NEUTROPHIL TO LYMPHOCYTE RATIO, A NOVEL BEDSIDE PREDICTOR OF ENDOSCOPIC DAMAGE IN CORROSIVE GI INJURIES

Gastroenterology

Noble Varghese Mathews

Resident, Institute of Medical Gastroenterology, Madras medical college, Chennai.

K. Premkumar*

Associate Professor, Institute of Medical Gastroenterology, Madras medical college, Chennai. *Corresponding Author

Murali Ramamoorthy

Associate Professor, Institute of Medical Gastroenterology, Madras medical college, Chennai.

A. Chezian

Assistant Professor, Institute of Medical Gastroenterology, Madras medical college, Chennai.

A. R. Venkateswaran

Professor, Institute of Medical Gastroenterology, Madras medical college, Chennai.

I. Shubha

Assistant Professor, Institute of Medical Gastroenterology, Madras Medical College, Chennai

ABSTRACT

AIM- To determine an association between neutrophil to lymphocyte ratio (NLR) and severity of endoscopic injury.

MATERIALS AND METHODS- A cross-sectional study of 153 adult patients admitted to Madras medical college, following history of caustic ingestion during a 6-month period. The association between NLR within 24 hours of ingestion and endoscopic injury based on Zargar classification was studied. The association between NLR and endoscopic findings were studied.

RESULTS AND DISCUSSION- Of the 153 patients studied, 117 had mucosal injuries and 36 normal. 54 of the 117 patients had multi-regional injury and 63 had single regional injuries. Of which, by Zargar classification, Grade I- 57, Grade II- 35 and Grade III-25 patients. Mean NLR of the sample was 3.4. AUC > 80% was noted for NLR cut-offs across all comparison groups namely, High vs lower grades (NLR $\geq$ 4.32, AUC:0.978, 95% CI 0.95-1.0, p<0.001), a similar Turkish study by Uyar et al had a cut off of 8.7, however the sample size was smaller with only ten patients having poorer graded injuries. The NLR cut-offs of Injured vs non-injured (NLR $\geq$ 1.49, AUC:0.845, 95% CI 0.78-0.91, p<0.001) and Single vs multi-regional injuries (NLR $\geq$ 2.27, AUC:0.86, 95% CI 0.80-0.93, p<0.001), were comparable to the previous study.

CONCLUSION- Higher NLR values predicted severe and multi-regional injuries. It helped to distinguish between mild and severe injuries, thereby serving as an inexpensive, non-invasive and bedside tool to predict and grade corrosive injuries for patients awaiting or inaccessible to immediate endoscopic evaluation and plan further care.

KEYWORDS

Corrosive GI injury, NLR

INTRODUCTION

Corrosive ingestion is a well-known form of self-harm which rarely results in death but the major concern being; lifelong morbidity associated with it in survivors [1]. Among adults, they occur following deliberate attempts to self-harm, however in a few as accidental ingestions or as a result of alcohol or recreational drug ingestion.

Caustic ingestions are mainly classified into two categories – acid and alkali ingestions. Alkali agents are most commonly in drain openers, toilet bowl, and oven cleaners. They contain sodium or potassium hydroxide. Alkali solutions are mostly odourless and tasteless, which may result in large amounts being swallowed accidentally.

Acid ingestion usually occurs from swallowing toilet cleaners, swimming pool cleaner, or battery acid. Acid ingestion mostly causes immediate pain, which results in the agent being immediately expelled. Household bleach may contain both acid and alkali but in a much-diluted concentration which results in mostly minor to no GI injuries [2]. Accidental ingestion is more commonly seen in children, however as mentioned above the suicidal intent is the usual cause in adults [3,4,5]. Also developing countries contribute to majority of the corrosive GI injuries [6,7]. Also it was believed that acids may cause greater injury to gastric mucosa and alkali effect on the esophagus may be more severe [8], however it has been proved beyond doubt that both agents affect either organs with no selective preference [9,10,11]. Upper gastrointestinal (GI) endoscopy and assessment of injuries by means of grading within 72-96 hours of ingestion plays a major role in predicting chronic complications such as stricture formation and further management, as the GI mucosa remains friable and prone to perforation between 5 to 15 days of ingestion. [12,13].

Hence, in situations where endoscopy cannot be performed immediately, an inexpensive, non-invasive and bedside tool would prove handy to predict endoscopic damage in remote settings and in

patients not fit for immediate endoscopy due to airway compromise. Many investigations such as computed tomography [14,15] and endoscopic ultrasound [13] have been used for GI injury assessment. White blood cell count (WBC), C-reactive protein (CRP), and arterial blood gas analysis are other tests used in a few studies for the same purpose. Cheng et al. evaluated arterial blood gas reports in caustic ingestions and inferred that arterial pH<7.22 or base excess<-12 indicate severe oesophageal injury and the need for immediate surgical intervention [16].

