

NEUTROPHIL LYMPHOCYTE RATIO IN PREDICTING SEVERITY OF INJURY, COMPLICATIONS AND MORTALITY IN CAUSTIC INGESTION CASES

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ABSTRACT

Background: Caustic ingestion is still a life-threatening condition. In this study, we investigated the significance of the neutrophil lymphocyte ratio (NLR) in predicting the severity of the injury, complications and mortality at an early stage in the emergency department.

Material and methods: 133 patients included in the study. Endoscopic findings and Complete Blood Count (CBC) parameters were retrieved from hospital files. The data were divided into two groups Zargar grade 0, 1 and 2A as Group 1, 2B, 3A and 3B as Group 2. The Zargar scores and the laboratory values were evaluated with Spearman's Correlation.

Results: We found that NLR and White Blood Cells (WBC) values of Group 1 cases were statistically significant and lower than NLR and WBC values of Group 2 cases ($p < 0,05$). Values in Group 2 patients showed that AUC value for the 6.99 cut-off value of the NLR was 0.913 sensitivity 100% and specificity was 78,3% ($p < 0,05$). The 0,801 AUC for the 11.9 value of the WBC, sensitivity 66,7 and specificity 84.4 were found to be statistically significant ($p < 0,05$). $NLR > 7,33$ AUC 0,915 ($p < 0,05$) and AUC value for $WBC > 11,9$ was found to be 0,870 ($p < 0,05$) for the patients with late complications. Interm of mortality no statistical relationship was found ($p > 0,05$).

Conclusion: Endoscopy (EGD) is the valid gold standard method to determine the injury. In the literature, which patient groups should undergo endoscopy is also unclear. In addition, performing endoscopy in each patient will increase both the cost and the possibility of endoscopy-related complications. In our study NLR was statistically significant in predicting the severity of injury and possibility of complications in corrosive ingestion. Moreover, it can be obtain through affordable and routine blood count.

Keywords: Emergency, caustic ingestion, neutrophil lymphocyte ratio.

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Introduction

Caustic ingestion is still a life-threatening condition in developing countries although admissions to emergency departments are not common. Every year, approximately 5000-15000 caustic ingestion cases are recorded in the United States of America (USA)^(1,2, 3). Caustic substances can be household cleaners, dish-washer soap or bathroom cleaning products, made of industrial materials^(4,5).

Caustic injuries will occur if the pH of the ingested substance is lower than 2 or higher than 12. Compared to acidic products, causing coagulation necrosis; alkaline products cause greater damage in the gastrointestinal system (GIS) due to liquefaction necrosis^(2, 5, 6). Previous studies suggested that alkaline products often damaged the esophagus while acids caused damage in the stomach^(6, 7). Corrosive ingestions often cause injury in the lips, oral cavity, pharynx, and the upper airway.

They also cause complications such as massive hemorrhage, gastrointestinal perforation, aorta-enteric/gastrocolic fistula, and tracheoesophageal fistula^(1,7). Corrosive agents create the biggest damage/injury in the esophagus. They cause esophageal perforation, stricture formation, and even esophageal cancer later^(1,8). It is usually highly difficult to classify the degree of the injury and determine the patient's prognosis based on the primary clinical manifestation. The gold standard method to classify the degree of the injury is esophago gastro duodenoscopy (EGD)^(9,10). However, EGD may not be available in every hospital at all times. Also, the patient's condition may not be suitable at all times to perform an EGD⁽⁴⁾. As corrosive substance intake is a very dangerous and life-threatening condition; the rate of the patients, who underwent EGD unnecessarily, is reported to be 60-82% in the literature⁽³⁾. The false-negative results occur at significantly high rates due to the lack of established correlation norms between the degree of the burn and the symptoms^(3,7,11,12). Therefore, there is a need for quantifiable, fast, inexpensive, and reproducible markers that can predict whether the corrosive substance has caused injury or not. Apart from the initial esophageal damage caused by the chemical substance, oxidative stress and related inflammatory processes also lead to further damage.

