

The importance of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio to prediction severity of esophageal injury after corrosive substance ingestion

La importancia del INL y el IML para predecir la gravedad de la lesión esofágica tras la ingestión de sustancias corrosivas

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Abstract

Objectives: The ability to predict the severity of corrosive injury in patients remains challenging. This study aims to explore the potential of the neutrophil-to-lymphocyte ratio (NLR) and the monocyte-to-lymphocyte ratio (MLR) as novel diagnostic markers to predict the severity of esophageal injury following corrosive substance ingestion (CSI). **Methods:** We conducted a retrospective cohort analysis on patients with CSI. Demographic data, complete blood counts, and endoscopic findings were collected and analyzed. Esophageal injuries were graded using Zargar's classification. The NLR and MLR were calculated and evaluated as potential predictors of injury severity. **Results:** The mean age, NLR, MLR, red distribution width (RDW), and platelet count were increased in the hospitalized patients. Patients with severe esophageal injury also had higher mean age, NLR, MLR, and RDW. In receiver operating characteristic analyses for patients with severe esophageal injury, the area under the curve for NLR and MLR in predicting injury severity and hospitalization was statistically significant. **Conclusions:** NLR, MLR, and RDW hold promise as easily accessible and cost-effective inflammatory markers for predicting esophageal injury severity in patients with CSI. These markers could assist healthcare providers in assessing injury extent, avoiding unnecessary esophagogastroduodenoscopy, and guiding treatment decisions.

Keywords: Caustic injury. Neutrophil-to-lymphocyte ratio. Monocyte-to-lymphocyte ratio. Red cell distribution. Esophagogastroduodenoscopy.

Resumen

Objetivo: Explorar el potencial del índice neutrófilos-linfocitos (INL) y del índice monocitos-linfocitos (IML) como nuevos marcadores diagnósticos para predecir la gravedad de la lesión esofágica tras la ingestión de sustancias corrosivas. **Métodos:** Se realizó un estudio de cohortes retrospectivo de pacientes con ingestión de sustancias corrosivas. Se recopiló y analizaron datos demográficos, hemogramas completos y hallazgos endoscópicos. Las lesiones esofágicas se calificaron utilizando la clasificación de Zargar. El INL y el IML se calcularon y evaluaron como predictores potenciales de la gravedad de la lesión. **Resultados:** La edad media, el INL, el IML, la amplitud de distribución eritrocitaria y el recuento de plaquetas aumentaron en los pacientes hospitalizados. La edad media, el INL, el IML y la amplitud de distribución eritrocitaria aumentaron en los pacientes con lesión esofágica grave. En los análisis ROC realizados en pacientes con lesiones graves en el esófago, el AUC del INL y del IML para predecir la gravedad de la lesión y la hospitalización fue estadísticamente significativo. **Conclusiones:** El INL, el IML y la amplitud de distribución eritrocitaria se muestran prometedores como marcadores inflamatorios de fácil acceso y rentables para predecir la gravedad de la lesión esofágica en pacientes con ingestión de sustancias corrosivas. Estos mar-

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cados podrían ayudar a los proveedores de atención médica a evaluar la extensión de la lesión, evitar una esofagogastro-duodenoscopia innecesaria y guiar las decisiones de tratamiento.

Palabras clave: Lesión cáustica. Índice linfocitos-neutrófilos. Índice monocitos-linfocitos. Distribución eritrocitaria. Esofagogastroduodenoscopia.

Introduction

Corrosive substance ingestions (CSIs) constitute a significant portion of emergency cases and pose a major health challenge, especially in developing countries, but also in developed ones. CSIs can occur either intentionally, as suicide attempts (often in adolescents and adults), or accidentally (mainly in children). The consequences can be devastating, resulting in individual suffering, disability, resource utilization, and costs. Common complications include the formation of gastrointestinal tract strictures, perforation, and hemorrhage. In addition, systemic effects such as disseminated intravascular coagulation, multi-organ system failure, and sepsis may occur. However, predicting which patients will develop such complications is a challenging task. Patient history and clinical findings are insufficient to reliably predict the severity of corrosive injury. Several studies have shown that clinical signs are not always reliable indicators of the degree of injury and the potential outcome of stricture formation.¹ Given that patient follow-up and treatment strategies depend on the severity of the injury, accurately determining the extent of damage is crucial. While esophagogastroduodenoscopy (EGD) is considered the gold standard for assessing the severity of caustic injury, it is invasive, expensive, and yields negative results in 60-82% of cases.^{2,3} Therefore, there is a pressing need for a quantifiable, rapid, inexpensive, and reproducible indicator to predict the severity of corrosive injury.

