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# Turkish Journal of **COLORECTAL DISEASE**

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# Turkish Journal of COLORECTAL DISEASE

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# Turkish Journal of COLORECTAL DISEASE

## AIMS AND SCOPE

Turkish Journal of Colorectal Disease is an open access, scientific and peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles of the Turkish Society of Colon and Rectal Surgery.

The journal is published quarterly in March, June, September, and December in print and electronically. The publication language of the journal is English.

This journal aims to contribute to science by publishing high-quality, peer-reviewed publications of scientific and clinical importance that address current issues at both national and international levels.

Furthermore, review articles, case reports, technical notes, letters to the editor, editorial comments, educational contributions, and congress/meeting announcements are released.

The journal scopes epidemiologic, pathologic, diagnostic, and therapeutic studies relevant to managing small intestine, colon, rectum, anus, and pelvic floor diseases.

The target audience of the Turkish Journal of Colorectal Disease includes surgeons, pathologists, oncologists, gastroenterologists, and health professionals caring for patients with a disease of the colon and rectum.

Turkish Journal of Colorectal Disease is currently indexed in TÜBİTAK/ULAKBİM, British Library, ProQuest, CINAHL, IdealOnline, EBSCO, Embase, Gale/Cengage Learning, Index Copernicus, Turkish Citation Index, Hinari, GOALI, ARDI, OARE, AGORA J-GATE and TürkMedline.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

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Turkish Journal of Colorectal Disease is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles of Turkish Society of Colon and Rectal Surgery. The journal is published quarterly in March, June, September and December in print and electronically. The publication language of the journal is English.

This journal aims to contribute to science by publishing high quality, peer-reviewed publications of scientific and clinical importance address current issues at both national and international levels. Furthermore, review articles, case reports, technical notes, letters to the editor, editorial comments, educational contributions and congress/meeting announcements are released.

The journal scopes epidemiologic, pathologic, diagnostic and therapeutic studies relevant to the management of small intestine, colon, rectum, anus and pelvic floor diseases.

Reviewed and accepted manuscripts are translated from Turkish to English by the Journal through a professional translation service. Before printing, the translations are submitted to the authors for approval or correction requests, to be returned within 7 days. The editorial board checks and approves the translation if any response is received from the corresponding author within this period.

All manuscripts submitted to the Turkish Journal of Colorectal Disease are screened for plagiarism using the 'iThenticate' software. This journal does not accept articles that indicate a similarity rate of more than 20%, according to iThenticate reports. Results indicating plagiarism may result in manuscripts being returned or rejected.

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As a peer-reviewed journal that is independent, impartial and in compliance with the principles of double-blinded peer review, after checking the compliance of the submitted manuscript with the writing rules and plagiarism control, all articles are reviewed by the editor-in-chief, section editor, at least two reviewers, and statistic editor. All evaluation process except Editor-in-Chief is done double-blinded. After all these processes are completed, the Editor-in-Chief decides whether to publish or reject the article. In the final stage, the plagiarism review is repeated once more

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Turkish Journal of Colorectal Disease follows the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (International Committee of Medical Journal Editors: *Br Med J* 1988;296:401-5).

Upon submission of the manuscript, authors are to indicate the type of trial/research and statistical applications following “Guidelines for statistical reporting in articles for medical journals: amplifications and explanations” (Bailar JC III, Mosteller F. *Ann Intern Med* 1988;108:266-73).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; 285:1987-91);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; 6(7): e1000097.);

STARD checklist for reporting studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Ann Intern Med* 2003;138:40-4.);

STROBE statement, a checklist of items that should be included in reports of observational studies;

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008-12).

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Use tab stops or other commands for indents, not the space bar.

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Full disclosures of potential conflicts of interest on the part of any named author, or a statement confirming that there are no conflicts of interest;

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This category includes original research, including both clinical and basic science submissions. The work must be original and neither published, accepted or submitted for publication elsewhere. Any related work, either SUBMITTED, in press, or published by any authors, should be clearly cited and referenced.



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Original Articles should not exceed 3000 words (excluding abstract, references, tables, figures and legends) and four illustrations.

### Original Articles should be organized as follows:

**Abstract:** The abstract must contain fewer than 250 words and should be structured as follows:

**Aim:** What was the purpose of the study?

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**Results:** What were the main findings?

**Conclusion:** What are the main conclusions or implications of the study?

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**Results:** Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your essential observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

### Discussion:

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3. Compare your finding with those of others.

No new data are to be presented in this section.

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**Article length:** Not to exceed 4000 words.

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Reviews should include a conclusion in which a new hypothesis or study about the subject may be posited. Do not publish methods for literature search or level of evidence. Authors who will prepare review articles should already have published research articles on the relevant subject. The study's new and important findings should be highlighted and interpreted in the Conclusion section. There should be a maximum of two authors for review articles.

### Case Reports

**Abstract length:** Not to exceed 100 words.

**Article length:** Not to exceed 1000 words.

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### Case Reports should be structured as follows:

**Abstract:** An unstructured abstract that summarizes the case.

**Introduction:** A brief introduction (recommended length: 1-2 paragraphs).

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**Discussion:** This section should include a brief review of the relevant literature and how the presented case furthers our understanding of the disease process.

**References:** See under 'References' above.

Acknowledgments.

Tables and figures.

### Technical Notes

**Abstract length:** Not to exceed 250 words.

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Technical Notes include a description of a new surgical technique and its application in a small number of cases. In case of a technique representing a major breakthrough, one case will suffice. Follow-up and outcome need to be clearly stated.

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**Abstract:** Structured "as above mentioned".

#### Indications

#### Method

**Comparison with other methods:** advantages and disadvantages, difficulties and complications.

References, in Vancouver style (see under 'References' above).

Acknowledgments.

**Tables and figures:** Including legends.

#### Video Article

**Article length:** Not to exceed 500 words.

**Reference Number:** Not to exceed 5 references

Briefly summarize the case describing diagnosis, applied surgery technique and outcome. Represent all important aspects, i.e. novel surgery technique, with properly labelled and referred video materials. A standalone video vignette describing a surgical technique or interesting case encountered by the authors.

**Requirements:** The data must be uploaded during submission with other files. The video should be no longer than 10 minutes in duration with a maximum file size of 350Mb, and 'MOV, MPEG4, AVI, WMV, MPEG-PS, FLV, 3GPP, WebM' format should be used. Documents that do not exceed 100 MB can be uploaded within the system. For larger video documents, please contact info@galenos.com.tr. All videos must include narration in English. Reference must be used as it would be for a Figure or a Table. Example: ".....To accomplish this, we developed a novel surgical technique (Video 1)." All names and institutions should be removed from all video materials. Video materials of accepted manuscripts will be published online.

#### Letters to the Editor

**Article length:** Not to exceed 500 words.

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We welcome correspondence and comments on articles published in the Turkish Journal of Colorectal Disease. No abstract is required, but please include a brief title. Letters can include 1 figure or table.

#### Editorial Comments

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# Retrospective Cohort Study of Non-Traumatic Jejunum and Ileum Perforation: A Multi-center Study

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## ABSTRACT

**Aim:** Non-traumatic jejunum and ileum perforation (NTJIP) is a rare clinical entity. Contrary to infective causes occurring in Eastern countries, immune-mediated pathologies are predominant in the West. The studies on NTJIP in Southeast Asia are lacking. This study is designed to describe the involved patients incidences, etiological patterns, and outcomes. This study analyzed the predictors of mortality in these patients.

**Method:** This retrospective cohort study involved patients with NTJIP who underwent surgery over 4 years from 2016 to 2019. Data were sourced from operative databases of five tertiary public hospitals in Sarawak, Malaysia. Small bowel perforation data were screened, and patients with adhesive obstruction from previous surgeries, trauma, and duodenal perforation were excluded. Patients' socio-demographic characteristics, surgical characteristics, and outcomes were stated in the prepared *pro forma*.

**Results:** From 2016 to 2019, a total of 42 patients with NTJIP were included in this study. The mean [standard deviation (SD)] age of incidence was 55.7 (19.3) years old. Twenty-nine presented within 3 days of symptoms. Their etiologies were attributed mainly to non-specific causes (29%), followed by radiation-associated perforation (17%). The mean (SD) hospital stay was 10 (3) days, with the post-operative complication rate of ileus at 21%, surgical site infection at 23%, and anastomotic leak at 23%. The mortality rate was 36%, and the Mannheim peritonitis index was a reliable predictor of mortality.

**Conclusion:** This study observed that radiation and vascular etiologies were the most common identifiable causes of NTJIP in the current series. Further research would prove beneficial to analyze inconclusive cases, as the dilemma surrounding etiologies for NTJIP remains.

**Keywords:** Ileum, jejunum, small bowel, perforated viscus, peritonitis

## Introduction

Small bowel perforation is common following penetrating injuries. Blunt traumatic small bowel injury ranges from 5% to 15%, with incidences of perforation occurring in <1% of them.<sup>1</sup> Life-threatening spontaneous bowel perforation among premature, low-birth weight infants secondary to necrotizing enterocolitis is commonly reported, with prevalence as high as 7%.<sup>2</sup> However, small bowel perforation due to non-traumatic causes in adults is a rare clinical entity,

with a reported incidence of 1 in 350,000 people/year.<sup>3</sup> The duodenum is the most common point of perforation due to *Helicobacter pylori* prevalence.<sup>4-6</sup> Spontaneous small bowel perforation was often reported in small series or case reports. As perforation is unusual in the jejunum and ileum, this study reports a series of 42 patients. Such a series is lacking in the regional context; hence, the study intends to describe the pattern of the pathologies, management strategy, and outcome. Therefore, this study analyzes the predictors of mortality.<sup>7</sup>



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## Materials and Methods

This retrospective cohort study involved patients with non-traumatic jejunum and ileum perforation (NTJIP) who underwent surgery over 4 years from 2016 to 2019. The data was retrieved from the operative databases of five tertiary public hospitals in Sarawak. All patients with small bowel perforation were screened. Those with previous surgery, adhesive obstruction, and traumatic and duodenal perforation were excluded. Patients' socio-demographic characteristics, surgical characteristics, and outcomes were entered in prepared *pro forma*. Presenting symptoms were stratified as acute in cases of abdominal pain within 7 days, and chronic constant symptoms were those lasting more than 3 months.<sup>8</sup> Intraoperative peritoneal fluid cultures were sent off to identify potential organisms. Blood and stool cultures were sent off to exclude *Salmonella typhi*. Resected bowel segments and mesenteric lymph nodes were sent off for histopathological analysis. This study was designed to describe the involved patients' incidences, etiologies, and outcomes. The Mannheim peritonitis index was calculated based on eight parameters, including age, sex, comorbidities, clinical parameters, and peritoneal fluid analysis, to prognosticate mortality.<sup>9</sup> Post-operative morbidity was graded and analyzed using the Clavien-Dindo classification.<sup>10</sup> Perioperative mortality was defined as any death occurring during the same admission following a surgical procedure under general anesthesia. Patients were followed up six months after discharge at a surgical outpatient clinic.

This study was in compliance with the ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. Ethical approval for this study was obtained from the Jawatankuasa Etika and Penyelidikan Perubatan Medical Research and Ethics Committee, Ministry of Health Malaysia (approval number: NMRR-19-3060-50836).

### Statistical Analysis

All data was compiled using SPSS analytical software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). All quantitative and qualitative data were analyzed using the t-test or chi-squared test to identify predictors for mortality, respectively. For normality testing, the Mann-Whitney test was used if variables were not normally distributed, and t-tests were used if data were normally distributed.