Several studies have investigated the role of certain inflammatory markers as prognostic factors. Only one study found out that the leukocyte count was associated with mortality in caustic ingestion but no significant correlation was found with the esophageal stricture⁽⁴⁾. Neutrophil/Lymphocyte Ratio (NLR) is used as a prognostic factor in many diseases such as sepsis, stroke, appendicitis and pancreatitis^(4, 13, 14, 15). In this study, we investigated the predictive role of NLR in estimating gastrointestinal damage, complications, and mortality in caustic substance ingestions because it can predict the presence of inflammation in the early period and can easily be calculated using the values from a routine blood count.

Material and method

Ethics committee approval was received for this study from the ethics committee of our University School of Medicine, the Human Ethics Review Board (Study number: 2018-GOKAE-0741). Written informed consent was not obtained due to the retrospective nature of the study and clinical and

pathologic data of the patients were de-identified and analyzed anonymously.

Patient Selection

This retrospective study was conducted from 1 January 2013 to 31 December 2018. An average of 800 patients is admitted to the emergency department of our hospital in 24 hours. Patients admitted to our emergency department due to corrosive substance exposure / ingestion were screened in the hospital database based on the ICD-10 codes. A total of 133 patients over 18 years of age who met the inclusion criteria were included in the study. Excluded patients were under 18 years of age, pregnant, undergoing radiotherapy-chemotherapy or diagnosed with trauma, haematological diseases, GIS malignancy, anemia (including those receiving B12 or iron therapy) or immunodeficiency. Patients who did not undergo endoscopy were excluded, too.

Data Collection

The relevant patient data in the hospital database were recorded; including the age, gender, chemical structure of the ingested substance (acid or alkali), the cause of exposure to the corrosive substance (suicide or inadvertent exposures), and the time elapsed from the emergency department admission until undergoing endoscopy. White blood cell (WBC) count, red blood cell distribution width (RDW), hematocrit (HCT), and neutrophil / lymphocyte ratio (NLR) values were obtained from the laboratory records and they were recorded in the specifically developed trial form for the study. Identification of at least one of the following; including gastrointestinal hemorrhage, perforation, fistulization, strictures, and stenosis, were recorded as the patient developed a complication.

Zargar described an endoscopic grading system used for scoring the mucosal damage in the intestinal tract⁽¹⁶⁾. The data obtained by EGD were recorded according to the Zargar grading system. The Zargar classification is an accepted method for defining endoscopy findings. In order to assess the damage, the data were divided into two groups as Zargar grade 0, grade 1, grade 2A were Group 1 and grade 2B, grade 3A, grade 3B were Group2. Endoscopic features and laboratory data of the groups were analyzed comparatively. Patients who died due to corrosive substance intake were recorded.

Statistical Method

Statistical analysis of the data was performed

with the IBM SPSS Statistics Version 24 software. To compare the categorical data between the groups, Pearson's Chi-Squared Test, Fisher's Exact Test, and Chi-square Trend Test were used. Kolmogorov-Smirnov test was performed whether the continuous data conformed to a normal distribution. It was determined that the data did not conform to a normal distribution ($p < 0.05$). Therefore, the Mann-Whitney U test was performed to compare two groups and Kruskal Wallis-H (the Mann Whitney U test with post-hoc Bonferroni correction) test was used for making intergroup comparisons among more than two groups. The Zargar scores and the laboratory values were evaluated with the Spearman's Correlation. The optimal cut-off values of the laboratory results were analyzed with the ROC analysis. A p-value of > 0.05 was considered statistically significant.

Results

Of the 133 patients included in the study, 48.9% were female and 51.1% were male. The age of the patients ranged from 29 to 59.5 years in women and from 26 to 63 in men.

| SUICIDAL ATTEMPT | Group | Substance | | Total |
|------------------|---------|-----------|--------|-------|
| | | Acid | Alkali | |
| NO | Group 1 | 20 | 62 | 82 |
| | Group 2 | 5 | 2 | 7 |
| | Total | 25 | 64 | 89 |
| YES | Group 1 | 11 | 22 | 33 |
| | Group 2 | 10 | 1 | 11 |
| | Total | 21 | 23 | 44 |
| Total | Group 1 | 31 | 84 | 115 |
| | Group 2 | 15 | 3 | 18 |
| | Total | 46 | 87 | 133 |

Table 1: Distribution of patients by type of ingested substance, suicidal attempt and zargar score.

Of the patients included in the study, 33% ingested the corrosive substance for suicidal attempt. Of the acid and alkaline ingestions; 45.7% and 26.4% were ingested for suicidal attempt, respectively. The ingestion of the acidic substances for suicidal attempt was statistically more common compared to the ingestion of alkaline substances.

