery, are predictive factors for anastomotic leakage. The CRP levels increased postoperatively in both groups, with a higher increase in the leakage group compared to the non-leakage group, showing a statistically significant difference and indicating the predictive value of CRP for anastomotic leakage. Platelet levels decreased postoperatively in both groups, with a greater decrease in the leakage group, reflecting the intensity of inflammation in the group with leakage. There was no significant difference in platelet count between the two groups on the third day after surgery, and the PLR values did not show statistical significance in the comparison between the two groups.

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