## Results

From 2016 to 2019, this study retrieved 17,145 emergency surgical cases from the operative databases of five tertiary public hospitals in Sarawak, Malaysia. Data from 99 patients

with non-traumatic small bowel perforation were retrieved. Forty-two patients with NTJIP were included for analysis after exclusion (Figure 1).

The mean [standard deviation (SD)] age of affected NTJIP patients was 55.7 (19.3) years old. Most participants (69%) were in the bottom 40% of the Malaysian income classification system. They had similar gender and racial distributions (Table 1). Twenty-nine out of 42 patients presented within 3 days of symptoms, and six presented after 14 days. There were 13 deaths, giving rise to a 31% mortality rate within the same admission. The surgical complication rates ranged between 21% to 26%. (Table 2).

Despite the standard algorithm for small bowel perforation in all tertiary hospitals being used to diagnose etiologies, 29% of the cases were inconclusively labeled with non-specific etiologies following laboratory and histopathological examination (HPE) correlation. Radiation-induced and vascular pathologies were leading etiologies for NTJIP, followed by infective and immune-related causes (Table 3). Six patients physiologically unsuitable for anastomosis had segmental bowel resection with stoma creation, and the rest had resection anastomosis. The current series included two patients with more than one perforation area due to vasculopathy or gastrointestinal lymphoma.

The analysis observed that a higher Mannheim peritonitis index (SD) of 32.9 (7.0) vs 20.6 (8.2) was predictive of mortality ( $p < 0.001$ ). Cardiorespiratory complications were predictive of mortality ( $p < 0.001$ ) (Table 4).

## Discussion

NTJIP is a rare clinical entity and almost always presents a diagnosis dilemma among clinicians. The clinical presentation of the non-traumatic small bowel perforation

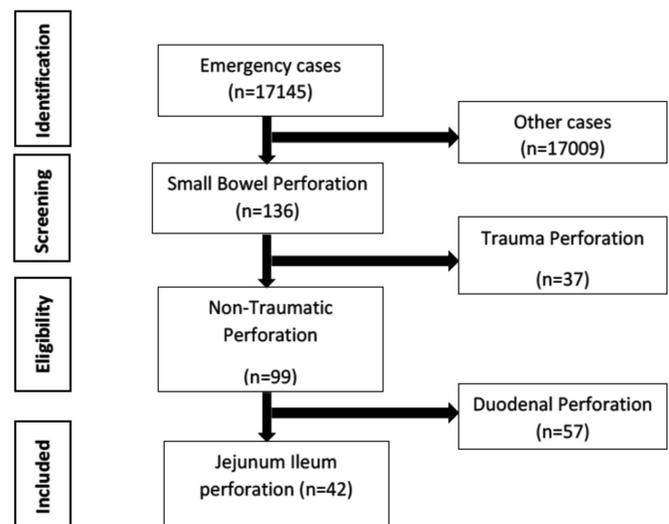


Figure 1. Study flow diagram

evolves from chronic abdominal pain to sudden abdominal distension, pain, and vomiting. NTJIP in developing countries is primarily associated with infective causes, whereas autoimmune etiologies are common in industrial countries.<sup>3,6</sup> Establishing a causative pathology based on clinical features and investigations is a challenge. Surgical management is urgently warranted; hence, a definitive preoperative diagnosis is nearly impossible. Delayed presentation and management may result in highly negative outcomes. The difficulty in classifying NTJIP based on clinical presentation, examination, serology, culture, and histopathology examinations is often regarded as a non-specific etiology.

The Dal et al.<sup>11</sup> single-center Turkish case study had comparable cases over 10 years with a similar mortality rate.

**Table 1.** Clinical characteristics of the subjects (n=42)

Factors	n (%) or mean (SD)
<b>Socio-demographic</b>	
Age (years), mean (SD)	55.67 (19.25)
<b>Gender</b>	
Male	20 (48%)
Female	22 (52%)
<b>Ethnicity</b>	
Malay	16 (38%)
Chinese	8 (19%)
Iban	10 (24%)
Bidayuh	8 (19%)
<b>Education level</b>	
Preschool	3 (7%)
Primary	27 (64%)
Secondary	12 (29%)
<b>Family Income Based on Malaysia Income Classification System*</b>	
Bottom 40%	29 (69%)
Middle 40%	13 (31%)
<b>Co-morbid condition</b>	
Hypertension	14 (33%)
Smoking	11 (26%)
Underlying malignancy	10 (24%)
Diabetes mellitus	2 (5%)
Dyslipidemia	2 (5%)
Cardiovascular	1 (2%)

\*Household Income Estimates and Incidence of Poverty Report, Malaysia 2020. SD: Standard deviation

A single-center study from a Singaporean group reported 47 patients with spontaneous small bowel perforation. The prevalent causes were foreign body ingestion (17.0%), adhesions (14.9%), idiopathic (14.9%), and malignancy (12.8%).<sup>7</sup> Contrary to the current series, no etiology pattern was revealed due to set exclusion criteria. Interestingly, the rate of idiopathic causes was 29%, much higher than

**Table 2.** Surgical outcome characteristics

Factor	n (%) or mean (SD)
<b>Duration of symptoms</b>	
Acute	29 (69%)
Subacute	7 (16.9%)
Chronic	6 (14.3%)
<b>Duration of Op (min.) mean (SD)</b>	148 (52)
<b>ASA score*, n (%)</b>	
1	10 (24%)
2	15 (36%)
3	14 (33%)
4	3 (7%)
<b>Mannheim Peritonitis Index Score mean (SD)</b>	24 (10)
<b>Perforation site</b>	
Jejunum	8 (29%)
Ileum	20 (71%)
<b>Number of perforations</b>	
Single	35 (92%)
Multiple	3 (8%)
<b>Duration of hospitalization (days) mean (SD)</b>	10 (3)
<b>Post-operative complication</b>	
Surgical site infection	10 (24%)
Anastomotic leak	9 (21%)
Ileus	10 (24%)
Respiratory	15 (36%)
Cardiovascular	18 (43%)
Surgical site infection	10 (24%)
<b>Mortality**</b>	
Same admission	13 (31%)
1 month	2 (5%)
3 months	0
6 months	0

\*ASA: American Society of Anesthesiology, \*\*Two cases of mortality after discharge, Min.: Minimum, SD: Standard deviation

in studies from the West with comparable morbidity and mortality.

In studies from low-income countries, such as Pakistan, infective causes such as tuberculosis are prevalent.<sup>12</sup> Despite Sarawak State Public Hospital catering to a lower-income population, this study did not observe a similar pattern, as there were only two cases of gastrointestinal tuberculosis in the study.<sup>13</sup> Additionally, the study did not identify any typhoid-related bowel perforations. Despite being in Southeast Asia, where pulmonary tuberculosis and typhoid are high, the current data from Sarawak revealed an opposite epidemiology.<sup>14,15</sup> Diversified pathologies of small bowel perforation are evident in each country despite being in the same region and having similar socio-economic statuses.

The current study observed 29% of HPE, and workups did not reveal an actual cause (Table 3). The rate was slightly higher than in the literature from the West.<sup>7</sup> As per the example mentioned above, there was no incidence of typhoid-related perforation, as the Widal test and HPE results were negative. The Widal test reported a mean sensitivity, specificity, and a positive and negative predictive value of below 80%. HPE tend to reveal a non-specific pattern with various immune cells and exhibit diffuse mononuclear cell infiltration with macrophage-rich hyperplasia and T-lymphocytes with lymphoplasmacytic infiltrate.<sup>12</sup> The reliabilities of individual diagnostic tests are inadequate, requiring multiple diagnostic tools and clinical features to increase their diagnostic value.<sup>16</sup> Therefore, taken together, these factors may falsely increase the rate of idiopathic causes.

The second common etiology was radiation-induced perforation. A considerable number of patients in this study presented with radiation-associated perforation

from a previously radiated pelvis, whereby five cervical adenocarcinoma and two rectal adenocarcinoma patients underwent pelvic radiation therapy for a mean duration of 10.2 months and 8 months, respectively. Radiation colitis is insidious and progressive in nature. It frequently develops following 6 months to 5 years following radiation and is rarely curable. The presence of radiation poses an additional risk for intestinal surgery, and its management remains a constant challenge due to the nature of progressive radiation evolution. Surgical intervention in perforated cases will require resection of the affected segment and anastomosis, which involves using a bowel segment that has not been exposed to radiation to reduce the risk of an anastomotic leak.<sup>17</sup>

The Mannheim peritonitis index in regards to cardiovascular and respiratory complications was considered to be significant predictors for post-operative mortality. The sub-analysis did not identify underlying malignancies as mortality predictors, as only two deaths were associated with them.

Despite the current study's limitation of only including a single state in Malaysia, the study subjects were representative of the whole country's racial profiles and included a multi-center database. Some intraoperative data was missing regarding anatomical site documentation and perforation number. Another potential confounding factor would be the lack of higher-income group patients, as they mostly visited the private hospital, which could not be included in this study. Nevertheless, the higher-income group has a comparatively lower incidence of small bowel perforation.<sup>13,15</sup>

## Conclusion

The Mannheim peritonitis index and associated cardiovascular and respiratory complications were key predictors for mortality following intestinal surgery for NJTIP. This study's etiological pattern of NTJIP is distinct from the studies of regional centers. This highlights the need for a national level of collaboration to attain better insight into this subject. This study observed that radiation and vascular etiologies were common identifiable causes of NTJIP. Further research would prove beneficial to analyze inconclusive cases, as the dilemma surrounding etiologies for NTJIP remains.

**Table 3.** Etiologies of non-traumatic jejunum ileum perforation

Etiology*	n (%)
Non-specific/idiopathic	12 (29%)
Radiation association perforation	7 (17%)
Vascular	5 (12%)
Crohn's disease	3 (7%)
Meckel's diverticulitis	3 (7%)
Adenocarcinoma	3 (7%)
Lymphoma	3 (7%)
Tuberculosis	2 (5%)
GIST	2 (5%)
Fungal infection	1 (2%)
Kikuchi-Fujimoto disease	1 (2%)

\*Following laboratory and histopathological correlation, GIST: Gastrointestinal stromal tumor

**Table 4.** Predictors of mortality in small bowel perforation

Predictors	Mean (SD) Death, (n=11)	Mean (SD) Survived, (n=31)	p-value <sup>a</sup>
Age	56.91 (18.00)	55.23 (20.00)	0.807
Duration of symptoms	1.55 (0.82)	1.42 (0.72)	0.633
Duration of surgery	143.36 (57.93)	150.39 (50.45)	0.705
Manheim Peritonitis Index	32.91 (6.978)	20.61 (8.151)	<0.001
Number of perforation	1.36 (1.206)	1.07 (0.267)	0.238

<sup>a</sup>Analyses were done with a t-test

Predictors	Death, n (%)	Survived, n (%)	p-value <sup>a</sup>
Male	4 (20.0%)	16 (80.0%)	0.491
Female	7 (31.8%)	15 (68.2%)	
Smoker	3 (27.3%)	8 (72.7%)	1.000
Non-smoker	8 (25.8%)	23 (74.2%)	
Diabetic	1 (50.0%)	1 (50.0%)	0.460
Non-diabetic	10 (25.0%)	30 (75.0%)	
Hypertensive	4 (28.6%)	10 (71.4%)	1.000
Non-hypertensive	7 (25.0%)	21 (75.0%)	
Underlying malignancy	2 (20.0%)	8 (80.0%)	1.000
No underlying malignancy	9 (28.1%)	23 (71.9%)	
ASA1	1 (10.0%)	9 (90.0%)	0.070 <sup>b</sup>
ASA2	4 (26.7%)	12 (75.0%)	
ASA3	4 (28.6%)	10 (71.4%)	
ASA4	2 (100.0%)	0 (0.0%)	
Surgical site infection	1 (10.0%)	9 (90.0%)	0.245
No surgical site infection	10 (31.2%)	22 (68.8%)	
Respiratory complication	9 (60.0%)	6 (40.0%)	<0.001
No respiratory complication	2 (7.4%)	25 (92.6%)	
Ileus	2 (20.0%)	8 (80.0%)	1.000
No ileus	6 (23.1%)	20 (76.9%)	
Cardiovascular complication	11 (61.1%)	7 (38.9%)	<0.001
No cardiovascular complication	0 (0.0%)	24 (100.0%)	
Anastomotic leak	2 (22.2%)	7 (77.8%)	1.000
No anastomotic leak	6 (22.2%)	21 (77.8%)	