The damage in the gastrointestinal tract resulting from the ingestion of the corrosive substance was evaluated according to the Zargar classification. Zargar is an endoscopic classification method used for grading the mucosal damage in the intestinal tract. According to the Zargar classification, grade 0, grade 1, grade 2A indicate normal findings or mild damage (Group 1); whereas, grade 2B, grade 3A, grade 3B indicate poor prognosis and increased risk

of developing complications (Group 2)⁽¹⁶⁾. While the rate of corrosive substance ingestion for suicidal attempt was 28.7% in Group 1, this rate was found out to be 61.1% in Group 2. Accidental intake of alkaline substances was more common than acidic substance ingestions (Table 1).

No statistical relationship was found between mortality and whether the cause of intake was to suicidal attempt. Similarly, there was not a statistical relationship between mortality and the ingestion of an acidic or alkaline substance. In regards to the laboratory values, no correlation of mortality was observed with RDW, HCT, NLR, and WBC values ($p > 0.05$).

Laboratory values at the time of emergency department admissions were matched with the Zargar scores obtained after EGD. There was a strong and positive correlation between the Zargar grades and NLR values; and a statistically significant, positive and moderate correlation between the Zargar scores and WBC values ($p < 0.05$). There was not a statistically significant correlation between the Zargar grades and the HCT and RDW values ($p < 0.05$) (Table 2).

| | ZARGAR | |
|-----|--------|-------|
| | r | P |
| NLR | 0,680 | 0,000 |
| WBC | 0,484 | 0,000 |
| HCT | 0,125 | 0,152 |
| RDW | 0,140 | 0,108 |

Table 2: Correlation of zargar score and laboratuar findings.

NLR: neutrophil to lymphocyte ratio. WBC: white blood cell. HCT: heamotocrit. RDW: red cell distribution width

The NLR and WBC values of Group 1 patients were statistically significantly lower than those of the Group 2 patients ($p < 0.05$). There was not a statistically significant difference in HCT and RDW values between the groups ($p < 0.05$) (Table 3). In Group 2, the results of the ROC analysis revealed an AUC value of 0.913 (95%CI: 0.862-0.964) for a 6.99 cut-off point for NLR with a 100% sensitivity and 78.3% specificity ($p < 0.05$). The AUC value for a cut-off value of 11.9 for WBC was found out to be 0.801 (95% CI: 0.693-0.909) with a sensitivity of 66.7% and specificity of 84.4% with statistical significance ($p < 0.05$). No statistical significance was found for the WBC and RDW values (Table 4) (Fig.1). The rate of late complications was higher in patients, who ingested corrosive substances for

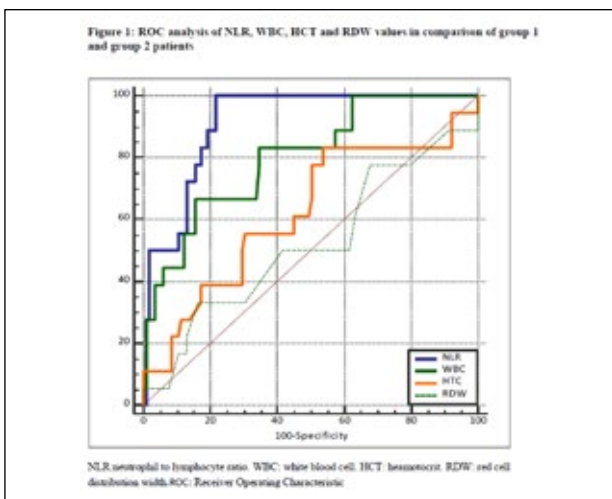
committing suicide. Of the 11 patients who developed late complications, 7 had ingested the corrosive substance for committing suicide. Statistically significant differences were found in the type of the ingested substance and the late complication rates between the groups ($p < 0.05$) (Table 4).

