NEUTROPHIL LYMPHOCYTE RATIO AS A PROGNOSTIC FACTOR IN ACUTE PANCREATITIS

Anjan Kumer Dey[1] Farid Uddin Ahmed[2*] Sujat Paul[3]

Abstract

Background: Different scoring systems are currently in use to stratify the severity of the acute pancreatitis to guide clinicians in triaging patients with the aim of improving outcomes. The Neutrophil-Lymphocyte Ratio (NLR) provides a rapid indication of the extent of an inflammatory process. Its value to predict the severity of acute pancreatitis has not been well studied. The aim of this study was to investigate the prognostic value of the NLR in acute pancreatitis patients.

Materials and methods: This hospital based observational study was conducted at Medicine ward of Chittagong Medical College Hospital (CMCH) for one year period from January 2015 to December 2015. One hundred and four adult patients with a diagnosis of acute pancreatitis who fulfilled the defined inclusion and exclusion criteria were selected for the study. After obtaining informed consent clinical interviewing and physical examination were done according to predesigned case record form. Then blood was collected within one hour of admission. After getting the result, final selection were done following exclusion criteria. The patients were arranged into three groups according to NLR tertiles. Main outcome measures were intensive Care Unit (ICU)/High Dependency Unit (HDU) admission, Length of Stay (LOS) in the hospital and in-hospital mortality.

Results: According to NLR tertiles, patients in the 3rd tertile (NLR≥7.6) had significantly more ICU/HDU admissions (40.6% vs. 0%), longer average LOS (7.91 vs. 4.03 days) and more death (12.5% vs. 0%) compared with those in the 1st tertile (NLR< 3.6). The higher the NLR tertile, the Modified Early Warning Score (MEWS) also increased significantly. According to the ROC curve, NLR values were superior in predicting ICU/HDU admission and hospitalization for ≥ 7 days compared to WBC and MEWS values.

Conclusion: Elevation of the NLR during admission was significantly associated with severe acute pancreatitis and is a negative prognostic indicator in acute pancreatitis. It is superior to total WBC and modified MEWS in predicting adverse outcomes of acute pancreatitis.

Key words

Neutrophil-Lymphocyte Ratio;Acute pancreatitis;Prognosis.

Introduction

Acute pancreatitis accounts for 3% of all cases of abdominal pain admitted to hospital. It affects 2-28 per 100,000 of the population and is increasing in incidence. The incidence varies in different countries. The estimated incidence in the United State is increasing and is now estimated to be 70 hospitalization/100,000 persons annually, thus resulting in >200,000 new cases of acute pancreatitis per year[1,2].

Though the disease is usually self-limiting process about one fourth of patients presents with or subsequently develops severe form of the disease that is associated with a mortality of up to 50%. Identification this patient is crucial so that they have managed in a specialized center with the aim of improving outcomes[3]. Multiple severity scoring systems have been developed to guide clinicians in triaging patients who are likely to require vigorous treatment in Intensive Care Unit (ICU). Ideally, these scoring systems should use predictive tools that are rapid, reproducible, inexpensive, minimally invasive and highly accurate[4].

The scoring system currently in clinical practice like Acute Physiology and Chronic Health Evaluation (APACHE II), Early Warning Score (EWS), Ranson criteria, Glasgow and Imrie scores, procalcitonin, interleukin-6 and interleukin-8 have been said to be able to predict severity of acute pancreatitis, but these are limited in our setting due to their complexity and non-availability[5-12].

1. OSD, DGHS, Dhaka.
2. Assistant Professor of Community Medicine Chittagong Medical College, Chattogram.
3. Professor of Medicine Chittagong Medical College, Chattogram.