<sup>a</sup>All analyses were performed using Fisher's exact test except, <sup>b</sup>chi-squared analysis. SD: Standard deviation, ASA: American Society of Anesthesiology

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## Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from the Jawatankuasa Etika and Penyelidikan Perubatan Medical Research and Ethics Committee, Ministry of Health Malaysia (approval number: NMRR-19-3060-50836).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

**Surgical and Medical Practices:** J.M., **Concept:** J.M., S.R.N.P., **Design:** J.M., S.R.N.P., M.A.B., **Data Collection or Processing:** J.M., S.R.N.P., S.M., T.J.H., Y.Y.G., K.T.T.L., S.D.T., S.S.S., **Analysis or Interpretation:** J.M., S.R.N.P., S.M., M.A.B., T.J.H., Y.Y.G., K.T.T.L., S.D.T., S.S.S., **Literature Search:** J.M., S.R.N.P., T.J.H., **Writing:** J.M., S.R.N.P., S.M., T.J.H.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Analysis of YouTube Videos on Rectal Cancer Surgery as Educational Resources

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## ABSTRACT

**Aim:** Today, the online information-gathering method is widely used by people in the healthcare industry. Currently, there is a lack of data regarding the use of YouTube™ videos as a source of information for rectal cancer surgery. This study aimed to evaluate the content, reliability, and quality of the most-viewed YouTube videos on cancer surgery and determine whether surgeons could benefit from watching these videos.

**Method:** We identified 1,356 videos through a search on <https://www.youtube.com/> using the keywords “rectal cancer surgery” via open internet access on December 4, 2020. All the videos were assessed independently by two physicians. The videos were classified as useful information (group 1) or misleading information (group 2) according to the score of the video and the assessment of the authors.

**Results:** A total of 167 videos qualified for the time period under the study’s protocol. Useful information videos had a significantly higher number of views per day, likes, dislikes, and comments ( $p<0.05$ ). The length of videos uploaded by individual surgeons was statistically significantly longer than those uploaded by organizations ( $p<0.001$ ). Videos uploaded by non-profit organizations had a statistically significantly higher number of views per day.

**Conclusion:** Social media is a frequently-used learning resource for rectal surgery, and its use is expected to become even more widespread. In today’s world, social media should be considered a common learning domain, and videos with a high level of instruction, reliability, and quality should be uploaded to social media platforms by competent people, groups, and institutions.

**Keywords:** Internet, online learning, rectal cancer, social media, YouTube

## Introduction

Rectal cancer is a separate subset of colorectal carcinoma that generally requires a dedicated approach, and surgery plays a dominant role in the treatment of the disease.<sup>1</sup> Rapidly developing and changing strategies for surgical treatment<sup>2</sup> are increasing the need for a global training platform that can easily and quickly reach surgeons everywhere.

Today, online information acquisition is a method frequently used by people in many areas of healthcare. Social media in particular has become a source of public information, a learning and development tool for healthcare professionals, and a communication network that can reach huge numbers of people.<sup>3</sup> Video learning tools have been shown to increase efficiency and confidence in young professionals, leading to improved clinical performance during tasks.<sup>4</sup> YouTube™ is a

platform with over a billion users that is used by both patients and healthcare professionals as an educational tool and a source of medical information.<sup>5</sup> When considering surgical healthcare professionals, surgery is rapidly developing and changing; new and diverse techniques are being introduced regularly, making social media an affordable, easy-to-access continuous platform on which surgeons from different parts of the world can share their techniques and enhance their skills. There are endless educational opportunities on social media, as clinicians around the world can now access expert opinions via telemedicine and distance education.

YouTube is the most commonly used platform for surgical training,<sup>6</sup> and video-based training on minimally invasive surgery is considered a useful teaching tool.<sup>7</sup> Currently, there is a lack of data on the assessment of YouTube videos as a source of information for rectal cancer surgery. The present



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study aimed to assess the content, reliability and quality of the most-viewed YouTube videos teaching rectal cancer surgery techniques and determine whether watching these videos is useful to surgeons.

## Materials and Methods

Our study examined 1,356 videos identified through a search on <https://www.youtube.com/> using the keywords “rectal cancer surgery” via open internet access on December 4, 2020. All videos were assessed independently by two physicians. Because of multiple irrelevant search results depending on different keywords, we restricted keywords to focus specifically on videos containing surgical footage. Those unrelated to rectal cancer surgery were excluded from the study. Among those relevant to rectal cancer, any videos other than those related mainly to surgery, those focused on surgical techniques, and those of an instructive nature were also excluded. Since search results on YouTube can change on a daily basis, the videos were saved in a playlist. For the videos included in the study, characteristics including video length (min), number of views, peer-review status, source of upload (uploader: non-profit organizations/for-profit organizations/individual surgeons), video quality (good/moderate/poor), date of upload, quality score, reliability

score, content (comprehensiveness) score, type of surgical technique (lap/robotic/open), number of likes, number of dislikes, number of comments, and duration on YouTube (days) were recorded. The videos were classified as useful information (group 1) or misleading information (group 2) according to the score of the video (quality, reliability, and comprehensiveness scores) and the assessment of the authors (Table 1). The videos were analyzed with regard to other characteristics, based on the upload source and the usefulness (group 1 or 2) categories.

Ethics committee approval and informed consent were not required in this study, as no human information was used or any animal experimentation was performed.

## Statistical Analysis

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) was used for statistical analyses. Descriptive statistics (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used to assess the study data. The normality of the quantitative data was tested using the Kolmogorov-Smirnov test and graphic assessments. Student's t-tests and Mann-Whitney U tests were used to compare normally and non-normally distributed quantitative variables, respectively, between the two groups, while Pearson's chi-squared test and Fisher's

**Table 1.** Assessment tools for reliability, global quality, and comprehensiveness of YouTube videos on rectal cancer surgery

### Reliability (1 point per question with a “yes” response)

1. Are the explanations presented in the video clear and understandable?
2. Are useful sources cited (publication cited, from valid studies)?
3. Is the information presented in the video balanced and neutral?
4. Are additional sources of information listed for viewer benefit?
5. Does the video mention areas of controversy or uncertainty?

### Global quality scale (scores as much as the item number)

1. Poor quality, poor flow, most information missing, not helpful for clinicians.
2. Generally poor quality, some information given but of limited use to clinicians.
3. Moderate quality, some important information is adequately discussed.
4. Good quality, good flow, most relevant information is covered, useful for clinicians.
5. Excellent quality, excellent flow, very useful for clinicians.

### Comprehensiveness (1 point per each covered in the video except for item 8)

1. Is the abdomen drawn topographically?
2. Are trocar locations shown?
3. Is the clinical summary of the patient provided?
4. Are the radiological characteristics of the patient shown?
5. Is the entire abdominal exploration described or demonstrated?
6. Is autonomic nerve preservation highlighted or demonstrated?
7. Is autonomic nerve preservation highlighted or demonstrated?
8. Are anatomical structures described or demonstrated? [Mesenteric area (1 point), superior pelvis (1 point), inferior pelvis (1 point)].
9. Is splenic flexure mobilization carefully explained or demonstrated?
10. Is the anastomotic technique carefully demonstrated or explained?

exact test were used to compare qualitative variables. The Kruskal-Wallis test was used to compare multiple quantitative variables without a normal distribution. The level of statistical significance was set at  $p < 0.05$ .

## Results

The study included 167 videos. Of these, 64.1% ( $n=107$ ) were uploaded by individual surgeons, 25.7% ( $n=43$ ) by non-profit organizations, and 10.2% ( $n=17$ ) by for-profit organizations. The rate of useful information and misleading information was 52.1% ( $n=87$ ) and 47.9% ( $n=80$ ), respectively. The YouTube duration was significantly longer for misleading videos than for useful information videos. Useful information videos had a significantly higher number of views per day, likes, dislikes, and comments ( $p < 0.05$ ). There was no statistically significant difference in video length and total view rate between groups 1 and 2. There was also no statistically significant difference in upload source (uploader: for-profit, non-profit organizations, and individual surgeons) between groups 1 and 2 (Tables 2, 3). Of the videos, 107 (64.1%) were uploaded by individual surgeons, 17 (10.2%) by for-profit organizations, and 43 (25.7%) by non-profit organizations. According to the source of upload, those videos uploaded by non-profit organizations had significantly higher reliability scores ( $p=0.014$ ). There was no statistically significant difference in the comprehensiveness score and global quality scale score according to the source of upload ( $p > 0.05$ ). Considering the total number of views according to the source of upload, the number of views of the videos uploaded by for-profit

organizations was statistically significantly higher than that of videos uploaded by non-profit organizations and individual surgeons ( $p=0.002$ ). The length of videos uploaded by individual surgeons was statistically significantly longer than that of videos uploaded by for-profit and non-professional organizations ( $p < 0.001$ ). The videos uploaded by non-profit organizations had a statistically significantly higher number of views per day compared with those from other upload sources ( $p=0.02$ ). There was no statistically significant difference in the number of likes, dislikes, and comments according to the source of upload (Tables 2, 3).

Considering pairwise comparisons according to the source of upload, the videos uploaded by non-profit organizations had statistically significant higher reliability and comprehensiveness scores than those uploaded by individual surgeons ( $p=0.002$  and  $p=0.046$ , respectively).

There were no statistical differences in technical approaches in the two groups ( $p=0.336$ ). There were 71 laparoscopic and 16 robotic videos in group 1, while there were two open, 70 laparoscopic videos, and 8 robotic videos in group 2.