| | GROUPS | | | | | p |
|-------------------|---------|-------------|---------|---------------|------|--------------|
| | GROUP 1 | | GROUP 2 | | | |
| | n | % | n | % | | |
| EX | Yes | 0 | 0,0 | 2 | 11,1 | 0,017 |
| | No | 115 | 100,0 | 16 | 88,9 | |
| Late complication | Yes | 0 | 0,0 | 11 | 61,1 | 0,000 |
| | No | 115 | 100,0 | 7 | 38,9 | |
| Suicidal attempt | Yes | 33 | 28,7 | 11 | 61,1 | 0,007 |
| | No | 82 | 71,3 | 7 | 38,9 | |
| Substance | ACID | 31 | 27,0 | 15 | 83,3 | 0,000 |
| | ALKALI | 84 | 73,0 | 3 | 16,7 | |
| NLR | | 3,04 (4,58) | | 13,56 (13,91) | | 0,000 |
| WBC | | 8,85 (4,03) | | 13,9 (13,23) | | 0,000 |
| HCT | | 40,6 (8,5) | | 43,95 (5,73) | | 0,103 |
| RDW | | 13,5 (1) | | 13,3 (1,63) | | 0,777 |

Table 3: Comparison of group 1 and group 2 patients according to the investigated parameters. *NLR: neutrophil to lymphocyte ratio. WBC: white blood cell. HCT: hematocrit. RDW: red cell distribution width.*

| Criterion | Sensitivity | Specificity | AUC (95% CI) | p |
|-----------|-------------|-------------|---------------------|-------------------|
| N/L >6.99 | 100.0 | 78.3 | 0.913 (0.862-0.964) | <0.0001 |
| WBC >11.9 | 66.7 | 84.4 | 0.801 (0.693-0.909) | <0.0001 |
| HCT >40 | 83.3 | 46.1 | 0.620 (0.470-0.769) | 0.1179 |
| RDW >14.2 | 33.3 | 83.5 | 0.521 (0.364-0.678) | 0.7955 |

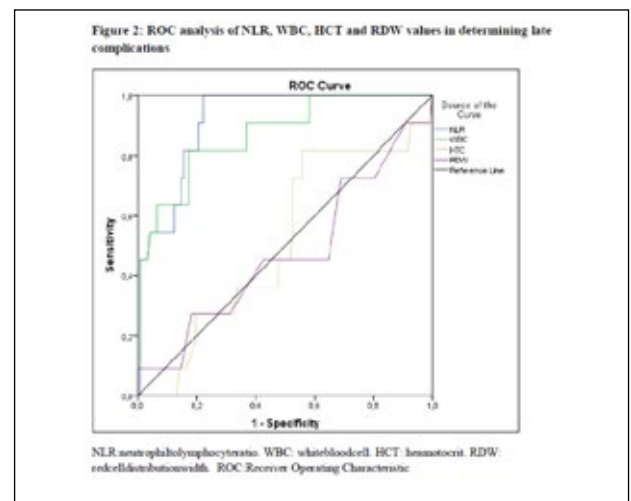
Table 4: ROC analysis of NLR, WBC, HCT and RDW values in comparison group 1 and group 2. *NLR: neutrophil to lymphocyte ratio. WBC: white blood cell. HCT: hematocrit. RDW: red cell distribution width.*



In the patients developing late complications, NLR values of $> 7.33/\mu\text{L}$, with an AUC value of 0.915 ($p < 0.001$) and WBC values of > 11.9 with an AUC value of 0.870 ($p < 0.0001$) were found. RDW and HCT values were not statistically significant (table 5) (Fig. 2).

| Criterion | Sensitivity | Specificity | AUC | (95% CI) | p |
|-----------------|-------------|-------------|-------|---------------|-------------------|
| N/L >7.33 | 100.0 | 77.9 | 0.915 | (0.856-0.975) | <0.0001 |
| WBC >11.9 | 81.8 | 82.8 | 0.870 | (0.759-0.981) | <0.0001 |
| HCT >40 | 81.8 | 44.3 | 0.512 | (0.343-0.681) | 0.890 |
| RDW ≤ 12.9 | 54.6 | 64.8 | 0.525 | (0.333-0.718) | 0.797 |

Table 5: ROC analysis of NLR,WBC,HCT,RDW values to determine late complications. *NLR: neutrophil to lymphocyte ratio. WBC: white blood cell. HCT: hematocrit. RDW: red cell distribution width.*



