

# The Role of the Immature Granulocyte Value in Predicting Oesophagojejunostomy Anastomosis Leakage after Total Gastrectomy

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## ABSTRACT

**Objective:** To evaluate the role of the immature granulocyte (IG) value in the diagnosis of oesophagojejunostomy anastomosis leakage (EJAL).

**Study Design:** A descriptive, analytical study.

**Place and Duration of the Study:** Department of Gastroenterology Surgery, Ankara Etlik City Hospital, Ankara, Turkiye, from October 2022 to November 2024.

**Methodology:** The study included 59 patients who underwent total gastrectomy for gastric cancer between 2022 and 2024. Age, gender, T stage, N stage, tumour grade, preoperative albumin level, ASA score, combined organ resection, and postoperative values of CRP, white blood cell (WBC) count, and IG values on day 1, 3, and 5 were compared. Student's t-test, Mann-Whitney U test, and Pearson's chi-square test were used to compare the two groups with or without EJAL.

**Results:** EJAL was observed in 5 (8.5%) cases. There was a statistically significant difference between the groups in the CRP and IG values on postoperative day 5. Among these statistically significant results, the most meaningful was the IG value on postoperative day 5, with a cut-off value of 0.11 (sensitivity 100%, specificity 85.19%).

**Conclusion:** In cases undergoing total gastrectomy for gastric cancer, the IG value on postoperative day 5 can be used to diagnose EJAL and is more significant than CRP and WBC values.

**Key Words:** *Gastric cancer, Oesophagojejunostomy leak, Immature granulocyte.*

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## INTRODUCTION

Gastric cancer is the 5<sup>th</sup> most common type of cancer and the 3<sup>rd</sup> most common cause of cancer-related deaths after lung and colorectal cancer.<sup>1</sup> Open or laparoscopic gastrectomy with D<sub>1</sub> or D<sub>2</sub> lymphadenectomy is the standard treatment for stomach cancer. Oesophagojejunal anastomosis, after total gastrectomy and proximal gastrectomy, is the standard treatment method for tumours of the upper third of the stomach and the oesophagogastric junction. Stapled anastomosis has recently emerged as an alternative. Oesophagojejunostomy anastomosis leakage (EJAL) is a serious and potentially fatal complication occurring in 2.1% to 14.6% of cases.<sup>2</sup> Biomarkers are used as signs of normal biological processes, pathogenic processes, or pharmacological reactions to curative intervention.

Multiple biomarkers, be a sign of different stages of ischaemia, inflammation, or necrosis, have been extensively investigated for their usability to predict and analyse EJAL after gastric cancer operation.<sup>3</sup>

Immature granulocytes (IGs) are neutrophils that mature from progenitor cells in the bone marrow. IGs, including promyelocytes, myelocytes, and metamyelocytes, are generally not released into and detected in the peripheral blood of healthy people. However, IGs may be released into the peripheral blood in response to infection, inflammation, and additional stimuli. Early response of IGs makes this value applicable for assessing early immune response and the severity of inflammation, which may be more exact than the neutrophil count.<sup>4</sup> The (IG) count has been linked to several conditions, such as pancreatitis and Coronavirus Disease 2019 (COVID-19).<sup>5</sup> According to the study by Ustuner and Yanik Ustuner, the IG value can be used for diagnosis, disease severity, and predicting mortality.<sup>6</sup>

This study aimed to assess the role of IG values in predicting anastomotic leakage in patients who underwent total gastrectomy for gastric cancer.

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## METHODOLOGY

The study included patients who underwent total gastrectomy for gastric cancer at the Department of Gastroenterology Surgery, Ankara Etlik City Hospital, Ankara, Turkiye, from October 2022 to November 2024. Cases with unavailable data and postoperative inflammatory complications other than EJAL were excluded from the study. The study was planned retrospectively, and information was obtained from patients' computer records. Ethical approval was obtained from the ethics board of the hospital. Consent was obtained from all the patients; they were divided into 2 groups: those with EJAL and those without EJAL. There were 54 patients in the group without EJAL and five patients in the group with EJAL. EJAL was diagnosed based on the drain content, endoscopic evaluation, or computed tomography. Age, gender, T stage, N stage, grade, preoperative albumin value, the American Society of Anaesthesiologists (ASA) score, combined organ resection, and postoperative values of CRP, white blood cell (WBC) count, and IGs on days 1, 3, and 5 were compared between the groups.