## Discussion

Virtual platforms play a huge role in the development of medical education. They enable students to interact with surgeons and learn more about surgical procedures. Also, patients are likely to watch and learn about their treatments. Poll-Franse et al.<sup>8</sup> showed that 71% of patients with cancer search the Internet after receiving a diagnosis. Unfortunately, it has been shown that the quality of the videos uploaded for patient education is low.<sup>9-11</sup> More

Table 2. Analysis of video characteristics by usefulness

Characteristics	Group 1 (useful information, $n=87$ ), median (min:max) <sup>a</sup>	Group 2 (misleading information, $n=80$ ), median (min:max) <sup>b</sup>	p-value
Total views	1,805 (12:87,155)	735.5 (8:1,254,989)	0.074
Video length(s)	737 (246:12,540)	728 (47:8,292)	0.352
Duration on YouTube per day (mean $\pm$ SD)	1,463.1 $\pm$ 952	1,822 $\pm$ 1,021	0.02*
Views per day	1.74 (0.02:53.31)	0.61 (0.01:398.5)	0.005*
Likes	9 (0:769)	4 (0:273)	0.001*
Dislikes	1 (0:22)	0 (0:140)	0.033*
Comments	5 (0:119)	0 (0:43)	0.005*
<b>Source of upload, n (%)</b>			
1. Non-profit organizations	26 (60.5%)	17 (39.5%)	0.42
2. For-profit organizations	9 (52.9%)	8 (47.1)	
3. Individual surgeons	52 (48.6%)	55 (51.4%)	

<sup>a</sup>Universities, institutions, organizations, and journals. <sup>b</sup>Corporations, private hospitals, and institutions, \* $p < 0.05$ . min: Minimum, max: Maximum, SD: Standard deviation

**Table 3.** Analysis of video characteristics by source of upload

	Non-profit sources <sup>a</sup> n (%) or median (min:max)	For-profit sources <sup>b</sup> n (%) or median (min:max)	Individual surgeons n (%) or median (min:max)	p-value
Number of videos, n (%)	43 (25.7%)	17 (10.2%)	107 (64.1%)	-
Reliability score	3 (1-5)	3 (1-4)	3 (1-5)	<b>0.014*</b>
Comprehensiveness score	4 (1-9)	4 (1-7)	4 (1-9)	0.129
Global quality score	3 (1-5)	4 (1-4)	3 (1-5)	0.125
Total views	2,625 (8:68,969)	3,468 (213:87,155)	737 (12:1,254,989)	<b>0.002</b>
Video length(s)	583 (77:7,682)	683 (180:12,540)	984 (47:8,752)	<b>&lt;0.001</b>
Duration on YouTube (days)	1,951 (190:4,168)	1,790 (273:4,025)	1,272 (186:3,840)	<b>0.02*</b>
Views per day	1.95 (0.01:51.28)	1.44 (0.09:53.31)	0.74 (0.02:398.5)	<b>0.02*</b>
Likes	9 (0:769)	7 (0:56)	6 (0:273)	0.19
Dislikes	1 (0:22)	0 (0:14)	0 (0:140)	0.073
Comments	0 (0:37)	0 (0:6)	0 (0:119)	0.097
Misleading information	17 (21.3%)	8 (10%)	55 (68.8%)	0.42
Useful information	26 (29.9%)	9 (10.3%)	52 (59.8%)	

<sup>a</sup>Universities, institutions, organizations, and journals. <sup>b</sup>Corporations, private hospitals, and institutions, \*p<0.05. min: Minimum, max: Maximum, SD: Standard deviation

instructional videos are better for patient education, but they may not engage users as well as lower-quality videos. It is unclear that videos created by trusted organizations for patient education purposes on YouTube.<sup>12</sup> Participation is required to direct and educate trainees using quality vetted surgical case preparation resources. This may indicate that surgical societies with video-sharing platforms should prioritize the creation and distribution of quality videos on easily accessible public platforms.<sup>13</sup>

This study's statistical analysis showed that video uploads by individual surgeons were longer, videos by for-profit organizations had more total views, and videos by non-profit organizations had more views per day. It also showed that videos by non-profit organizations had higher reliability and comprehensiveness scores than those uploaded by individual surgeons. However, the most important finding of the present study revealed that there was no significant association between the source of videos (for-profit/non-profit/individual) and those containing useful/misleading information. Another remarkable finding was that almost half (47.9%) of all uploaded videos were evaluated as misleading. Conversely, there are studies on other subjects that have found YouTube videos to be mostly useful.<sup>5</sup>

In today's world, with the levels of knowledge increasing enormously, it is more important to teach the source of information than to teach the information itself.<sup>14</sup> Social media is now being used to help residents in surgical training, and YouTube provides a good source of videos on surgical preparation.<sup>15</sup> YouTube videos demonstrate

multiple surgical techniques, all with the click of a mouse. It is regularly used by surgeons for both educational and refresher purposes.<sup>16</sup> Videos enable the standardization of surgical training among people from different countries, cultures, and practices.<sup>6</sup>

However, there is scant literature on instructional videos. Although there is no definitive video as yet, one on rectal cancer surgery should be made by international authorities. Currently, there are not enough high-quality videos on rectal cancer available on YouTube, which suggests that we are in the early stages of online video education.

Many factors determine the quality of a video and the number of views. A study evaluating videos on breast cancer showed that healthcare professionals usually upload medium-quality videos.<sup>17</sup> Previous studies have shown that usually, short videos are mainly watched compared with long videos.<sup>18,19</sup> Various rating systems are used in the literature to rate the quality and scientific accuracy of videos on the Internet.<sup>20,21</sup>

Regrettably, YouTube lists search results according to an algorithm based on parameters such as total views and comments rather than quality, which is something that may serve commercial interests but not educational ones. Rodriguez et al.<sup>22</sup> reported that only a very few of the most popular videos provide a critical approach to safe surgical practices in cholecystectomy. Some studies also suggested that videos uploaded by medical associations and journals have more reliability,<sup>23</sup> while videos posted

by physicians have higher information quality.<sup>24</sup> De'Angelis et al.<sup>25</sup> reported that laparoscopic videos are a useful and convenient teaching tool but have not been adequately reviewed to achieve standard quality.

We believe that a social media platform should be created for surgical students to upload their videos to, which could be peer reviewed by other surgeons. This platform would allow surgical students to gain a wide reach among their fellow students. Also, we believe that it is necessary for surgeons to create a YouTube channel so that they can share their videos with their peers, similar to what medical journals do.

### Study Limitations

This study has several limitations. In addition to the low number of videos and the relative assessment of those videos, the study only included videos on YouTube in the English language. In the meantime, studies have shown that YouTube is the preferred source for online learning and allows maximum access to professionals who are preparing for surgical cases.<sup>6</sup> However, the videos included in the study had been watched a total of 2,089,868 times, which increases the significance of the videos and the value of the study.

### Conclusion

Social media is a frequently-used learning resource for rectal surgery, and it is expected to become even more commonplace. In today's world, social media should be considered a common learning domain, and videos of high levels of instruction, reliability, and quality should be uploaded to social media platforms by competent people, groups, and institutions.

### Ethics

**Ethics Committee Approval:** Ethics committee approval was not required in this study, as no human information was used or any animal experimentation was performed.

**Informed Consent:** Informed consent approval was not required in this study, as no human information was used or any animal experimentation was performed.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: E.Ç., Concept: N.İ., Design: N.İ., Data Collection or Processing: E.Ç., Analysis or Interpretation: N.İ., Literature Search: E.Ç., Writing: E.Ç.

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# Are Neutrophil-to-Lymphocyte, Platelet-to-Lymphocyte, and Lymphocyte-to-Monocyte Ratios Predictive of Postoperative Complications and Mortality in Patients with Inflammatory Bowel Disease?

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## ABSTRACT

**Aim:** Although clinicians try to control inflammatory bowel diseases with medical treatment, surgical intervention may be required due to complications. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) could be potential biomarkers of systemic inflammation in chronic diseases. This study aims to determine whether these ratios could be predictive of postoperative complications, mortality, and reoperation in patients operated on for inflammatory bowel disease complications.

**Method:** Patients who were operated on for inflammatory bowel disease between 2010-2021 were analyzed retrospectively. The patients were divided into two groups: the Crohn's disease (CD) group and the ulcerative colitis (UC) group. Descriptive statistics were carried out between the two groups. Moreover, this study analyzed the effects of NLR, PLR, and LMR on short- and long-term postoperative complications, mortality, and reoperation.

**Results:** A total of 42 patients were included in this study, 29 (69%) of them were men and 13 (31%) were women, and 24 (57%) of them were operated on for CD. NLR and PLR were significantly higher in patients with UC ( $p=0.031$ ,  $p=0.009$ ). However, none of these ratios were related to postoperative early and delayed complications, mortality, and reoperation in patients who were operated on for inflammatory bowel disease complications.

**Conclusion:** NLR, PLR, and LMR cannot be used to predict postoperative complications, mortality, and reoperation in patients that were operated on for inflammatory bowel disease complications.

**Keywords:** Inflammatory bowel disease, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio

## Introduction

Inflammatory bowel diseases (IBD) have an increasing prevalence worldwide: almost 0.5% in western countries.<sup>1,2</sup> Although clinicians try to control IBDs with medical treatment, surgical intervention may be required as a result of complications.<sup>3</sup> Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte (LMR) ratios could be potential biomarkers of systemic inflammation in chronic diseases. There are many

articles that define NLR as a valuable biomarker that can be used to predict the severity of IBD in patients.<sup>3,4</sup> Although these biomarkers are used to determine the severity and prognosis of the disease, there are limited studies on their use in predicting postoperative complications in IBD.<sup>5</sup> This study aims to determine the effects of NLR, PLR, and LMR in predicting postoperative complications and mortality in patients operated on for IBD.



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## Materials and Methods

This is a single-center retrospective study that was conducted in accordance with the ethical standards of the Helsinki declaration. The protocol of this study was approved by the Local Ethics Committee of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (approval number: 21, date: 17.01.2022). Informed consent was not provided by the patients as this was a retrospective study.

Patients who underwent emergency operations for IBD complications in Tepecik Training and Research Hospital between January 2010 and January 2021 were analyzed retrospectively. Age, sex, comorbidities, NLR, PLR, LMR, postoperative complications, mortality, and postoperative hospital stays were defined as parameters. Patients under the age of 18 who had a history of previous abdominal surgery were excluded from this study, and 1-year patient follow-ups were examined. The patients were divided into two groups: the Crohn's disease (CD) group and ulcerative colitis (UC) group, and descriptive statistics were carried out between them. Moreover, short-term complications were defined as complications that appeared during the postoperative hospitalization period. Long-term complications were defined as complications that occurred after discharge or at a one-year follow-up. Furthermore, this study analyzed the effects of NLR, PLR, and LMR on short- and long-term postoperative complications, mortality, and reoperation.

### Statistical Analysis

All statistical analyses were performed using the SPSS statistics software, version 25.0. Continuous variables with normal distribution were presented as mean and standard deviation. Variables without normal distribution were presented as the median (Q1-Q3) and compared using the Mann-Whitney U test. Moreover, variables with normal distribution and continuous variables were compared using the  $\chi^2$  test. Univariate analysis was performed to find potential risk factors, and multivariate analysis was used to identify independent factors. Furthermore,  $p < 0.05$  was considered statistically significant.

## Results

A total of 42 patients were included in this study, 29 (69%) of them were men and 13 (30%) were women, and 24 (57%) of them were operated on for CD. The most common complication leading to the operation was mechanical bowel obstruction, and other causes are summarized in Table 1 in detail. The median age was 60.5 (40.8-68) years, and the age was significantly higher in patients with UC ( $p=0.010$ ). In the CD group, 16 (67%) patients underwent right hemicolectomy, five (21%) patients underwent segmental small bowel resection, two (8.3%) patients underwent left hemicolectomy, and one (4.2%) patient underwent subtotal colectomy. In the UC group, nine (50%) patients underwent Hartmann's procedure, eight (44.4%) patients underwent total proctocolectomy, and one (5.5%) patient underwent abdominoperineal resection. The American Society of Anesthesiologists (ASA) score was significantly higher in patients with UC ( $p=0.042$ ). The median length of hospital stays was 8 (6-12) days. Although the lymphocyte count was significantly higher in patients with CD, NLR was significantly higher in patients with UC ( $p=0.010$ ,  $p=0.031$ ). Furthermore, PLR was significantly higher in patients with UC ( $p=0.009$ ). There were no differences in the lymph node count, postoperative hospital stay, short-term postoperative complications, mortality, reoperation, and long-term postoperative complications between the UC and CD groups (Table 2). The Clavien-Dindo complication score was 1 in all patients with CD who experienced short-term complications. Moreover, the Clavien-Dindo complication score was 1 in one patient, two in one patient, and three in one patient with short-term complications in the UC group. The difference between the two groups for the Clavien-Dindo complication score was not statistically significant ( $p=0.361$ ). Furthermore, this difference was not associated with the complexity of the surgery, and postoperative complications and their details are defined in Table 3. None of these ratios were found as predictive parameters for postoperative short- and long-term complications, mortality, and reoperation in multivariate analysis (Table 4).