***Correspondence:** **Dr. Farid Uddin Ahmed**
E-mail: fuahmed_34@yahoo.com
Cell : 01727 78 97 00

Submitted on : 11.07.2020
Accepted on : 20.07.2020

The White Cell Count (WCC) is a routine serum hematological test that is already incorporated in many of the current acute pancreatitis scoring systems, and routinely performed on all surgical emergency admissions. Components of the total WCC include neutrophils and lymphocytes, both of which can be used individually as markers of inflammation. Neutrophils propagate SIRS and the inflammatory cascade in acute pancreatitis whereas lymphocyte depletion occurs in severe sepsis, and is associated with a poor outcome[13,14]. An increased neutrophil count with a concomitant decreased lymphocyte count has previously been associated with severe sepsis, bacteremia, and surgical stress[13,15]. The Neutrophil-lymphocyte Ratio (NLR) is a measure of the divergence of these two WCC components, and may be more accurate than the total WCC or individual neutrophil-lymphocyte counts in predicting poor outcome in benign and malignant surgical conditions[16,17].

NLR has been studied as a prognostic marker in acute pancreatitis[18,19]. But the findings are difficult to generalize as the study population and the hospital settings were completely different from ours. Comparing to other scoring systems which are used to triage this patient, NLR is rapid, reproducible, inexpensive, and minimally invasive and accurate. This study was conducted to evaluate the NLR as a prognostic factor in acute pancreatitis in our setting.

Materials and methods

This prospective observational study was conducted in Chittagong Medical College Hospital (CMCH) Chattogram from January 2015 to December 2015. One hundred and four diagnosed patients of acute pancreatitis admitted in different Medicine and Surgery Units were enrolled in the study. Acute pancreatitis was diagnosed if two of the following three features were present: upper abdominal pain consistent with acute pancreatitis (Acute onset of persistent, severe epigastric pain often radiating to the back) serum amylase or lipase levels more than 3 times upper level of normal, and characteristics findings of acute pancreatitis on abdominal ultrasonography. Patients aged > 80 years, having a diagnosis of cancer or hematological proliferative disease under treatment, those were on steroid or chemotherapy and those refused to participate were excluded. Sample size was calculated with expected proportion of events p=50% (As frequency of abnormal NLR in the patients of acute pancreatitis varies from 40% to 70% in previous studies[18,19]. Prior approval was taken from the Ethical Review Committee of CMC.

After inclusion in the study, history taking and clinical examination was done as per hospital protocol. With all aseptic precaution 10 cc of venous blood was collected and sent to laboratory for haematocrit, white blood cell, neutrophil, lymphocyte and monocyte count as well as for serum amylase/ lipase. All relevant data were noted in the pre tested data sheet. After getting the laboratory report, the patients who met the selection criteria were finally selected for my study. Treatment protocols of the patient were not interrupted and he/she got the treatment as per available hospital protocol. Patients were followed up daily during their hospital stay to measure the outcome (Length of Hospital Stay, ICU/HDU admission and mortality). Indication of ICU/HDU admission was severe acute pancreatitis on the basis of Modified EWS (MEWS)[20].

During the data collection period 149 patients were assessed for eligibility according to their clinical feature. Among them 45 patients were excluded due to unavailable records and negative enzyme and/or radiological findings. Rests of the 104 patients were stratified into tertile model according to each NLR.

Data were processed and analyzed by using computer bases software SPSS- 18 (Statistical Package for Social Science). Continuous variables were expressed as mean (±SD) and F test (ANOVA) of significance were done to determine whether an observed difference of the means of continuous variables among three groups could be considered statistically significant. Categorical variables were expressed as frequency (Percentage). Chi-square tests were done between categorical variables to check for the statistical significant association between different variables. Receiver operator characteristic (ROC) curve was plotted to compare the area under the curve (AUC) values of NLR, WCC and MEWS for prediction of adverse outcome. Statistical significance was defined as $p < 0.05$ and confidence interval set at 95% level.

Results

The overall and NLR tertile based baseline characteristics of the 104 patients were shown in Table I. There was no significant difference among NLR tertiles in terms of age, sex, BMI and etiology of acute pancreatitis. However, unfavorable trends of clinical and laboratory parameters were noted as the NLR tertile increased (Table I) .

Table I : Baseline characteristics of the patients of acute pancreatitis sorted by tertiles of the admission NLR (n=104).