SPSS version 26.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Distributions of numerical variables were examined using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were expressed as mean ± standard deviation (SD) for continuous variables with a normal distribution, as median (IQR) for continuous variables not following a normal distribution, and as counts (n) and percentage (%) for categorical variables. Comparisons were performed using Student's t-test for normally distributed data, Mann-Whitney U test for non-normally distributed data, or Pearson's chi-square and Fisher's exact test for categorical data. A p-value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to investigate the sensitivity and specificity of CRP, IGs, and WBC count for the detection of EJAL in patients who underwent total gastrectomy for gastric cancer.

## RESULTS

A total of 59 patients were evaluated, of whom 47 (79.6%) were male, and 12 (20.4%) were female. T stages were T1 or T2 in 17 (28.8%) cases and T3 or T4 in 42 (71.2%) cases. Regarding the N stage, 29 (49.1%) cases were N0 or N1, and 30 (50.9%) were N1 or N2. An ASA score of 2 was recorded in 6 (10.2%) cases, while an ASA score of 3 was recorded in 53 (89.8%). Combined organ resection was performed only in 6 (10.1%) cases; EJAL was observed in 5 (8.5%) cases.

When the cases with and without EJAL were compared, no statistically significant difference was determined between the groups in terms of age, gender, T stage, N stage, stage,

preoperative albumin value, ASA score, combined organ resection, postoperative 1<sup>st</sup> day CRP value, postoperative 3<sup>rd</sup> day CRP value, postoperative 1<sup>st</sup> day WBC value, postoperative 3<sup>rd</sup> day WBC value, postoperative 5<sup>th</sup> day WBC value, and postoperative 1<sup>st</sup> day IG value (p >0.05). Statistically significant differences were observed between the groups with and without EJAL in terms of postoperative 5<sup>th</sup> day CRP value and postoperative 5<sup>th</sup> day IG value (p <0.05, Table I).

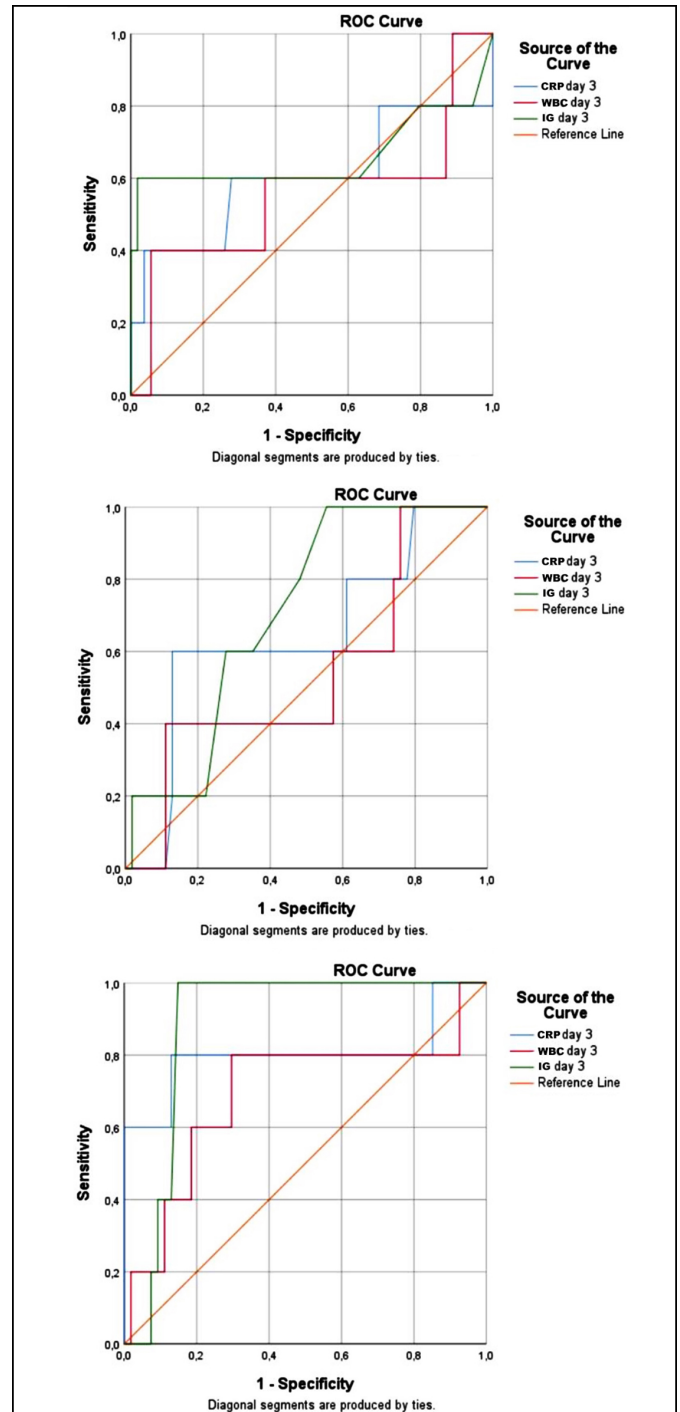


Figure 1: ROC analysis of inflammatory parameters on postoperative days 1, 3, and 5.