The neutrophil-lymphocyte ratio (NLR) is a test which is cost-effective, easily available and considered an important measure of systemic inflammation [17]. It is also used as a marker of inflammation in various diseases such as cancer, inflammatory diseases, hypertension, diabetes, obesity, dyslipidemia and vascular disorders [17,18]. High NLR values are associated with poor survival and increased morbidity in various chronic conditions [19]. Elevated NLR levels have also proven to be associated with poor survival of patients undergoing CABG [20] and many survival studies in cancer patients have shown NLR to be a predictor of overall and disease-specific survival in their patient cohorts [21,22,23].

AIM

In this study we aimed to determine the severity of endoscopic caustic injury using the Neutrophil to Lymphocyte Ratio (NLR) and correlate with an established severity grading system (Zargar classification) and to determine an optimal cut-off value for the prediction of endoscopic injuries.

METHODOLOGY

This cross-sectional study included 153 patients with history of caustic ingestion admitted to RGGGH from July 2019-January 2020. Age, gender, NLR, and the endoscopic findings were recorded.

According to the Zargar classification, patients were studied under 3 categories, Injured vs non-injured, Grade 0-2A vs Grade 2B and 3 injuries, Single vs multi-regional injuries. NLR of the comparison groups, in each of the three categories were correlated with the endoscopic findings. The Statistical Package for Social Sciences (SPSS) 18.0 for Windows was used to analyse the data. Continuous Values were presented as mean $\pm$ standard deviation. Comparisons of percentages between different groups of patients were carried out using the Chi-Square test. All normally distributed data were analysed using unpaired or paired student t test. Utility of NLR for predicting injury and its severity was evaluated by ROC curve analysis to obtain optimal cut off value. The study included all patients admitted to RGGGH with alleged history of caustic ingestion in whom an upper GI endoscopy was performed. Patients less than 16 years of age, pregnant patients, those without a documented CBC report within 24 hours of corrosive ingestion, those with haematological or rheumatological disease, those with malignancy or receiving chemotherapy (in the previous month), those with chronic liver disease, on steroids, antibiotics or have received blood transfusion (in the previous month) or with findings/symptoms of infections of other organ systems were excluded.

RESULTS

Of the 153 patients included in the study, 62 were males and 91 females. 117 patients had endoscopic injury on evaluation and 36 were normal. Among the injured, 54 had multiregional injuries and 63 had single regional injuries.

Table 1 – Demographic Characteristics

Variable	Values
Male:Female	62:91
Injured	117
Non-injured	36

Table 2 – Grading Of Injury And NLR

Grade	N	Mean NLR	Std. Deviation	P value
0	36	1.41	0.47	<0.001
1	57	1.93	0.75	
2A	35	3.98	2.59	
2B and 3	25	8.81	1.88	
Total	153	3.40	2.99	
NLR range – 0.88 to 13				

Table 3 – NLR As Predictor For Differentiating Between Study Groups

FINDINGS	N	MEAN NLR	Std Deviation	P value
Injured vs non injured				
Injured	117	4.01	3.17	<.001
Non-injured	36	1.41	0.47	
Low vs higher grades of injury				
High(2B,3)	25	8.81	1.88	<.001
Low(0,1,2A)	128	2.34	1.78	
Single vs multiregional injuries				
Multiple	54	6.09	3.43	<.001
Single	63	2.23	1.34	

Table 4 – NLR Cut-off For Each Group

	NLR cutoff	Sen.	Spe.	PPV	NPV	P value
1.	≥ 1.49	80.3	75	91.2	54	<0.001
2.	≥ 4.32	100	92.9	73.5	100	
3.	≥ 2.27	90.7	73	74.2	90.2	

1. Injured vs Non injured
2. Low vs High grades
3. Single vs multiregional

Fig 1.– Receiver Operating Characteristic (ROC) Curve Of NLR In Differentiating Injured Vs Non Injured. (AUC-0.845)

There was no significant difference in the number of patients that fell into each of the injury grade groups as seen in table 2. The NLR of the patient cohort ranged from 0.88 to 13. We analyzed our results under 3 separate categories namely, Injured vs non-injured, High grade(2B,3) vs Low grade(0,1,2A) injuries and single vs multiregional injuries. There was a significant difference in NLR values among the three comparison groups as shown in table 3. The patients with endoscopic evidence of mucosal injuries had a higher NLR as compared to non-injured. Also, patients with higher endoscopic grade and multiregional injuries had a higher NLR as compared to lower grade and single regional injuries respectively. Further using ROC curve analysis, AUC was calculated and NLR cutoffs were obtained for each of the study groups with a significant P value as shown in table 4.