**Table 1.** Operation indications of the patients

Operation indications	All patients, n (%)	Crohn's disease, n (%)	Ulcerative colitis, n (%)
Mechanical bowel obstruction	22 (52.4)	14 (58.3)	8 (44.4)
Perforation	12 (28.6)	8 (33.3)	4 (22.2)
Bleeding	6 (14.3)	0	6 (33.3)
Enterocutaneous fistula	2 (4.8)	2 (8.3)	0

**Table 2.** Factors associated with Crohn's disease and ulcerative colitis

	All patients (n=42)	Crohn's disease (n=24)	Ulcerative colitis (n=18)	p-value
Age, median (Q1-Q3)	60.5 (40.8-68)	47.5 (39.3-63.8)	66.5 (58.3-73)	<b>0.010</b>
<b>Sex, n (%)</b>				0.700
Male	29 (69)	16 (66.7)	13 (72.2)	-
Female	13 (31)	8 (33.3)	5 (27.8)	-
Diabetes mellitus, n (%)	5 (11.9)	2 (8.3)	3 (16.7)	0.636
Hypertension, n (%)	11 (26.2)	8 (33.3)	3 (16.7)	0.299
<b>ASA score, n (%)</b>				<b>0.042</b>
1	10 (23.8)	8 (33.3)	2 (11.1)	
2	21 (50)	13 (54.2)	8 (44.4)	
3	11 (26.2)	3 (12.5)	8 (44.4)	
WBC (10 <sup>3</sup> /uL), median (Q1-Q3)	12.5 (7.3-17.2)	11.7 (7.1-14.9)	13.8 (7.5-18.6)	0.340
NEU# (10 <sup>3</sup> /uL), median (Q1-Q3)	9.1 (4.7-14.2)	9.1 (3.9-11.4)	9.800 (5.7-18.2)	0.155
LYM# (10 <sup>3</sup> /uL), median (Q1-Q3)	1.3 (0.8-2)	1.3 (1.1-2.2)	0.9 (0.7-1.3)	<b>0.010</b>
MON# (10 <sup>3</sup> /uL), median (Q1-Q3)	0.7 (0.4-1)	0.8 (0.4-1.1)	0.6 (0.4-1)	0.655
PLT (10 <sup>3</sup> /uL), median (Q1-Q3)	285.5 (225.5-407.3)	266 (228-400.8)	336 (213.8-428.3)	0.741
NLR, median (Q1-Q3)	6.1 (3.6-14.5)	5 (1.8-9.2)	9.4 (4.3-22.5)	<b>0.031</b>
PLR, median (Q1-Q3)	259.4 (153.6-462.5)	186.2 (138.3-310.7)	331.6 (217.4-676.3)	<b>0.009</b>
LMR, median (Q1-Q3)	1.93 (1.36-3.5)	2.01 (1.45-5)	1.88 (1.25-2.18)	0.093
Lymph node count, median (Q1-Q3)	10 (2.8-25.5)	10 (3.3-19.8)	11 (0.8-36.8)	0.628
Postoperative hospital stay, median (Q1-Q3)	8 (6-12)	8 (6.3-9.8)	8.5 (5.8-16.3)	0.646
Postoperative short-term complications, n (%)	6 (14.3)	3 (12.5)	3 (16.7)	1.000
Mortality, n (%)	3 (7.1)	0	3 (16.7)	0.071
Postoperative long-term complications, n (%)	8 (19)	6 (25)	2 (11.1)	0.431
Reoperation, n (%)	7 (16.7)	4 (16.7)	3 (16.7)	1.000

ASA: American Society of Anesthesiologists

**Table 3.** Postoperative complications and their details

Postoperative complications	Crohn's disease, (n=24)	Ulcerative colitis (n=18)
<b>Short-term complications, n (%)</b>		
Surgical site infection	2 (8.3)	1 (5.6)
Low-output enterocutaneous fistula	1 (4.2)	0
Intraabdominal abscess	0	1 (5.6)
Perforation	0	1 (5.6)
<b>Long-term complications, n (%)</b>		
Brid ileus	6 (25)	1 (5.6)
Incisional hernia	2 (8.3)	0
Surgical site infection	0	1 (5.6)

**Table 4.** Multivariate analyses for postoperative short-term complications, reoperation, and postoperative long-term complications

Variables	Short-term complications		Reoperation		Long-term complications	
	Multivariate analyses		Multivariate analyses		Multivariate analyses	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	1.02 (0.95-1.10)	0.528	0.98 (0.91-1.06)	0.641	1.06 (0.98-1.15)	0.175
Male	0.73 (0.09-5.63)	0.761	1.38 (0.17-11.01)	0.764	3.59 (0.30-43.33)	0.315
NLR	0.99 (0.95-1.02)	0.427	1.00 (0.92-1.08)	0.931	1.02 (0.96-1.09)	0.491
PLR	1.00 (1.00-1.01)	0.377	1.00 (0.99-1.00)	0.354	1.00 (0.99-1.01)	0.476
LMR	0.46 (0.16-1.37)	0.164	1.35 (0.84-2.17)	0.223	1.28 (0.81-2.02)	0.292
Crohn's disease	1.65 (0.16-17.07)	0.676	0.25 (0.02-2.95)	0.274	3.14 (0.27-36.53)	0.361
ASA3	0.92 (0.06-13.47)	0.950	1.37 (0.13-14.43)	0.792	0.06 (0.00-2.93)	0.156

CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio

## Discussion

Inflammatory bowel disease has an increasing prevalence worldwide, and it is primarily controlled through medical treatment. Intermittent attacks may occur during the course of the disease, and these attacks, for which medical treatment is usually sufficient, may become complicated according to the progression of the disease. In these situations, surgical intervention may be required. Therefore, it is important to keep the disease under control and reduce the attacks as much as possible. While many inflammatory parameters are used in the course of the disease, the ratios formed through these parameters have started to gain popularity recently. Among these, the most common parameter is NLR, and many studies have stated the use of this ratio in determining the severity and course of the disease. In addition, LMR and PLR are popular parameters that began to be used in detecting the severity of the disease. Azab et al.<sup>6</sup> showed that NLR is a more effective parameter than white blood cells in predicting the prognosis of acute pancreatitis. Furthermore, there are studies emphasizing that these ratios are not useful in showing the severity of the disease.<sup>7</sup> Although there are many studies that show the relationship between the ratios and the severity of the disease, studies exploring the relationship between these ratios and postoperative complications are limited. Kang et al.<sup>8</sup> showed that an NLR greater than 4.1 increases the risk for postoperative complications by 2.782 times. Moreover, in a study by Nishida et al.<sup>9</sup>, NLR was detected as a prognostic marker for the development of pouchitis in patients with UC who underwent ileal pouch-anal anastomosis. Furthermore, in a study by Argeny et al.<sup>10</sup>, preoperative NLR levels were not associated with postoperative complications in patients with symptomatic CD. Mullin et al.<sup>11</sup> reported inflammatory markers as predictive parameters in patients who underwent gastrointestinal surgery for CD. Moreover, in a

study performed by Tsunoda et al.<sup>12</sup> and published in 2022, it was reported that NLR was a useful marker for predicting postoperative complications in CD. This study could not find any correlation between postoperative complications and these ratios. Singh et al.<sup>13</sup> reported a systematic review and meta-analysis in 2015, and they found no difference in mortality between elective and emergency surgeries for UC. They stated that mortality was higher in patients who underwent emergency surgery in CD. In this study, although the difference was not statistically significant, mortality was higher in patients with UC. This may be a result of the higher age and ASA scores in patients with UC rather than the complexity of the surgery. In addition, the Clavien-Dindo complication scores were higher in patients with UC; however, this difference was not statistically significant.

## Conclusion

NLR, PLR, and LMR are not predictive inflammatory biomarkers for postoperative complications, mortality, and reoperation in patients who underwent emergency surgery for IBD complications.

## Ethics

**Ethics Committee Approval:** The protocol of this study was approved by the Local Ethics Committee of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (approval number: 21, date: 17.01.2022).

**Informed Consent:** Informed consent was not provided by the patients as this was a retrospective study.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: G.K.T., S.A., K.E.K., Concept: G.K.T., K.E.K., Design: G.K.T., K.T., S.A., Data Collection or Processing: G.K.T., K.T., Analysis or Interpretation: G.K.T.,

K.T., Literature Search: G.K.T., S.A., Writing: G.K.T., S.A., K.E.K.

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# Effect of 30% Silver Nitrate Treatment in Anal Fistulas: A Pilot Study

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## ABSTRACT

**Aim:** Anal fistulas constitute a challenging entity for general surgeons. To date, there is no optimal treatment for anal fistulas. This study aims to determine the rate of complete clinical healing after applying a 30% silver nitrate solution to treat anal fistula.

**Method:** Consecutive adult patients with symptomatic, either primary or recurrent, crypto glandular anal fistulas presenting between February 2019 and January 2020 in one center were prospectively included in the study. Fistula tracts were irrigated with a 30% silver nitrate solution in an outpatient clinic, and irrigation was repeated when necessary. The primary outcome was the rate of complete clinical healing after the treatment. Factors that may have affected healing were also analyzed.

**Results:** Among 83 consecutive patients with anal fistulas admitted to one center between February 2019 and January 2020, 72 were included in the study. After 30% silver nitrate irrigation, 34 (47%) patients had complete clinical healing. Patients were followed up for a median of 9 (4-16) months after treatment. The patients (n=15) followed up at 12 months and beyond exhibited 73% (n=11) complete clinical healing, while those (n=57) followed-up before 12 months only had 40% (n=23) complete clinical healing (p=0.002). Kaplan-Meier analysis showed that the estimated rate of complete clinical healing was 88% throughout the 15-month follow-up period.

**Conclusion:** This study showed that 30% silver nitrate treatment is effective and safe for anal fistulas

**Keywords:** Anal fistula, proctology, silver nitrate

## Introduction

Although anal fistulas were defined centuries ago, their optimal treatment has not yet been identified, and they still present a big dilemma for surgeons. The prevalence of anal fistulas is given as 0.01%.<sup>1</sup> Anal fistulas rarely heal spontaneously because they are lined with epithelial tissue, and there is a chronic gland infection.<sup>2</sup> The goal of anal fistula treatment is to reduce the recurrence rate, prevent anal abscess formation, and preserve sphincter function. To overcome the risk of fecal incontinence, many sphincter preserving techniques have been used, such as anorectal flaps, bioprosthetic plugs, and laser ablation of fistula tract (LAFT) and ligation of intersphincteric fistula tract (LIFT) treatments.<sup>3,4</sup> It has been reported that the causes of treatment failure are unnoticed concomitant tracts, insufficient drainage of the intersphincteric area, and the remnant epithelial or granulation tissue residues of the

fistula tract.<sup>5</sup> In a previous study, this team showed that a chemical agent, 1% silver nitrate solution, is effective in fistula treatment with complete healing in approximately 50% of patients.<sup>6</sup> Silver nitrate causes ablation of fistula epithelial tissue and leads to healing with fibrosis and eventual tract closure without surgical intervention.

This study aims to determine the complete clinical healing rate after applying 30% silver nitrate solution for treating anal fistulas.

## Materials and Methods

### Study Design and Patients

This study was conducted prospectively. Adult patients with cryptoglandular anal fistulas admitted to the general surgery outpatient clinic in Marmara University Hospital between February 2019 and January 2020 were evaluated for inclusion in the study. Patients older than 18 years diagnosed with



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primary or recurrent cryptoglandular anal fistula admitted consecutively to the general surgery outpatient clinic were included in the study. Patients with Crohn's disease, patients who were not followed up after treatment, and patients who did not provide written informed consent were excluded from the study. This study was approved by the Marmara University Faculty of Medicine Ethics Committee (approval number: 09.2020.681, date: 24.07.2020), and all patients provided written informed consent.