The neutrophil-to-lymphocyte ratio (NLR) and the monocyte-to-lymphocyte ratio (MLR) are inexpensive and easily accessible inflammatory indicators that can be calculated using a simple blood count. These ratios, especially MLR, reflect the balance between innate and adaptive immunity, offering a straightforward measure of immune status and inflammation level. Numerous studies in the literature have demonstrated associations between NLR and MLR with various inflammatory diseases, several types of cancer, and various liver conditions.⁴⁻⁷

However, the predictive value of NLR and MLR in assessing the severity of esophageal injury in patients

with CSIs has not yet been explored. In this study, we introduce novel diagnostic markers, NLR and MLR, for predicting the severity of CSIs.

Methods

This retrospective cohort analysis consecutively enrolled a series of patients with CSIs who were admitted to the emergency department and underwent EGD between May 2016 and December 2022. Data from medical records included patients' age, sex, duration between corrosive ingestion and hospital presentation, treatment modality, and complications. A complete blood count (CBC) was obtained upon admission, and EGD was performed within 48 h of the initial injury by experienced endoscopists. Esophageal injuries were graded using the method of Zargar et al. as follows: grade 0: normal; grade 1: mucosal edema and hyperemia; grade 2a: hemorrhagic, bullous mucosa, exudates, fibrinous membranes, or superficial ulceration; grade 2b: circumferential ulceration in addition to grade 2a; grade 3: scattered small necrotic areas, multiple and deep ulcerations; grade 3b: extensive necrosis; and grade 4: perforations.⁸ Grades 1 and 2a were defined as mild-moderate lesions, while grades 2b and 3 were defined as severe lesions. Subsequently, patients were divided into two groups: mild-moderate injury and severe injury.

General information was collected, including gender, age, and comorbidity. Laboratory blood results were obtained, including hemoglobin, platelet count (PLT), neutrophil count, lymphocyte count, monocyte count, mean platelet volume (MPV), and red distribution width (RDW). The MLR was calculated as the ratio between the absolute monocyte and lymphocyte counts, and the NLR was calculated as the ratio between the absolute neutrophil and lymphocyte counts.

Exclusion criteria included the presence of other conditions such as malignancy, hematologic disease, use of immunosuppressants, active infection within 1 month before admission, severe hepatic or renal dysfunction, major trauma, or surgery; and missing blood parameter data at admission.

All patients were categorized into two groups: mild-moderate injury and severe injury. In addition, they were further divided into two groups: hospitalized patients and discharged patients. These groups were then compared in terms of demographic and laboratory parameters.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences for Windows, Version 25.0, Armonk, NY, USA: IBM Corp. Qualitative data were expressed as frequency and percentage (n [%]), while quantitative data were expressed as mean and standard deviation (SD). The Chi-square test was used for qualitative variables, one-way analysis of variance (F test) for quantitative variables, and *post hoc* Tukey honestly significant difference test for pairwise comparisons. Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) and 95% confidence intervals were calculated for the studied hemogram parameters. Sensitivity and specificity values were determined based on cut-off points identified as the value closest to 1 in the ROC curves. A $p < 0.05$ was considered significant.

Results

EGD was performed on 168 patients due to CSI. Among them, 123 patients exhibited corrosive damage during endoscopy. Thirty-three patients were excluded due to comorbid diseases and missing data.

Of the 90 patients included in the study, 43 were male, and 47 were female. The youngest patient was 21 years old, and the oldest was 85 years old. The mean age was 52.5 ± 14 years. The distribution of patients according to Zargar's classification and the severity of internalization are presented in table 1.