Fig 2. - Receiver Operating Characteristic (ROC) Curve Of NLR In Differentiating High Grade Vs Low Grade Injuries. (0.978)

Figures 1, 2 and 3 depicts the ROC curve plots and the AUC values in the separate comparison groups.

Fig 3. - Receiver Operating Characteristic (ROC) Curve Of NLR In Differentiating Multiple Vs Single Regional Injuries. (AUC-0.867)

DISCUSSION

Upper GI endoscopy has been considered as a cornerstone in the initial evaluation following corrosive substance ingestion, because the classification of injuries remains pivotal in the management and determining prognosis in this group of patients. Patients belonging to groups 0 to 2A usually do not develop strictures and can be safely discharged on oral medications and diet once symptoms have reduced. However, the same is not true for the higher grade of injuries. Many studies have shown that strictures develop in as much as 71% of patients with grade 2B and 100% of patients with grade 3 injuries [12,24].

Despite the importance of early upper GI endoscopy in prognosis and management, it may not always be available in remote hospital settings or the patient's clinical condition may contraindicate the procedure. For example, in cases with glottic or supraglottic injuries with oedema [3]. Some studies claimed that upper GI endoscopy should not be performed on all patients with caustic ingestion, because 10–30% of such ingestions did not cause any GI injury [3,7,25,26]. Oxidative stress forms the principle mechanism of injury in most toxin-caused diseases [27,28,29,30]. Similarly, oesophageal injury is

complicated by oxidative stress, leading to lipid peroxidation, after initial burn injury upon corrosive ingestion. High levels of free radicals, and low antioxidant reserves, have been reported after corrosive oesophageal injury [31,32,33]. When the production of free radicals surpasses the antioxidant reserve, the NLR changes, triggered by oxidative stress [29,34,35].

So, early haematological parameters may prove to be a valuable, rapid, non-invasive, bedside tool to predict GI injuries following corrosive ingestion. In a paediatric study, total leucocyte count was found to be significantly higher in children with high-grade injury than low-grade injury [36]. However, it was a paediatric population with much lower mean age. Hovanond et al. stated that total leucocyte count was an independent predictor for high-grade corrosive injury [37]. Also, another study by Rigo et al suggested prognostic relevance of total counts > 20,000 cells/cu.mm to be considered a predictor of poor outcome [38]. By far, there is only one Turkish study that has evaluated the role of NLR in predicting oesophageal injury secondary to corrosive ingestion [39].

In our study, NLR as a predictive marker to differentiate between the comparison groups showed promising results. In our study, NLR value ≥ 4.32 predicted a high grade (2B,3) injury with a sensitivity of 100% and a negative predictive value of 100%. (AUC-0.978, 95% CI 0.956-1.000, P value < 0.001), though the positive predictive value was only 73.53% (Fig.2 and Table.4). This value is lower than the cut off of 8.71 in a similar study by Uyar et al [39], this difference could be attributed to the smaller sample size in that study and the fact that the cohort of patients in the higher grade group in that study was a small number of 10, compared to 25 in our study, moreover they included grade 4 injuries (perforation) which causes severe systemic inflammation and skews the cut off towards a higher NLR value. In our other comparison groups, an NLR of ≥ 1.49 was noted to predict GI injury and differentiate them from non-injured (AUC-0.845, 95% CI 0.78-.910, P value < 0.001), this was similar to the previous study by Uyar et al which reported an NLR cut off of > 2.56 . This minor difference could be due to the larger number of patients belonging to grade 0 and 1 combined with a lower mean NLR that resulted in a lower cut off. However the significance of this value (1.49) needs to be taken in the correct clinical context as it falls in the range for normal people. We also compared single vs. multiregional injuries and noted an NLR cut off of ≥ 2.27 to differentiate multiple from single (AUC-0.867, 95% CI - 0.802-0.932, P value < 0.001). Though the value attained statistical significance, it had lower specificity and positive predictive value. Another study by Kim et al. [40] with a much smaller sample size also noted an NLR cut off of > 2.72 to differentiate complicated uncomplicated, but with a different study design from ours.

Though our study is one of the very few published studies to assess the role of NLR in corrosive GI injuries, it too had limitations. NLR is not specific for corrosive injuries, as it is only a measurable parameter of systemic inflammation. Exclusion was based purely on patient's history. Extrapolation of the results to predict stricture formation may not be viable in all cases, as it depends on the dimensions of injured mucosa which may be underestimated by NLR.