### Data Collected

Data regarding patients' demographics, complaints (discharge, itching, and perianal pain), comorbidities, alcohol consumption, smoking, history of anal surgery, and physical examination findings were recorded prospectively. Perianal magnetic resonance imaging (MRI) was performed for all patients before administering 30% silver nitrate, and fistulas were categorized according to Parks' classification. Patients with complaints such as bloody mucus stool, diarrhea, weight loss, and suspected inflammatory bowel disease (IBD) underwent colonoscopy and were referred to the gastroenterology department for IBD evaluation.

### Silver Nitrate Application Procedure

After the patients were placed in the left lateral decubitus position, an 18 G cannula was inserted through the fistula's external orifice. Irrigation was applied to the fistula tract with a 30% silver nitrate solution (Figure 1). Depending on the length and width of the fistula, approximately 1-2 mL of silver nitrate was administered. During irrigation, whether the silver nitrate solution reached the internal orifice was confirmed by asking the patient to state when they felt a



Figure 1. Irrigation of the fistula tract by silver nitrate solution

cold or burning sensation (due to the silver nitrate solution) in the anal canal. Subsequently, the cannula was retracted slowly while irrigation was performed up to the external orifice.

### Follow-up

The patients were called to the outpatient clinic 2 months after the irrigation and evaluated in terms of perianal pain and discharge complaints. The second irrigation was applied to the patients whose discharge did not stop. Irrigation with a 30% silver nitrate solution was applied every 2 months (up to five times) for these patients. Complete clinical healing was defined as no discharge and closure of the external orifice for at least 30 days after the treatment, while treatment failure was defined as no discharge reduction. Patients with complete clinical healing were radiologically evaluated by perianal MRI 2 months after healing.

### Statistical Analysis

SPSS 23.0 (SPSS, Inc., Chicago, IL, USA) was used to analyze the data. The t-test or Mann-Whitney U test was used to analyze continuous data. Fisher's exact test or the chi-squared test was used to analyze categorical data. All tests were two-sided. P-values less than 0.050 were considered statistically significant. The cumulative probability of fistula healing after treatment was estimated using Kaplan-Meier analysis. A logistic regression model was used for multivariate analysis.

### Outcomes

The primary outcome of this study was to determine the complete clinical healing rate after 30% silver nitrate treatment. The secondary outcome was to identify the factors affecting healing.

### Results

Between February 2019 and January 2020, 83 consecutive patients with complaints of anal fistulas applied to the general surgery outpatient clinic in the Marmara University Hospital. Seventy-five of these patients were diagnosed with cryptoglandular anal fistulas. The remaining eight patients were diagnosed with anal fistulas secondary to IBD. Silver nitrate treatment was recommended for all patients diagnosed with cryptoglandular anal fistulas, and 74 of them received this treatment. One of the patients refused the treatment with silver nitrate. Two patients were excluded from the study because they were not followed up after treatment. A total of 72 patients were included in the study. The median age was 43 (18-64), and 56 (78%) patients were male. All patients had complaints of discharge. Thirty-four (47%) of the patients complained of daily discharge, and the rest defined

their discharge as intermittent. Fifty-eight (81%) patients described pain due to fistulas, and the median visual analog scale pain score (out of 10) was above 5 for 35 (60%) of them. Irrigations were applied twice to 29 (40%) patients and thrice to 27 (38%). One irrigation was applied to the remaining 16 (22%) patients.

The patients were followed up for a median of 9 (4-16) months after treatment (Table 1). Complete clinical healing was achieved in 34 (47%) patients after 30% silver nitrate treatment (Figure 2, 3). Using Kaplan-Meier analysis, the estimated complete healing rate was 88% after the 15-month follow-up period (Figure 4).

The number of patients with intersphincteric fistulas was significantly higher among patients with complete clinical healing than among those with failure to heal [27 (79%) vs 21 (55%), respectively,  $p=0.030$ ] (Table 2).

Compared with patients with continuous discharge ( $n=31$ ), patients with intermittent discharge ( $n=36$ ) had a significantly higher rate of complete clinical healing (31% vs 64%,  $p=0.005$ ) (Table 2). The patients with a follow-up period of  $\geq 12$  months ( $n=15$ ) after the first irrigation with silver nitrate had a higher complete clinical healing rate than those with a follow-up period  $<12$  months ( $n=57$ ) [73% ( $n=11$ ) vs 40% ( $n=23$ )], respectively,  $p=0.020$ .

Fifteen (21%) patients were determined to have no change in discharge symptoms. However, 23 (32%) patients were determined to have between 40% and 80% reduction in discharge after treatment compared with that before treatment. While 58 (81%) patients had pain due to fistulas before treatment, only seven (10%) had this pain after treatment. This decrease was statistically significant ( $p<0.001$ ). Only one (3%) of the patients who did not describe complete healing accepted fistula surgery. However, the patients without complete healing described a significant increase in their quality of life due to decreased discharge and pain. Furthermore, they did not feel the need for the surgical treatment that had been recommended after their silver nitrate treatment failed. Mild perianal pain was described during silver nitrate irrigation in 16 (22%) patients. Two patients developed temporary induration along the fistula tract after irrigation during the early follow-up period. A small perianal abscess developed in two (3%) patients during the follow-up period after irrigation, and drainage occurred spontaneously without any intervention.

## Discussion

In this single-center study, 30% silver nitrate treatment was applied to 72 patients with a crypto glandular fistula. The study showed that after applying 30% silver nitrate treatment, nearly half of the patients had complete clinical healing. Significant reductions in pain and discharge



Figure 2. View of the external orifice after healing

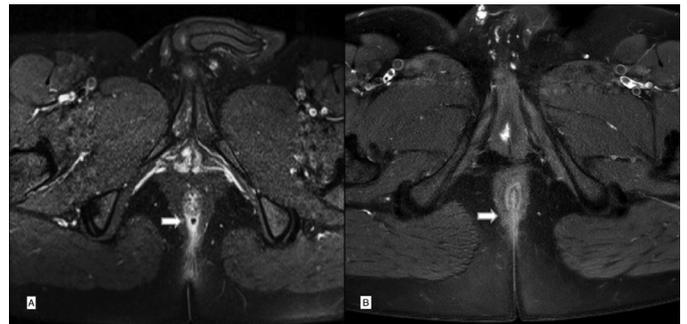


Figure 3. Pre-treatment (A) and post-treatment (B) contrast-enhanced magnetic resonance images

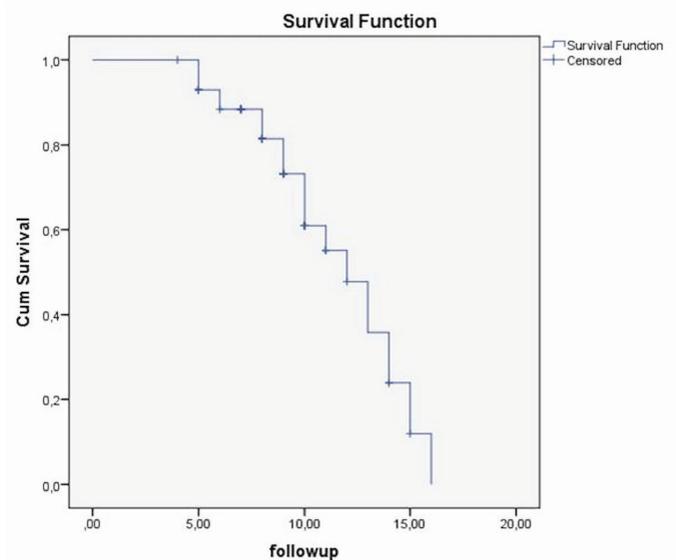


Figure 4. Estimated healing rate based on Kaplan-Meier analysis for all patients

**Table 1.** Demographic and clinical characteristics of the patients

<b>Age, years, median (range)</b>		43 (18-64)
<b>Gender, n (%)</b>		
Male	56 (78%)	
Female	16 (22%)	
Body mass index, median (range)	28 (16-42)	
Primary fistula	61 (85%)	
Recurrent fistula	11 (15%)	
Duration of discharge before treatment (months), median (range)		12 (1-360)
<b>Discharge frequency, n (%)</b>		
Continuous	34 (47%)	
Intermittent	38 (53%)	
Pain complaints, n (%)	58 (81%)	
Pain VAS score, median (range)		4 (0-10)
Itching, n (%)	47 (65%)	
<b>Comorbidity, n (%)</b>		
Hypertension	10 (14%)	
Diabetes mellitus	3 (4%)	
Coronary artery disease	5 (7%)	
Smoking, n (%)	22 (31%)	
Alcohol consumption, n (%)	3 (4%)	
History of hemorrhoidectomy, n (%)	4 (6%)	
History of anal fissure surgery, n (%)	4 (6%)	
<b>External orifice</b>		
Single	64 (89%)	
Multiple	8 (11%)	
<b>Type of fistula, n (%)</b>		
Intersphincteric	49 (68%)	
Transsphincteric	17 (24%)	
Extrasphincteric	1 (1%)	
Horseshoe	5 (7%)	
<b>Number of irrigations, n (%)</b>		2 (1-5)
Single	10 (14%)	
Multiple	62 (86%)	
<b>Complications, n (%)</b>		
Induration	2 (3%)	
Abscess	2 (3%)	
<b>Duration of follow-up (months), median (range)</b>		9 (4-16)

VAS: Visual analog scale

symptoms were observed in most patients who were not described as completely healing. The clinical complete healing rate was higher in patients with longer follow-up periods after treatment. To the best of this study's knowledge, this is the first study to use 30% silver nitrate in adult patients for treating anal fistulas. The strengths of this study are the prospective design, inclusion of consecutive patients, and radiological confirmation of clinical healing. The advantages of this treatment modality are that it can be easily applied in outpatient clinics without anesthesia, is reproducible and cheap, and does not cause any major side effects. The limitations of this study are the lack of a control group and the short follow-up period. The success rate of fistulotomy, which has been used for a long time in treating anal fistulas, is still high. However, this surgery's serious complications, such as fecal incontinence, made it necessary to develop alternative modalities.