Characteristics	All (n = 104)	NLR<3.6 (n = 34)	3.6≤NLR<7.6 (n = 38)	NLR≥7.6 (n = 32)	p value
Demographic characteristics					
Age, years	50.32 (±14.53)	49.53(±13.22)	47.82(±14.02)	53.16(±12.09)	>0.05
Male	54 (51.92)	17(31.5)	20(37)	17(31.5)	>0.05
BMI, kg/m^2	22.84 (±3.89)	21.65(±3.13)	22.39(±3.22)	23.44(±3.41)	>0.05
Cause of acute pancreatitis					
Idiopathic	73 (70.2)	24 (70.6)	29 (76.3)	20 (62.5)	>0.05
Gall stone	15 (14.4)	4 (11.8)	5 (13.2)	6 (18.8)	>0.05
Alcohol abuse	5 (4.8)	3 (8.8)	0 (0)	2 (6.3)	>0.05
Ascariasis	9 (8.7)	3 (8.8)	4 (10.5)	2 (6.3)	>0.05
Clinical presentation					
Pain duration (hrs)	11.12 (±4.5)	11.03 (±4.5)	11.95 (±4.6)	10.25 (±4.8)	<.001
RR, /min	16.19(±2.2)	15(±1)	15(±2)	18(±3)	<.001
SBP, mm Hg	115(±10.55)	120(±19)	116(±10)	102(±13)	<.001
DBP, mm Hg	73.790(±5)	76(±8)	74(±4)	72(±9)	<.001
Heart rate, /min	85(±6.3)	79(±7.5)	78(±6.3)	90(±13.8)	<.001
Temperature, ^{O}C	37.99(±.75)	37.23(±.53)	37.13(±.35)	38.03(±1.05)	<.001
MEWS	1.13(±1.11)	0(±0)	0.47(±1.11)	2.75(±2.05)	<.001
In-hospital laboratory data					
Serum amylase, U/l	894(±280)	777(±258)	886(±250)	1205(±384)	<.001
Serum lipase, U/l	704(±257)	638(±233)	660(±239)	747(±257)	<0.05
Hematocrit, %	45.44(±1.29)	44.76(±2.05)	45.34(±1.19)	45.12(±1.04)	>0.05
WBC, $\times 10^3 \mu l$	14524(±1429)	10423(±934)	14376(±1392)	16370(±2090)	<.001
Lymphocyte, %	14.41(±2.54)	23.39(±2.66)	13.61(±2.42)	8.94(±1.11)	<.001
Neutrophil, %	79.17(±1.84)	70.35(±1.76)	78.03(±1.76)	84.25(±4.51)	<.001

Data are presented in either means ±SD or n (%); p values were derived either from Chi-square test or F (ANOVA) test, BMI: Body Mass Index, RR: Respiratory Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MEWS: Modified Early Warning Sign, WBC: White Blood Cell.

Out of 104 patients, 1 patient requires HDU admission and 18 patients require ICU admission and rest of the patients were treated in general ward. All of the patient having NLR 3.6 were treated in general ward, whereas 59.4% of patient with NLR≥7.6, were treated in general ward. The admission rates for ICU/HDU increased significantly as the NLR tertile increased (p<0.001).

Similarly patients in the 3rd tertile (NLR≥7.6) had statistically significant longer average length of stay (7.91 vs. 4.03 days, p<0.001) compared with those in the 1st tertile (NLR<3.6). Though, five patients died in-hospital and incidence of death increased as the NLR tertiles the difference failed to reach statistical significance (Table II).

Table II: Relation between NLR tertiles and outcome variables of the patient (n=104).

Characteristics	NLR<3.6 (n = 34)	3.6≤NLR<7.6 (n = 38)	NLR≥7.6 (n = 32)	p value
Received treatment in				
Ward	34 (100)	32 (84.2)	19 (59.4)	<0.001
ICU/HDU	0 (0)	6 (15.8)	13 (40.6)	
Length of hospital stay				
Mean (±SD), days	4.03 (±0.78)	6.00 (±1.53)	7.91 (±2.76)	<0.001
In hospital mortality				
No	34 (100)	37 (97.8)	28 (87.5)	>0.05
Yes	0 (0)	1 (2.6)	4 (12.5)	

Data are presented in either means ±SD or n (%), p values were derived either from Chi-square test or F (ANOVA) test.