A summary of the comparison of demographic and laboratory parameters is provided in table 2. Mean age, NLR, MLR, RDW, and PLT were increased in hospitalized patients with severe injuries. Mean age, NLR, MLR, and RDW were also increased in patients with severe esophageal injuries (Table 2).

The ROC curve analysis for NLR and MLR demonstrated statistically significant predictive value for both the severity of injury and hospitalization (Tables 3 and 4, Figs. 1 and 2).

In the ROC analyses conducted for hospitalized patients, the AUC was found to be 0.821 (95%

Table 1. Endoscopic findings and the distribution of the patients according to the Zargars' classification

Grade	Outpatient	Inpatient	Total	p
Zargar Grade				0.000
Grade 1	25	0	25	
Grade 2a	19	4	23	
Grade 2b	1	18	19	
Grade 3a	0	12	12	
Grade 3b	0	11	11	
Total	45	45	90	
Severity				0.000
Mild-moderate	45	22	67	
Severe	1	22	23	
Total	46	44	90	

confidence interval: 0.72-0.91) for the selected cut-off value of 2.1 for NLR, with a sensitivity of 77.7% and specificity of 77.1%. For MLR, the AUC was found to be 0.784 (95% confidence interval: 0.68-0.88), with a sensitivity of 77.3% and specificity of 77.1% for the selected cut-off value of 0.26 (Fig. 1).

In the ROC analyses conducted for patients with severe esophageal injuries, the AUC was found to be 0.841 (95% confidence interval: 0.75-0.93) for the selected cut-off value of 2.3, with a sensitivity of 76.2% and specificity of 80.0% for NLR. For MLR, the AUC was found to be 0.796 (95% confidence interval: 0.69-0.88), with a sensitivity of 76.2% and specificity of 78.3% for the selected cut-off value of 0.27 (Fig. 2).

Discussion

Esophageal corrosive injuries are common clinical problems, often requiring immediate attention. It is essential to identify the severity of injury accurately to determine appropriate treatment and predict the prognosis of patients. However, endoscopy, the gold standard for evaluating corrosive injuries, is an invasive procedure that may not always be feasible or safe in certain clinical scenarios, such as unstable patients or those with contraindications. Therefore, the search for non-invasive markers to predict the severity of corrosive injuries is of great importance. In this study, we investigated the utility of two easily accessible and cost-effective markers, NLR and MLR, in predicting the severity of esophageal injuries in patients with CSIs. Our results indicate that both NLR and MLR are significantly associated with the severity of corrosive injuries and hospitalization.

Table 2. Comparison of the demographic and laboratory parameters of all patients

Variables	Outpatient (n = 45)	Inpatient (n = 45)	p	Mild-moderate (n = 46)	Severe (n = 46)	p
Sex (m)	19	24	0.55	32	11	0.23
Age (y)	45.2 ± 12.7	55.5 ± 10.6	0.013	46.1 ± 13.1	55.05 ± 10.7	0.015
NLR	1.81 ± 0.6	5.06 ± 3.5	0.000	2.0 ± 1.8	4.9 ± 3.3	0.000
MLR	0.24 ± 0.1	0.53 ± 0.40	0.000	0.27 ± 0.2	0.51 ± 0.34	0.007
RDW	12.8 ± 1.1	13.7 ± 2.3	0.000	12.8 ± 1	13.8 ± 2.38	0.000
PLT	231.4 ± 55.8	268.89 ± 96.2	0.000	241.8 ± 71.3	258.7 ± 89	0.12
MPV	10.3 ± 1.9	10.6 ± 1.1	0.051	9.9 ± 1.9	10.8 ± 162	0.058

NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; RDW: red cell distribution width; PLT: platelet; MPV: mean platelet volume.