Although many treatments have been described for anal fistulas, there is no optimal treatment with consensus. New surgical techniques such as LIFT, LAFT, and video-assisted anal fistula treatment have been described in the last two decades.<sup>2</sup> The success rates of different anal fistula treatments vary widely according to the technique applied. The success rate of the LIFT technique was reported as between 40% and 95%.<sup>7</sup> However, no sufficient data regarding fecal incontinence after treatment with the LIFT technique has been reported. In this study, the success rate of silver nitrate irrigation without any surgical intervention is close to that of the LIFT treatment. Furthermore, incontinence is not expected in silver nitrate irrigation since no surgical procedure was performed, and no patient complained of fecal incontinence after treatment in this study. Wilhelm<sup>9</sup> performed LAFT on 33 patients with anal fistulas and achieved complete healing in 26 (78%) patients

**Table 2.** Characteristics of patients segregated based on treatment outcome

	Patients with complete clinical healing (n=34)	Patients with failure to heal (n=38)	P
Age, years, median (range)	46 (21-64)	38 (18-63)	0.060
Gender, n (%)			0.800
Female	8 (23%)	8 (21%)	
Male	26 (77%)	30 (79%)	
Body mass index, median (range)	27 (21-42)	27 (16-37)	0.700
Duration of discharge before treatment (months), median (range)	15 (1-360)	12 (3-240)	0.500
Smoking, n (%)	13 (38%)	9 (23%)	0.200
Alcohol consumption, n (%)	0 (0%)	3 (7%)	0.200
Comorbidity, n (%)	7 (21%)	5 (13%)	0.300
History of anal fistula surgery, n (%)	5 (14%)	6 (15%)	0.900
External orifice			1,000
Single	30 (88%)	34 (89%)	
Multiple	4 (12%)	4 (11%)	
<b>Type of fistula, n (%)</b>			
Intersphincteric	27 (79%)	21 (55%)	0.03
Transsphincteric	5 (18%)	11 (29%)	0.3
Extrasphincteric	0 (0%)	1 (0.3%)	
Suprasphincteric	0 (0%)	0 (0%)	
Horseshoe	2 (6%)	3 (8%)	0.4
Discharge frequency, n (%)			0.005
Continuous	11 (32%)	25 (66%)	
Intermittent	23 (68%)	13 (34%)	
Number of irrigations, median (range)	2 (1-5)	3 (1-5)	0.1
Duration of follow-up before treatment (months), median (range)	10 (5-16)	8 (4-15)	0.08

after a mean follow-up period of 7.4 months. However, Ozturk et al. reported a success rate of 60% in patients treated by LAFT in a series of 20 patients, and it was found that this success rate decreased in long-term follow-ups. In the previous LAFT studies, these success rates are caused by combined additional procedures, such as bridging with seton, internal orifice closure during primary surgery, and excision of the distal part of the fistula tract, rather than laser treatment alone. Furthermore, the authors stated that the LAFT technique could not close secondary tracts.<sup>9</sup>

However, the authors of this study believe that silver nitrate in solution form can ablate the primary and secondary tracts. Some disadvantages of using LAFT include anesthesia requirements, the high cost, and the possibility of widening the fistula diameter in some patients. This study achieved complete healing using only silver nitrate irrigation and without applying combined processes. Further studies with silver nitrate combined with other procedures, such as internal orifice closure, bridging with seton, internal orifice closure, or excision of the distal part of the fistula tract, may cause higher success rates in the future. In the LAFT technique, the fistula is healed by ablating the epithelial tissue of the fistula tract using laser energy.

This study used silver nitrate solution as a corrosive chemical agent instead of a laser probe for ablating the epithelial tissue of the fistula tract, and it showed similar healing rates. Silver nitrate is a cost-effective treatment and can be applied in outpatient conditions without anesthesia. This makes this treatment advantageous compared with the LAFT technique. The silver+ ( $\text{Ag}^+$ ) ion, the active biological form of the silver molecule, shows its effect in two phases. In the early phase,  $\text{Ag}^+$  ions denature proteins. In the late phase, the silver proteinate progressively ionizes and thus creates a slow but long-lasting effect. The  $\text{Ag}^+$  ions also have an antiseptic effect by denaturing bacterial cell wall proteins. This study found that the silver nitrate molecule causes fistulas to heal with its corrosive and antibacterial effects.<sup>10-12</sup> Silver nitrate treatment for anal fistulas was described for the first time by Attaallah et al.<sup>6</sup> in 2014. After irrigating anal fistulas with 1% silver nitrate, complete clinical healing was achieved in 52% of patients.<sup>13</sup> Although a higher concentration of silver nitrate (30%) was used in this study, a higher healing rate was not achieved compared with the previous study. The authors of this study believe that further studies need to use combined methods, such as internal orifice closure combined with silver nitrate irrigation, which could improve the outcomes. Doll and Vassiliu<sup>14</sup> reported a 27% success rate in a series of 15 patients who were treated with 1% silver nitrate irrigation. The authors stated the relatively low success rate in this study to have possibly been due to the short follow-up period after treatment.

In a study conducted by Tomasello et al.<sup>15</sup>, after using Argentum-quartz solution as a corrosive agent, they stated that two out of three patients had complete healing. Placer-Galán et al.<sup>16</sup> reported a complete healing rate of 44.4% after treatment with silver nitrate 1% solution in recurrent or persistent anal fistulas. The authors stated that in a recurrent or persistent complex anal fistula, local conservative treatment with a 1% silver nitrate solution instillation is an alternative that should be considered to reduce the risk of incontinence.<sup>16</sup> In a series of 76 patients treated by Iqbal et al.<sup>17</sup>, the complete healing rate was 76.3% after using a 1% silver nitrate solution. The high rate of complete healing in that study can be explained by the combination of silver nitrate irrigation with curettage of the fistula tract with a blunt-tipped cannula before irrigation. In a series of 113 infants treated by Utsunomiya et al.<sup>18</sup>, 30% silver nitrate solution was used, and it was reported that 76% of the patients healed without serious complications. In a prospective study of 49 patients with intersphincteric and transsphincteric fistula by Kaya et al.<sup>19</sup>, a 67% complete healing rate was achieved after using 20% silver nitrate solution.

Intermittent discharge frequency was a good prognostic factor for healing (Table 2). It can be explained by the minimal complications, and smaller fistulas may have closed easily with fibrosis after silver nitrate irrigation. Furthermore, the longer follow-up period after treatment was also a good prognostic factor for healing. This can be explained by fibrosis being a time-consuming process. Curettage of the fistula tract with an endoscopic brush before irrigation may have been a cause of higher rates of complete healing in that study. No serious complications were observed in this study. The study used a 30% silver nitrate solution as effectively as it was reported by the previous studies.<sup>14-19</sup> Due to the coronavirus disease pandemic, most elective surgeries became unavailable, patient waiting times were prolonged, patients became afraid of hospitalization, and operations for benign diseases, such as anal fistula, were postponed. In such situations, outpatient conservative treatments with silver nitrate may be a good alternative treatment for anal fistulas. However, based on these prospective results, more comprehensively planned, prospective, randomized controlled studies need to be conducted.

## Conclusion

This study showed that 30% silver nitrate is an effective and safe treatment for anal fistulas. Due to its advantages of being non-invasive and cost effective; having acceptable healing rates, no major complications, and no need for anesthesia; and providing outpatient applicability, it can be used as the

first-line anal fistula treatment. Surgical treatment is still an option for patients whose silver nitrate treatment fails.

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### Ethics

**Ethics Committee Approval:** This study was approved by the Marmara University Faculty of Medicine Ethics Committee (approval number: 09.2020.681, date: 24.07.2020).

**Informed Consent:** All patients provided written informed consent.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: W.A., A.T., Concept: W.A., A.T., Design: W.A., A.T., Data Collection or Processing: W.A., A.T., Analysis or Interpretation: W.A., A.T., Literature Search: W.A., A.T., Writing: W.A.

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# The Effectiveness of the Serum Neutrophil-lymphocyte Ratio in the Determination of an Advanced Stage in Colorectal Cancers

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## ABSTRACT

**Aim:** Patients with colorectal cancer (CRC) have a poor prognosis in the advanced stages. Although advanced imaging methods contribute to the diagnosis process, there is a need for potential biomarkers to help identify patients with poor prognoses. The neutrophil-lymphocyte ratio (NLR) is one of these potential biomarkers, and many studies have found that a high NLR is a predictive marker for a poor prognosis in various cancers. This study aims to determine whether there is a relationship between the NLR and the tumor stage in CRC patients.

**Method:** We retrospectively assessed patients who underwent elective curative resection for CRC between January 2016 and July 2019. The demographic information, preoperative NLR, and detailed pathological data were recorded and analyzed. The study's primary aim was to investigate whether there was a relationship between the pathological stage and the NLR. The secondary aim was to examine the relationship between the number of positive and removed lymph nodes, tumor biology, and the NLR.

**Results:** No statistically significant correlation existed between the tumor stage, the number of positive and removed lymph nodes, and the NLR. However, a statistically significant negative correlation was found between tumor differentiation and the NLR.

**Conclusion:** Although a relationship between the tumor stage and the NLR was shown in the authors' study, this did not reach the level of statistical significance. Likewise, there was no significant relationship between the lymph node involvement and the NLR; only the degree of differentiation of the tumor and the NLR were significantly correlated. Therefore, prospective randomized studies with large patient cohorts would be useful in evaluating the clinical use of the NLR in CRC.

**Keywords:** Colorectal cancer, neutrophil-lymphocyte ratio, stage, survival, differentiation, lymphatic infiltration, vascular invasion, perineural invasion

## Introduction

Colorectal cancer (CRC) is one of the most common types of cancer worldwide.<sup>1</sup> Despite the advancement of new therapeutic strategies in surgery, chemotherapy, radiotherapy, and molecular therapy, the overall prognosis of advanced CRC is still poor, with a 5-year survival rate of less than 15%.<sup>2</sup> Although advanced imaging methods contribute to the diagnosis process, there is a need for potential biomarkers to help identify patients with poor prognoses.

Local immune response and systemic inflammation have been shown to play important roles in cancer progression

and survival.<sup>3</sup> The clinical utility of inflammatory prognostic biomarkers has been described in many different forms of cancer.<sup>4</sup> The neutrophil-lymphocyte ratio (NLR), lymphocyte-C-reactive protein ratio, platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio are some of these biomarkers. Zhou et al.<sup>5</sup> showed that the NLR was significantly higher in patients with CRC compared with patients with colorectal polyps and healthy controls.

Many studies have found that a high NLR is a predictive marker for poor prognoses in various cancers, including gastric, esophageal, and colorectal.<sup>6</sup> Increased pretreatment



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NLR has been linked to disease progression, poor treatment response, and reduced chances of survival in CRC and other cancers.<sup>6-9</sup> Considering the importance of systemic inflammatory reactions in tumor development and treatment, it is thought that NLR levels might reflect systemic inflammatory reactions in CRC, and there may be a correlation between the tumor stage and the NLR.<sup>10</sup>

This study aims to determine whether there is a relationship between the NLR and the tumor stage in CRC patients by examining the preoperative neutrophil and lymphocyte values and postoperative pathological findings of patients operated on for CRC in the center's general surgery department.

## Materials and Methods

The study protocol was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Ümraniye Training and Research Hospital (approval number: 142, date: 21.11.2018). The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

We retrospectively assessed patients (age >18 years) who underwent elective curative resection for CRC between January 2016 and July 2019. Patients who underwent emergency surgery, had severe comorbid disease (American Society of Anesthesiologists score; >3), or had lost data were excluded from the study.

The patients' data were obtained from the hospital's data processing department. The patients' demographic information, preoperative neutrophil and lymphocyte counts, surgical procedure details, number of lymph nodes removed during surgery, tumor positive lymph node count, tumor differentiation rate, presence of lymphatic, vascular, and perineural invasion, and pathological stage were recorded and analyzed.

The study's primary aim was to investigate whether there is a relationship between the pathological stage and the NLR in CRC. The secondary aim was to examine the relationship between the number of positive lymph nodes and removed lymph nodes, the tumor biology (differentiation and lymphatic, vascular, and perineural invasion), and the NLR ratio.

The eighth edition of the American Joint Commission on Cancer's tumor-node-metastasis (TNM) staging system was used in the study.<sup>11</sup> For calculating the NLR, patients' complete blood counts obtained on the day of admission to the hospital were used. The NLR was calculated as neutrophil counts divided by lymphocyte counts. The reference values for neutrophils and lymphocytes were 2.00-7.00  $10^3/uL$  and 0.80-4.00  $10^3/uL$ , respectively.