CONCLUSION

NLR as a predictor has a significant association with extent and grade of involvement GI involvement following corrosive ingestion. It is an easily available, inexpensive, bedside and rapid marker of inflammation. High NLR levels may be a predictor of severe corrosive injuries and widespread involvement. Hence, it could be an effective guide for the management of patients for the emergency physician or resident while triaging patients for endoscopic evaluation and prognosticating patients who do not have immediate access to upper GI endoscopy within 72-96 hours of ingestion.

However, further prospective, multicentre, controlled studies with larger populations and long term follow up should give more useful information and predict complications such as stricture formation.

REFERENCES:

- [1] Kamat R, Gupta P, Reddy YR, Kochhar S, Nagi B, Kochhar R. Corrosive injuries of the upper gastrointestinal tract: A pictorial review of the imaging features. *Indian J Radiol Imaging*. 2019;29(1): 613-601. doi: 10.4103/ijri.IJRI.349.18
- [2] Patrick R, Pfau, Mark Benson. Foreign Bodies, Bezoars, and Caustic Ingestions, In: Mark Feldman, Lawrence S. Friedman, Lawrence J. Brandt (Eds). *Sleisenger & Fordtran's Gastrointestinal & Liver diseases*. 11th edition, Saunders Elsevier Science, USA 2021, pp 399-410.
- [3] Contini S, Scarpignato C. Caustic injury of the upper gastrointestinal tract: A comprehensive review. *World J Gastroenterol*. 2013; 19:3918-30.