**Table I: Clinical and demographic characteristics of patients.**

Variables	Without EJAL n = 54 (91.5%)	With EJAL n = 5 (8.5%)	p-values	95% confidence interval
Age <sup>a</sup>	68.30 ± 9.77	68.40 ± 6.34	0.982	-9.06 to 8.86
Gender (male) <sup>b</sup>	43 (79.6 %)	4 (80.0 %)	>0.99	
T stage <sup>b</sup>			>0.99	
1-2	16 (29.6 %)	1 (20.0 %)		
3-4	38 (70.4 %)	4 (80.0 %)		
N stage <sup>b</sup>			>0.99	
0-1	27 (50.0 %)	2 (40.0 %)		
2-3	27 (50.0 %)	3 (60.0 %)		
Stage <sup>b</sup>			>0.99	
1-2	26 (48.1 %)	2 (40.0 %)		
3-4	28 (51.9 %)	3 (60.0 %)		
Albumin <sup>a</sup>	39.50 ± 4.53	39.18 ± 4.84	0.879	-3.94 to 4.59
ASA scores <sup>b</sup>			>0.99	
2	6 (11.1 %)	0 (0 %)		
3	48 (88.9 %)	5 (100.0 %)		
Combined Organ Resection <sup>b</sup>			>0.99	
No	48 (88.8 %)	5 (100.0 %)		
Yes	6 (11.2 %)	0 (0 %)		
CRP PO day 1 <sup>a</sup>	139.13 ± 77.42	177.40 ± 133.36	0.326	-115.58 to 39.04
CRP PO day 3 <sup>a</sup>	165.70 ± 77.61	210.00 ± 85.54	0.222	-118.29 to 28.10
CRP PO day 5 <sup>c</sup>	79.00 (72.00)	265.00 (244.00)	0.026*	
WBC PO day 1 <sup>c</sup>	13195 (5320)	15340 (14890)	0.703	
WBC PO day 3 <sup>c</sup>	10690 (4198)	10220 (7105)	0.765	
WBC PO day 5 <sup>c</sup>	7995 (3415)	10680 (7340)	0.157	
IG PO day 1 <sup>c</sup>	0.05 (0.04)	0.18 (0.25)	0.239	
IG PO day 3 <sup>c</sup>	0.05 (0.05)	0.09 (0.12)	0.121	
IG PO day 5 <sup>c</sup>	0.04 (0.06)	0.12 (0.03)	0.005*	

ASA: American Society of Anesthesiologists; PO: Postoperative; CRP: C-reactive protein; WBC: White blood cell; IG: Immature granulocyte; \*Statistically significant at  $p < 0.05$ . <sup>a</sup> Student's t-test, <sup>b</sup> Pearson's chi-square test, <sup>c</sup> Mann-Whitney U test.

**Table II: ROC analysis of inflammatory parameters.**

Variables	AUC	95% confidence interval of AUC	Cut-off value	Sensitivity	Specificity	p-values
CRP PO day 1	0.602	0.258 to 0.946	>264	40.0 %	96.30 %	0.454
CRP PO day 3	0.644	0.380 to 0.908	>252	60.0 %	87.04 %	0.288
CRP PO day 5	0.804	0.511 to 1.000	>149	80.0 %	87.04 %	0.026*
WBC PO day 1	0.552	0.220 to 0.883	>21970	40.0 %	94.44 %	0.703
WBC PO day 3	0.541	0.271 to 0.811	>14680	40.0 %	88.89 %	0.765
WBC PO day 5	0.693	0.402 to 0.983	>8810	80.0 %	70.37 %	0.157
IG PO day 1	0.659	0.291 to 1.000	>0.13	60.0 %	98.15 %	0.242
IG PO day 3	0.709	0.532 to 0.887	>0.04	100.0 %	44.44 %	0.124
IG PO day 5	0.883	0.799 to 0.967	>0.11	100.0 %	85.19 %	<0.005*

PO: Postoperative; CRP: C-reactive protein; WBC: White blood cell; IG: Immature granulocyte; \*Statistically significant at  $p < 0.05$ .