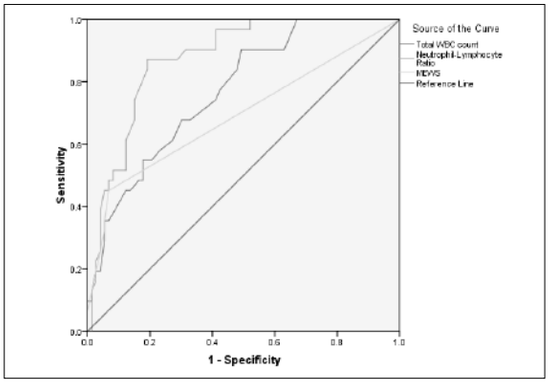

Fig 1: ROC curve of NLR, total WBC and MEWS score in predicting hospitalization ≥ 7 days for acute pancreatitis.

Figure 1 illustrate the superiority of NLR (AUC: 0.875, 95% CI: 0.808-0.942, p<0.001) to predict length of hospital stay, when LOS is dichotomized to ≥7 days versus <7 days; in comparison to total WBC count (AUC:0.770, 95%CI: 0.676-0.863, p<0.001) and MEWS score (AUC:0.692; 95% CI: 0.570-0.814, p=0.002).

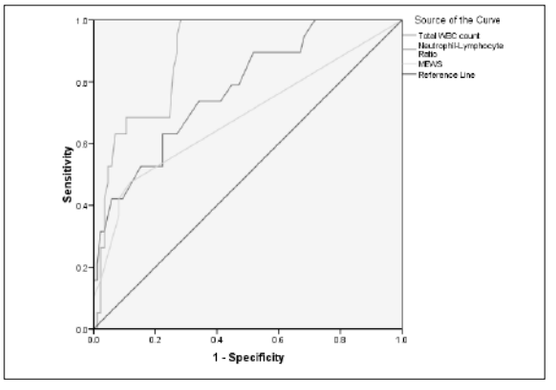

Fig 2: ROC curve of NLR, total WBC and MEWS score in predicting ICU admission for acute pancreatitis.

Figure 2 illustrate the superiority of NLR (AUC 0.889; 95% CI: 0.823-0.955, p<0.001) to predict ICU admission in comparison to total WBC count (AUC: 0.777, 95% CI: 0.665-0.891) and MEWS score (AUC:0.685, 95% CI: 0.535-0.834, p=0.012).

Discussion

The current study was done to determine the patterns of NLR in the patients of acute pancreatitis in respect to the outcome of the patietns. The main findings of my study was that incidence of ICU/HDU admission, length of hospital stay and death increased as NLR of the patients increased. Regarding baseline characteristics, temperature, respiratory rate, heart rate were found significantly higher in higher NLR tertile group. Systolic and diastolic blood pressure was found significantly lower in the higher NLR tertiles. There was no significant difference of BMI in the NLR tertiles. In respect to their laboratory findings, significantly higher serum amylase, total WBC count and Neutrophil percentage values in the higher NLR tertiles and significantly lower lymphocyte percentage in the higher NLR tertiles has been noticed. Suppiah et al investigated the prognostic value of NLR in acute pancreatitis three days following admission[19]. They observed that, NLR in severe acute pancreatitis was significantly higher than in the favorable pancreatitis group on all three days and subsequently concluded that elevation of the NLR during the first 48 hours of admission was significantly associated with severe acute pancreatitis. However, as antibiotics can alter WCC by reducing inflammatory process and patients of acute pancreatitis are invariably receive antibiotic in their management, continuous NLR monitoring on each day of admission to get a reflection of the outcome in acute pancreatitis is controversial.