Discussion

Corrosive substances were ingested for committing suicide by 33.8% of the male patients and 32.3% of the female patients. Park et al, J. Kim et al, and Meena et al, reported that caustic substance ingestions in adults are often associated with a suicidal intent leading to life-threatening conditions frequently^(2,4,12). Hashimi et al, Park et al and Meena et al, found that; in developing countries, both the ingestion of acidic substances and the ingestion of these substances with suicidal intentions occurred at high rates. The underlying reason for these findings was explained by the fact that acidic substances had recently been used in household cleaning products at increasing rates^(1,2,12). In our study, the rate of the acid ingestion for suicidal purposes was higher than the ingestion of alkaline substances. However, accidental ingestion occurred at a higher rate. Similarly,

Icme et al, have found out that the accidental intake is higher in adults because retail packaging has not often been made for household cleaning agents in our country and they are contained in the emptied food containers at home. Furthermore, that study reported that the amount of the accidentally ingested substances was less compared to the amount taken for suicidal purposes⁽⁵⁾.

In our study, the amount of the ingested substance could not be obtained from the records. We believe that the unavailability of the ingested amount in our hospital database is a limitation for our study. However; when we examined the findings of our study, we observed that the Zargar grades were high and the gastrointestinal damage was extensive in suicidal ingestions. In our study, suicidal intake of corrosive substances was found in 28.7% of group 1 with mild to moderate injury, and 61.1% in group 2 with severe injury. Therefore, we estimate that the amount of the ingested corrosive substance is higher when taken for committing suicide compared to accidental ingestions.

EGD is accepted as the gold standard method to determine the damage and contribute to treatment planning in patients presenting with corrosive substance ingestions. Hashimi et al, Alipour et al, and Chiru et al, reported that EGD can be performed within 12-72 hours, 24-49 hours, and 3-48 hours, respectively, after the admission^(1, 17, 18). However, the World Society of Emergency Surgery consensus conference recommended it to be performed within 3-6 hours⁽⁹⁾. Although no time interval from admission to EGD has been established in the literature, it was calculated to be performed in an average 13 hours in our study, consistent with the reported length of time in the literature.

Also, the characteristics of patient groups requiring endoscopy have not been clarified in the literature. Moreover, performing endoscopy in every patient will increase both the costs and the risks of endoscopy-related complications. However, Bird et al, Kluger et al, and Meena et al, have stressed that EGD is contraindicated in patients with respiratory distress, hemodynamic instability, suspected perforation, severe laryngeal edema, 3rd-degree burns of the hypopharynx, and necrosis of the lips and the oral cavity^(7,10,12). Çelik et al. conducted a study and reported that; in the study period of 10 years, 9 out of 102 patients underwent EGD in the acute stage after accidental ingestion of a corrosive substance and admission to the emergency department but the remaining patients were advised to undergo EGD

and they were treated as outpatients. The long-term results of 120 months showed that only 2.4% (3 patients) of these patients developed esophageal strictures⁽¹⁹⁾. Similarly, Aydın et al, reported that 60-82% of the performed EGDs were unnecessary⁽³⁾. Kluger et al, conducted a review and reported that 10-30% of the patients undergoing EGD had no esophageal or stomach injuries and that it was not necessary to perform EGD in every patient. The benefits of EGD remains to be controversial⁽¹⁰⁾.

HCT is the ratio of the red cell volume in the blood to the blood volume. It is specified as a ratio. Normal values are 40-54% for men and 36-48% for women. In our study, no significant relationships were found among the HCT values, Zargar grades, mortality, and complications. Lee et al, and Sarı et al, reported that the HCT values had no relationships with morbidity in critically ill patients and in esophageal perforation patients, respectively^(20,21).

RDW is the quantitative variation in the size of circulating red blood cells (RBCs). The rise of RDW values indicates that the circulating erythrocytes are in variable volumes and shapes. RDW increases in coronary artery disease, stroke, renal failure, and severe infections⁽²²⁾. Tahtacı et al, found that RDW can predict pancreatitis-related complications and the severity of pancreatitis⁽²³⁾. Aydın et al. reported that; in pediatric patients with corrosive substance exposure, RDW values of 12.20 were significant with 84.2% sensitivity and 59.2% specificity⁽³⁾. Our study did not find any correlation of the RDW values with the severity of the damage, mortality, and complications.