Table 3. ROC curve was used to evaluate the predictive value of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio for hospitalization

Test variable (s)	AUC	Asymptotic significant	CI	Cut off	sens	1-spes
NLR	0.821	0.000	0.72-0.91	2.1	77.7	77.1
MLR	0.784	0.001	0.68-0.88	0.26	77.3	77.1

AUC: area under curve; Sig: significance; CI: confidence interval; Sens: sensitivity; Spes: specificity; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

Table 4. ROC curve was used to evaluate the predictive value of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio for the severity of esophageal injury

Test variable (s)	AUC	Asymptotic significant	CI	Cut-off	Sens	Spes
NLR	0.841	0.000	0.75-0.93	2.3	76.2	85.4
MLR	0.794	0.000	0.70-0.89	0.26	81.2	69.4

AUC: area under curve; Sig: significance; CI: confidence interval; Sens: sensitivity; Spes: specificity; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

Looking at the studies on CSI, most of them have been conducted in children, while the incidence of caustic substance ingestion in adults is not low. Each year, a total of 5,000-15,000 CSI cases are reported.⁹ CSI poses a significant health challenge, particularly in developing countries. The severity of injury and subsequent complications can vary greatly among individuals, making it crucial to identify patients at risk. Clinical signs alone are often insufficient for accurately predicting the extent of corrosive injury, and endoscopy, while considered the gold standard, has its limitations, including invasiveness and

false-negative results.¹⁰ Upper gastrointestinal endoscopy is necessary to assess the severity of the injury. However, EGD is not always easily accessible, and it is invasive, expensive, and yields false-negative results in 70% of cases.¹¹ In addition, some researchers are cautious about early EGD in cases of suspected esophageal injury due to the risk of perforation. The supine position during esophagoscopy under general anesthesia can cause reflux of the corrosive agent from the stomach to the esophagus, increasing the risk of damage. Furthermore, EGD does not always provide an accurate assessment of the degree of esophageal injury.^{12,13} Therefore, there is a need for a more easily accessible, inexpensive, and safe test to determine the severity of esophageal damage. Identifying such a test that can at least predict which patients should undergo endoscopy would be valuable.

In this study, the gender distribution between the groups was equal. Patients with severe injury and/or hospitalized patients were older than the other groups. The NLR, MLR, RDW, and PLT count showed significant differences when evaluating endoscopic severity and CBC parameters in hospitalized patients. The mean PLT count was higher in patients with mild-moderate injury and discharged patients, although it was only statistically significant for hospitalization.

RDW, NLR, MLR, and PLT count are quantitative measurements of variability that is routinely reported in CBC, widely available, inexpensive, and highly reproducible tests. RDW, calculated by dividing the MPV by the SD of erythrocytes and then multiplying by 100 to express the data as a percentage, has long been used for the differential diagnosis of anemias and has emerged as a new risk marker for many different diseases associated with acute and chronic

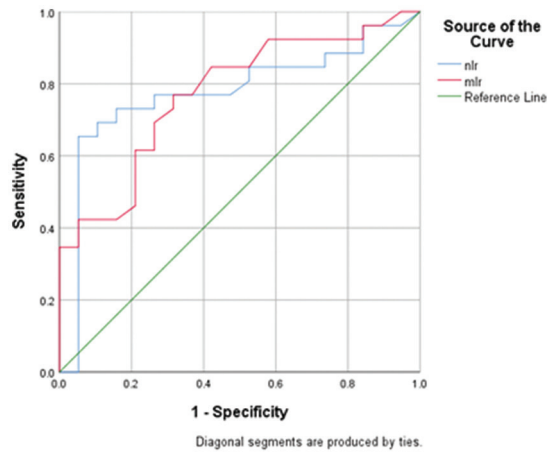


Figure 1. Receiver operating characteristic curve analysis for hospitalization in patient with caustic substance intake.

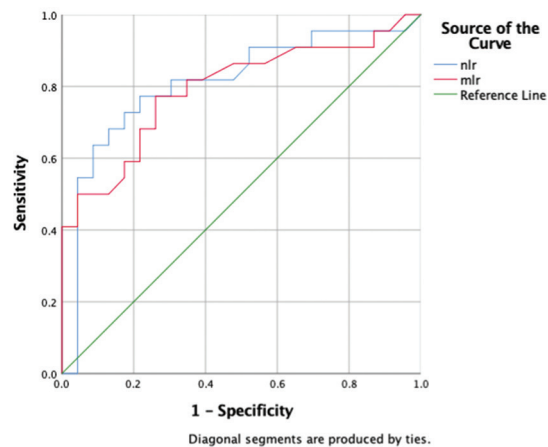


Figure 2. Receiver operating characteristic curve analysis for the severity of esophageal injury in patient with caustic substance intake.

inflammation.^{14,15} In our study, we found some important results. RDW was higher in hospitalized patients and patients with severe esophageal injury compared to others. We speculate that the inflammation caused by the caustic substance may shorten the half-life of erythrocytes, alter membrane characteristics, and increase RDW values.