- [4] Gumaste VV, Dave PB. Ingestion of corrosive substances by adults. *Am J Gastroenterol*. 1992;87:1-5.
- [5] Lakshmi CP, Vijayahari R, Kate V, Ananthakrishnan N. A hospital-based epidemiological study of corrosive alimentary injuries with particular reference to the Indian experience. *Natl Med J India*. 2013; 26:31-6.
- [6] Ananthakrishnan N, Parthasarathy G, Kate V. Acute corrosive injuries of the stomach: A single unit experience of thirty years. *ISNR Gastroenterol*. 2011; 2011:914013.
- [7] Ramasamy K, Gumaste VV. Corrosive ingestion in adults. *J Clin Gastroenterol*. 2003; 37:119-24.
- [8] Lahoti D, Broor SL. Corrosive injury to the upper gastrointestinal tract. *Indian J Gastroenterol*. 1993; 12:135-41.
- [9] Nagi B, Kochhar R, Thapa BR, Singh K. Radiological spectrum of late sequelae of corrosive injury to upper gastrointestinal tract. A pictorial review. *Acta Radiol*. 2004; 45:7-12.
- [10] Zargar SA, Kochhar R, Nagi B, Mehta S, Mehta SK. Ingestion of corrosive acids: Spectrum of injury to upper gastrointestinal tract and natural history. *Gastroenterology*. 1989; 97:702-7.
- [11] Zargar SA, Kochhar R, Nagi B, Mehta S, Mehta SK. Ingestion of strong corrosive alkalis: Spectrum of injury to upper gastrointestinal tract and natural history. *Am J Gastroenterol*. 1992; 87:337-41.
- [12] Zargar SA, Kochhar R, Mehta S, Mehta SK. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointestinal Endosc*. 1991; 37:165-9.
- [13] Chiu HM, Lin JT, Huang SP, Chen CH, Yang CS, Wang HP. Prediction of bleeding and stricture formation after corrosive ingestion by EUS concurrent with upper endoscopy. *Gastrointestinal Endosc*. 2004; 60:827-33.
- [14] Ryu HH, Jeung KW, Lee BK (2010) Caustic injury: can CT grading system enable prediction of esophageal stricture? *Clin Toxicol (Phila)*. 2010;48: 137-142.
- [15] Bahrami-Motlagh H, Hadizadeh-Neisanghalb M, Peyvandi H. Diagnostic accuracy of computed tomography scan in detection of upper gastrointestinal tract injuries following caustic ingestion. *Emerg (Tehran)* 2017;5:e61.
- [16] Cheng YJ, Kao EL (2003) Arterial blood gas analysis in acute caustic ingestion injuries. *Surg Today* 33: 483-485.
- [17] Imtiaz F, Shafique K, Mirza SS (2012) Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med* 5:2.
- [18] Balta S, Celik T, Mikhaillidis DP (2016) The Relation Between Atherosclerosis and the Neutrophil-Lymphocyte Ratio. *Clin Appl Thromb Hemost* 22: 405-411.
- [19] Isaac V, Wu CY, Huang CT (2016) Elevated neutrophil to lymphocyte ratio predicts mortality in medical inpatients with multiple chronic conditions. *Medicine (Baltimore)* 95: e3832.
- [20] Gibson PH, Croal BL, Cuthbertson BH (2007) Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J* 154: 995-1002.
- [21] Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ (2005) Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol* 91: 181-184.
- [22] Sarraf KM, Belcher E, Raevsky E, Nicholson A, Goldstraw P, et al. (2009) Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 137: 425-428.
- [23] Shariha RZ, Halazun KJ, Mirza F (2011) Elevated preoperative neutrophil-lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. *Ann Surg Oncol* 18: 3362-3369.
- [24] Baskin D, Urganci N, Abbasoglu L, Alkim C, Yalcin M, Karadag C, et al. A standardised protocol for the acute management of corrosive ingestion in children. *Pediatr Surg Int*. 2004; 20:824-8.
- [25] Salzman M, O'Malley RN. Updates on the evaluation and management of caustic exposures. *Emerg Med Clin North Am*. 2007; 25:459-76.
- [26] Nunez O, Gonzlez-Asanza C, de la Cruz G, Clemente G, Banares R, Cos E, et al. [Study of predictive factors of severe digestive lesions due to caustics ingestion]. *Med Clin (Barc)*. 2004; 123:611-4.
- [27] Hernndez AF, Lacasn A, Gil F, Rodrguez-Barranco M, Pla A, Lopez-Guarnido O. Evaluation of pesticide-induced oxidative stress from a gene-environment interaction perspective. *Toxicology*. 2013; 307:95-102.
- [28] Stohs SJ. The role of free radicals in toxicity and disease. *J Basic Clin Physiol Pharmacol*. 1995; 6:205-28.
- [29] Dundar ZD, Ergin M, Koylu R, Ozer R, Cander B, Gunaydin YK. Neutrophil-lymphocyte ratio in patients with pesticide poisoning. *J Emerg Med*. 2014; 47:286-93.
- [30] Liu F, Jiang MZ, Shu XL, Zhang XP. [Role of oxidative stress in the pathogenesis of esophageal mucosal injury in children with reflux esophagitis]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2009; 11:425-8.
- [31] Erel O. A new automated colorimetric method for measuring total oxidant status. *Clin Biochem*. 2005; 38:1103-11.
- [32] Kiyani G, Aktas S, Ozel K, Isbilen E, Kotiloglu E, Dagli TE. Effects of hyperbaric oxygen therapy on caustic esophageal injury in rats. *J Pediatr Surg*. 2004; 39:1188-93.
- [33] Guven A, Demirbag S, Uysal B, Topal T, Erdogan E, Korkmaz A, et al. Effect of 3-amino benzamide, a poly (adenosine diphosphate-ribose) polymerase inhibitor, in experimental caustic esophageal burn. *J Pediatr Surg*. 2008; 43:1474-9.
- [34] Ranjbar A, Solhi H, Mashayekhi FJ, Susanabdi A, Rezaie A, Abdollahi M. Oxidative stress in acute human poisoning with organophosphorus insecticides; a case control study. *Environ Toxicol Pharmacol*. 2005; 20:88-91.
- [35] Ranjbar A, Pasalar P, Abdollahi M. Induction of oxidative stress and acetyl cholinesterase inhibition in organophosphorus pesticide manufacturing workers. *Hum Exp Toxicol*. 2002; 21:179-82.
- [36] Kaya M, Ozdemir T, Sayan A (2010) The relationship between clinical findings and esophageal injury severity in children with corrosive agent ingestion. *Ulus Travma Acil Cerrahi Derg* 16: 537-540.
- [37] Havanond C, Havanond P (2007) Initial signs and symptoms as prognostic indicators of severe gastrointestinal tract injury due to corrosive ingestion. *J Emerg Med* 33: 349-353.
- [38] Rigo GP, Camellini L, Azzolini F, Guazzetti S, Bedogni G, et al. (2002) What is the utility of selected clinical and endoscopic parameters in predicting the risk of death after caustic ingestion? *Endoscopy* 34: 304-310.
- [39] Seyit Uyar, Mehmet Kok (2017) Neutrophil to Lymphocyte Ratio as a Predictor of Endoscopic Damage in Caustic Injuries. *J Clin Toxicol* 7: 349. doi:10.4172/2161-0495.1000349
- [40] Jun Hyung Kim et al.: Haematological Parameters Predicting Complications of Caustic Ingestion: A Retrospective Study. *Toxicology* volume 26, 6, 2015