WBC count is the sum of circulating nucleated cells. These cells are responsible for phagocytosis and they are involved in immunity. They count normally in the range of 4000-10000 / ml in the blood. They are classified as granulocytes, lymphocytes, and monocytes. Granulocytes are further subclassified as neutrophils, eosinophils, and basophils. Increased oxidative stress leads to leukocytosis, neutrophilia, monocytosis, and lymphopenia⁽²⁴⁾. Kluger et al. conducted a review and reported that a WBC of $> 20 \times 10^9/L$ requires monitoring and follow-up of the patient⁽¹⁰⁾. Noures et al. found out that; in corrosive substance ingestions, a WBC count of $> 20 \times 10^9/L$ was an independent risk factor for mortality⁽⁸⁾. In our study, a WBC of $\geq 11.9 \times 10^9/L$ was found to be statistically significant to predict damage at Group 2. However, the sensitivity was calculated as 66.7% and the specificity was found to be 84.4%. Studies and meta-analyses demonstrate that each WBC subtype increases to dif-

ferent levels as a response of the body based on different types of pathophysiological events. Changes in any of the subtypes of WBC such as lymphocytes, monocytes, and neutrophils will be reflected as an increase or decrease in the WBC count. We suggest that the significance of the WBC count of $>11.9 \times 10^9 / L$ found in our study occurred resulting from the increased counts of the WBC subtypes.

Our study did not find a statistical significance of HCT or RDW in predicting the grade of the injury, occurrence of complications, and mortality. Aydın et al, in a pediatric study of accidental corrosive substance ingestion, found out that an RDW level of >12.2 was significant in the patients with injuries identified by EGD. However, the positive predictive value of this value was found to be 38.6%⁽³⁾. We investigated the grade of the injury and its relationship with complications in corrosive substance ingestions in the adult population. We found that the grade of the damage according to the Zargar classification did not correlate with the RDW values; it didn't show the extent of the damage, and it was not associated with complications or mortality. It may be suggested that ingestion of corrosive substances may cause the development of infection, leading to shortened erythrocyte half-life and altered volume of distribution. However; since inflammation and corrosive substance damage develop quite rapidly, RDW increases may not be detected in patients with severe damage. Therefore, we suggest that the predictive power of RDW in making the distinction between severe damage and the mild injury was found statistically insignificant because of the low number of patients in Group 2.

NLR is calculated using the subtype counts of WBC and it is a robust parameter and easy to calculate to evaluate inflammatory conditions^(14,19,25). Uyar et al. conducted a study on patients, who ingested corrosive substances and compared the NLR values of the patients with Zargar grades of 0,1,2 with those having Zargar grades of 3 and 4. The investigators found out that NLR values were significant in distinguishing the patients with a mild injury from those severely injured⁽²⁶⁾. In our study, the NLR values were statistically significant in predicting the injury especially in the Group 1 in the patients, who ingested a corrosive substance. The endoscopic study of Zargar et al, conducted for the classification of GIS injuries, report that grades 0, 1, and 2A heal without any sequelae and 71.4% of the patients with grade 3 injuries develop esophageal-gastric scars and complications that require surgery⁽¹⁶⁾.

Similarly, Park et al, Naoures et al, and Meena et al, reported that there was a 70-100% risk of developing strictures in the patients with Zargar 2B and 3A injuries^(2,8,12). Therefore, different from the study of Uyar et al, we examined the NLR values in patients with Zargar grades 2B, 3A and 3B. Other complications that may develop in corrosive substance ingested patients include perforation, hemorrhage, organ necrosis, gastric outlet obstruction, and late-stage esophageal malignancy, other than strictures. The conditions that are associated with an increased risk of complications are the ingestion of potent acidic or alkaline substances, suicidal intention, the amount of ingestion, and the duration of exposure⁽²⁶⁾.

In our study, 11 patients in Group 2 developed these complications and the complication rate was found out to be high in ingestions with a suicidal intention. NLR was found to be 7.33 in patients who developed complications. In other words, patients with NLR values of 7.33 and above should be hospitalized for a longer period and a follow-up schedule with more frequent visits should be organized for them. Thereby, possible complications can be treated faster and earlier.

In conclusion: High levels of NLR indicate severe caustic damage, extensive involvement, and the likelihood of developing complications with high sensitivity. A low NLR may be directive in deciding a hospital discharge.

Limitation of study; The most important limitation of this study is that it is retrospective. Another limitation is the low number of cases. Lack of serial measurement is another limitation

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