NLR is an inexpensive inflammatory indicator that can be calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from a CBC. Numerous publications in the literature have shown that NLR is associated with various inflammatory diseases, and it has become widely accepted as a useful tool for evaluating inflammatory activity.¹⁶ Azab et al. determined the normal range of NLR to be

between 1.7 and 2.28 in their study with 9427 individuals, while Aydın et al. from Turkey determined the normal range to be between 1.0 and 2.3.^{17,18} In our study, we found that NLR was significantly higher in patients with severe esophageal injury and hospitalized patients compared to the others. Furthermore, we demonstrated that an NLR over 2.1 could be used to predict hospitalization with 77.7% sensitivity and 77.7% specificity, and an NLR of 2.3 could be used to predict severe esophageal injury with 76.2% sensitivity and 85.4% specificity.

MLR has gained interest as a biomarker. As a new, inexpensive, and readily available inflammatory and infectious biomarker, MLR has been shown to be applicable in predicting and prognosticating various inflammatory diseases. MLR reflects the balance of change between innate and adaptive immunity and provides a simple indicator of immune status and inflammation level.¹⁹⁻²¹ To the best of our knowledge, no studies have reported on the predictive value of MLR for the severity of esophageal injury in patients with CSI. In our study, we found that MLR was significantly higher in patients with severe esophageal injury and hospitalized patients compared to the others. In addition, we demonstrated that MLR values above 0.26, as determined by the ROC curve, can predict hospitalization with 77.3% sensitivity and 77.1% specificity, and predict severe esophageal injury with 81.2% sensitivity and 69.4% specificity.

PLT, which can be easily and promptly evaluated upon admission in most clinical settings, was significantly decreased in hospitalized patients, although there was no thrombocytopenia in our study. There is now a large body of evidence showing that platelets play a central role in inflammatory reactions. Moreover, in some studies, thrombocytopenia has been associated with increased mortality, highlighting the beneficial roles of platelets in inflammation.²² The measurement of platelets upon admission to the emergency room may be one of the most accurate and convenient parameters for precisely assessing the prognosis of patients with caustic injury.

Regarding the relationship between age and the severity of esophageal injury, the literature presents conflicting results. In our study, we found that patients with severe esophageal injury and hospitalized patients were older than the others.^{10,23} Based on this finding, we can predict that older patients may develop more severe esophageal injury.

It is important to acknowledge certain limitations of our study, including its retrospective design and

relatively limited sample size. We could not analyze some contributing factors such as the specific caustic substances ingested. However, this study is the first one in the literature to demonstrate the correlation between NLR and MLR values and the severity of esophageal injury.

Conclusions

Although EGD is considered the gold standard for determining the severity of esophageal injury, it has several disadvantages as previously mentioned. Therefore, the necessity of endoscopy in patients with caustic substance ingestion is still controversial, and there is no definitive recommendation. Our study highlights the potential of NLR and MLR as valuable and easily accessible diagnostic markers for predicting the severity of esophageal injury in patients with CSI. By incorporating these markers into clinical practice, healthcare providers may be able to better assess the extent of injury, guide treatment decisions, and improve patient outcomes. Further research is needed to fully elucidate the mechanisms underlying the associations observed in this study and to validate our findings in larger, prospective cohorts.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed. The Research Ethics Board of the Research Institute of the Tokat Gaziosmanpasa University Faculty of Medicine approved the study (study code 23-KAEK-276), which was conducted in accordance with the Declaration of Helsinki.

Declaration on the use of artificial intelligence.

The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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