## Statistical Analysis

Statistical analyzes were performed using the SPSS® software (version 20.0, SPSS Inc., Chicago, IL, USA). The descriptive analyzes were presented as means  $\pm$  standard deviations, medians and interquartile range (IQR), and percentages. The distribution normality was obtained using the graphical representation and the Kolmogorov-Smirnov test. While the ages of the patients were normally distributed in the Kolmogorov-Smirnov test ( $p=0.200$ ), the number of lymph nodes removed ( $p<0.001$ ), lymphocyte ( $p<0.001$ ), and neutrophil ( $p<0.002$ ) values were not normally distributed. In cases where the data were unsuitable for normal distribution, the Kruskal-Wallis H test, Mann-Whitney U test, and chi-squared test were used to measure the differences in discrete variables between the groups. The Spearman's rank correlation co-efficient was used to measure the relationship between the variables. Binary logistic regression was used if the dependent variable was binary discrete, and multinomial logistic regression was used if it was multiple. The results were evaluated at the 95% confidence interval at the  $p<0.05$  significance level.

## Results

Two hundred twenty-eight patients who met the inclusion criteria were included in this retrospective study. The mean age was  $59.9\pm 11.9$ , and 137 (60%) patients were male. No statistically significant difference was found in age according to gender ( $p=0.16$ ).

The most common surgical procedure was low anterior resection (43.8%). Table 1 shows the patient characteristics and the surgical procedures performed. The median number of lymph nodes removed was 21 (IQR; 15-31). According to the TNM classification, most patients were in stage 2 in the postoperative pathological evaluation, while stages 1, 3, and 4 were 9.2%, 39.9%, and 7%, respectively.

While most tumors were moderately differentiated (85%), 4.9% were well differentiated, 8.8% were poorly differentiated, and 1.3% were undifferentiated. Lymphatic invasion was found in 33.7% of the patients, vascular invasion in 24.5%, and perineural invasion in 51.3%.

The median neutrophil value of the patients was  $4.69 \cdot 10^3/uL$  (IQR: 3.52-5.80), and the median lymphocyte value was  $1.90 \cdot 10^3/uL$  (IQR: 1.29-2.41). The median NLR was 2.23 (IQR: 1.59-3.56), 2.59 (IQR: 1.67-3.87), 2.78 (IQR: 1.89-3.81), and 2.40 (IQR: 1.79-3.86) in patients with stage 1, 2, 3, and 4, respectively. There was no statistically significant difference between the tumor stages regarding the NLR ( $p=0.46$ ).

The relationship between the NLR and the tumor stage was investigated by multinomial regression. The variables were

statistically analyzable when the stage 1 reference category was taken ( $p>0.05$ ; goodness-of-fit). Compared with stage 1, the NLR of stage 2 and stage 3 increased approximately 1 time, although it was not statistically significant ( $p>0.05$ ). Compared with stage 1, the NLR of stage 4 decreased 0.88 times, although it was not statistically significant ( $p>0.05$ ) (Table 2).

The relationship between the number of harvested and positive lymph nodes and the NLR was investigated, and no statistically significant correlation was found ( $r=0.032$ ,  $r=0.06$ ,  $p>0.05$ , respectively) (Table 3).

The relationship between the NLR and differentiation was investigated by multinomial regression. Patients with undifferentiated tumors were excluded from the analysis,

**Table 1.** Patient characteristics

Variable	n (%)
Age, mean (standard deviation)	59.9±11.9
<b>Gender</b>	
Female	91 (40)
Male	137 (60)
Neutrophil, $10^3/uL$ , median (IQR)*	4.69 (3.52-5.80)
Lymphocyte, $10^3/uL$ , median (IQR)	1.90 (1.29-2.41)
<b>Surgical procedure</b>	
Low anterior resection	100 (43.8)
Right hemicolectomy	51 (22.4)
Left hemicolectomy	41 (17.9)
Anterior resection	25 (10.9)
Abdominoperineal resection	7 (0.3)
Total colectomy	4 (0.2)
<b>Stage</b>	
1	21 (9.2)
2	100 (43.8)
3	91 (39.9)
4	16 (7.1)
Presence of lymphatic invasion	77 (37.7)
Presence of vascular invasion	56 (24.5)
Presence of perineural invasion	117 (51.3)
<b>Differentiation</b>	
Well	11 (4.9)
Moderately	194 (85)
Poorly	20 (8.8)
Undifferentiated	3 (1.3)

\*IQR: Interquartile range

and the analysis was continued with 225 patients. The variables were statistically analyzable when the group with poorly differentiated tumors was taken as the reference category ( $p>0.05$ ; goodness-of-fit). Compared with the patients with poorly differentiated tumors, the NLR of patients with well-differentiated tumors decreased by 0.94 times, although it was not statistically significant ( $p>0.05$ ), while the NLR of patients with moderately differentiated tumors was statistically significantly reduced by 0.88 times ( $p<0.05$ ) (Table 4).

The relationship between the lymphatic, vascular, and perineural invasion and the NLR was investigated by logistic regression. Although not statistically significant, the NLR decreased approximately 0.95-fold in patients with lymphatic infiltration ( $p>0.05$ ), while it increased 1-fold in patients with vascular and perineural invasion ( $p>0.05$ ) (Table 5).

## Discussion

In the authors' study, patients who were operated on for CRC were evaluated, and it was investigated whether there was a correlation between the preoperative NLR and the pathological stage. Accordingly, the use of the NLR as a biomarker in patients with CRC was questioned. Although the results showed no significant relationship between the NLR and the pathological stage, the NLR was significantly higher in patients with poorly differentiated tumors than in patients with moderately differentiated tumors.

Biomarkers are important tools in early detection and predicting the prognosis, survival, and treatment response in CRC. Some previous studies have focused on the utility of inflammatory indices, such as the NLR and the PLR, in CRC patient prognosis or treatment response. The NLR has been proposed as a straightforward index of systemic inflammatory response. The cancer-associated systemic inflammatory response is often correlated with increased circulating neutrophil counts. Neutrophils secrete cytokines and chemokines, which play crucial roles in cancer progression. Moreover, lymphocytes can promote a cytotoxic immune response to cancer<sup>4</sup>. Simply, neutrophilia occurs during systemic inflammation, and lymphopenia is a marker of depressed cell-mediated immunity.<sup>12</sup>

In 2001 Zahorec<sup>12</sup> first described the role of the NLR in critically ill patients and found the NLR to be associated with the severity of the clinical condition. Walsh et al.<sup>13</sup> first reported a correlation between preoperatively elevated NLR and overall and cancer-specific survival in colon cancer. Proctor et al.<sup>14</sup> analyzed 12,118 patients, including 1,413 CRC patients, and indicated that the NLR was a significant marker for overall and cancer-specific survival.

**Table 2.** The relationship between the neutrophil-lymphocyte ratio and the tumor stage\*

Stage	B	Standard error	Wald	p	Exp(B)	95% CI for exp(B)	
						Lower bound	Upper bound
2	0.081	0.101	0.638	0.424	1.084	0.889	1.323
3	0.072	0.102	0.494	0.482	1.074	0.88	1.312
4	-0.128	0.192	0.443	0.506	0.88	0.604	1.282

\*Multinomial regression; stage 1 reference category. CI: Confidence interval

**Table 3.** The correlation between the number of harvested and positive lymph nodes and the neutrophil-lymphocyte ratio

	r*	p
Harvested lymph nodes	0.032	0.628
Positive lymph nodes	0.065	0.538

\*Spearman's rank correlation coefficient

**Table 4.** The relationship between the neutrophil-lymphocyte ratio and differentiation\*

Differentiation	B	Standard error	Wald	p	Exp(B)	95% CI for exp(B)	
						Lower bound	Upper bound
Well	-0.062	0.068	0.851	0.356	0.940	0.823	1.073
Moderately	-0.124	0.053	5.363	0.021	0.884	0.796	0.981

\*Multinomial regression; poorly differentiated tumors reference category. CI: Confidence interval

**Table 5.** The relationship between the neutrophil-lymphocyte ratio and the lymphatic, vascular, and perineural invasion\*

	B	Standard error	Wald	p	Exp(B)	95% CI for exp(B)	
						Lower bound	Upper bound
Lymphatic invasion	-0.049	0.049	1.002	0.317	0.952	0.865	1.048
Vascular invasion	0.013	0.044	0.084	0.772	1.013	0.930	1.103
Perineural invasion	0.053	0.043	1.496	0.221	1.054	0.969	1.148

\*Logistic regression. CI: Confidence interval

Many studies have focused on the effects of the NLR on the prognosis of CRC.<sup>4</sup> Recently, a meta-analysis by Naszai et al.<sup>15</sup> found that high pretreatment blood NLR was associated with poor overall survival and surrogate endpoints in CRC patients. Jia et al.<sup>10</sup> retrospectively analyzed CRC patients for the relationship between the NLR, PLR, and tumor TNM stages. They observed that the levels of both markers were significantly higher in CRC patients than in healthy controls. Furthermore, the increase in the NLR and the PLR correlated with the TNM stages.<sup>10</sup> Pereira et al.<sup>16</sup> found that the NLR was significantly higher in patients with T3-T4 tumors than in T1-T2 tumors (5.8 vs 2.6,  $p < 0.001$ ). In a meta-analysis, Li et al.<sup>6</sup> presented data on the NLR and the TNM stages in three studies, showing that patients with a high NLR

tended to the advanced TNM stage. Although there was no statistically significant relationship between the tumor stage and the NLR in the authors' study, a tendency for increased NLR was found in advanced-stage patients. It is thought that the inconsistency of these results with the literature may be due to the lack of homogeneity in the stage distribution of the cohort. Like the authors' study, Kwon et al.<sup>17</sup> did not find a significant relationship between the tumor stage and the NLR in 200 CRC patients.

There is a lack of studies in the literature that specifically examine the relationship between the NLR and the lymph node status. According to Caputo et al.<sup>18</sup>, when the NLR's cut-off value was taken as 3.7, it showed that a high NLR was predictive of lymph node metastasis in patients with T1

CRC. Khan et al.<sup>19</sup> showed that a elevated NLR was associated with a positive nodal status in rectal cancer patients. The authors' study evaluated the relationship between the number of harvested and positive lymph nodes and other histopathological results with the NLR. No correlation was found between the number of harvested and positive lymph nodes and the NLR.

The patients with moderately differentiated tumors had a statistically lower NLR of 0.88 times compared with patients with poorly differentiated tumors ( $p < 0.05$ ). Four studies that examined the relationship between the NLR and tumor differentiation in the literature also support this finding.<sup>20-23</sup>

### Study Limitations

This study inevitably has limitations due to its retrospective nature, single-center design, and the low number of patients. However, the NLR value and its relationship with the tumor stage, lymph node metastases, tumor differentiation, and vascular, lymphatic, and perineural invasion in patients with CRC have been thoroughly evaluated. Larger prospective studies will need to be performed for the clinical use of the NLR.

### Conclusion

In conclusion, most of the studies in the literature have shown a significant relationship between the NLR and the tumor TNM stage and prognosis. However, although a relationship between the tumor stage and the NLR is shown in the authors' study, this did not reach the level of statistical significance. Likewise, no significant relationship could be demonstrated between the lymph node involvement and the NLR; only the degree of differentiation of the tumor and the NLR were significantly correlated. Therefore, prospective randomized studies with large patient cohorts would be useful in evaluating the clinical use of the NLR in CRC.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Ümraniye Training and Research Hospital (approval number: 142, date: 21.11.2018).

**Informed Consent:** Retrospective study.

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### Authorship Contributions

Surgical and Medical Practices: H.Ç., A.T., Ö.F.Ö., Ö.D., Concept: H.Ç., A.T., Ö.F.Ö., Design: H.Ç., Ö.D., Data Collection or Processing: H.Ç., Ö.F.Ö., Analysis or Interpretation: H.Ç., E.S., Literature Search: H.Ç., E.S., Ö.F.Ö., Writing: H.Ç., E.S.

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