When the cut-off value of CRP on the 5<sup>th</sup> postoperative day was set as 149, the AUC was 0.804. When the cut-off value of IG on the 3<sup>rd</sup> postoperative day was set at 0.04, the AUC value was 0.709, and when the cut-off value of IG on the 5<sup>th</sup> postoperative day was set at 0.11, the AUC was 0.883. From these statistically significant results, the most significant result was the IG value on the 5<sup>th</sup> day after surgery (sensitivity 100%, specificity 85.19%; Table II, Figure 1).

## DISCUSSION

Despite advances in surgical techniques and postoperative management, gastrectomy can cause many postoperative complications, the most lethal of which is EJAL, with a postoperative mortality rate of up to 60%. The incidence of EJAL after total gastrectomy has been reported to range from 4% to 15%,<sup>7</sup> and in the current series, it was 8.5%. Many risk factors, such as ischaemia, patients' nutritional status, decreased blood supply, anastomotic tension, and

surgery time and techniques, have been mentioned in previous literature.<sup>8</sup> The clinical condition of patients varies depending on the size of the defect, the drainage of the leak, the degree of sepsis, underlying medical comorbidities, and the time from leak detection to intervention.<sup>9</sup> EJAL is detected based on patients' clinical condition (fever, abdominal pain, and signs of sepsis) and is diagnosed from oral contrast radiological examination, abdominal drain with digestive system content or vital dye, and computed tomography.<sup>10</sup>

Numerous studies have attempted to correlate the use of different biomarkers with the development of EJAL after total gastrectomy. In a study by Clemente-Gutierrez *et al.*, the neutrophil/lymphocyte ratio is a marker that can be used to evaluate oesophagojejunostomy leakage.<sup>11</sup> Ji *et al.* evaluated CRP, and based on the AUC value determined as 0.99, it was concluded that the CRP value can be used to detect EJAL.<sup>12</sup> A study by Cetin *et al.* found that the CRP value on the 3<sup>rd</sup> and

5<sup>th</sup> postoperative days and the neutrophil/lymphocyte ratio on the 5<sup>th</sup> postoperative day were statistically significant in evaluating EJAL.<sup>13</sup> According to Schietroma *et al.*, the Systemic Inflammation Response Index can be used to evaluate oesophagojejunostomy leakage.<sup>14</sup> In a study by Luo *et al.*, it was reported that CRP is the best marker that can be used to evaluate EJAL.<sup>15</sup> Cananzi *et al.* also stated that the CRP value can be used to evaluate anastomotic leakage after esophagogastric surgery, and procalcitonin is not superior to CRP.<sup>16</sup> According to the current study results, the IG value on the 3<sup>rd</sup> and 5<sup>th</sup> postoperative days and the CRP value on the 5<sup>th</sup> postoperative day can be used to evaluate EJAL.

New-generation haemogram devices used in recent years can calculate the number and percentage of IGs, thereby providing an easily and quickly accessible marker at no additional cost. Multiple studies have shown prognostic importance of IGs in patients with sepsis and bacteremia.<sup>17</sup> According to a study by Bhansaly *et al.*, the IG value is the earliest biomarker in the diagnosis of sepsis.<sup>18</sup> Cimenti *et al.* showed that the IG value can be used in the diagnosis of sepsis,<sup>19</sup> and Durak *et al.* concluded that IG values could be used to indicate intestinal necrosis in patients with mesenteric ischaemia.<sup>20</sup> According to a study by Altiner *et al.*, IG values can be used to evaluate complicated or perforated appendicitis in patients aged >65 years.<sup>17</sup> Moreover, Unal *et al.* reported that the percentage of IGs can be used to evaluate the severity of acute cholecystitis.<sup>21</sup> The current study reported that the IG value can be used to evaluate EJAL.

The limitations of this study include the small number of cases and its retrospective design. More meaningful studies can be conducted with a larger sample size.

## CONCLUSION

The IG value may be considered a useful marker for the evaluation of EJAL, as it has high sensitivity and specificity and can be easily measured as part of routine haemogram testing. This provides more significant results than CRP. While these preliminary findings are promising, further validation through larger, prospective studies is warranted to establish their definitive role in clinical practice.

### ETHICAL APPROVAL:

The study was approved by the Local Ethics Committee of Ankara Etlik City Hospital, Ankara, Turkiye (Ref. No. AESH-BADEK-2024-997; dated: 25<sup>th</sup> December 2024).

### PATIENTS' CONSENT:

Written informed consent was obtained from all patients for the publication of the data.

### COMPETING INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

AS, UO, AS, NTB, HS, MTB: Conception and design of the study; acquisition, analysis, and interpretation of the data; drafting and critical review of the manuscript.

All authors approved the final version of the manuscript to be published.

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