In the current study, a trend of more adverse outcomes has been found with high total WBC count, low lymphocyte and high neutrophil counts and all were statistically significant similar to NLR. Azab et al investigated the role of NLR in acute pancreatitis and they reported NLR to be superior to the total WBC count or individual neutrophil and lymphocyte counts in predicting ICU admission and death in patients with acute pancreatitis[18]. They noticed a trend of more adverse outcomes with low lymphocyte and high neutrophil

counts but neither had a significant p value in contrast to NLR. These dissimilarities were due to probably the very small sample size of the present study as well as due to the sampling technique.

However, according to the ROC curve, NLR values were superior in predicting ICU admission and hospitalization for ≥7 days in acute pancreatitis compared to total WCC.

In the current study, both NLR and MEWS remained statistically significant predictors of the severity of acute pancreatitis upon presentation of the patient to the hospital. Patients in the 3rd tertile (NLR ≥ 7.6) had statistically significant longer average LOS (7.91 vs. 4.03 days, $p<0.001$) compared with those in the 1st tertile (NLR<3.6). However, in ROC curve analysis, NLR (AUC 0.875) was superior to predict LOS, when LOS was dichotomized to ≥7 days versus <7 days; in comparison to total WBC count (AUC 0.770) and MEWS score (AUC 0.692). In predicting ICU admission NLR (AUC 0.889) was superior too in comparison to total WBC count (AUC 0.777) and MEWS score (AUC 0.685). Similar results were also found in the previous studies[18-20].

Limitations

Certain limitations should be kept in mind while deciding on the implications of the findings of the study. The study was conducted in a selected department of a selected hospital of Bangladesh and did not include representatives from the entire population. Non-probability sampling technique was another limitation. Because of the low number of adverse outcomes, it was only possible to assess the NLR association with ICU admission and LOS rather than mortality and organ dysfunction. The value of NLR after admission and throughout the hospital course was not evaluated in my study.

Conclusions

The present study adds to the growing body of evidence that NLR rather than the total WBC count is better in the risk scoring systems and in triaging patients of acute pancreatitis. The predicting value of NLR in determining adverse outcomes in cases of acute pancreatitis in respect of ICU admission, length of hospitalization and mortality is superior to total WBC count and modified MEWS score.

Recommendations

Additional rigorously conducted multicenter studies with frequent follow-up in representative large samples are strongly suggested. If larger studies are confirmatory, NLR should be considered for inclusion into established scoring systems. The benefit of NLR is that it is simple, cheap and routine part of a CBC done during initial emergency room evaluation of patients.

Acknowledgments

It was a self funded study. The authors would like to thank all survey participants for their involvement, as well as the Physicians of the Medicine and Surgery wards of CMCH for their collaboration and cooperation.

Contribution of authors

AKD: Conception, designing, data collection, manuscript drafting and final approval

FUA: Data analysis, manuscript drafting and final approval.

SP: Conception, interpretation of data, critical revision and final approval.

Disclosure

All the authors declared no competing interest.

References

1. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States. Gastroenterology. 2012; 143(5):1179-1187.

2. Spanier BW, Dijkgraaf MG, Bruno MJ. Epidemiology, aetiology and outcome of acute and chronic pancreatitis: An update. Best Pract Res Clin Gastroenterol. 2008;22(1):45–63.

3. Pavlidis TE, Pavlidis ET, Sakantamis AK. Advances in prognostic factors in acute pancreatitis: a mini-review. Hepatobiliary Pancreat Dis Int. 2010;9(5): 482-486.

4. Minne L, Abu-Hanna A, de Jonge E. Evaluation of SOFA-based models for predicting mortality in the ICU: A systematic review. Crit Care. 2008;12(6): 1-13.

5. Dambrauskas Z, Gulbinas A, Pundzius J, Barauskas G. Value of the different prognostic systems and biological markers for predicting severity and progression of acute pancreatitis. Scand J Gastroenterol. 2010;45(7–8): 959-970.

6. Pavlidis TE, Pavlidis ET, Sakantamis AK. Advances in prognostic factors in acute pancreatitis: a mini-review. Hepatobiliary Pancreat Dis Int. 2010;9(5): 482-486.

7. Balthazar EJ, Robinson DL, Megibow AT, Ranson HE. Acute pancreatitis: Value of CT in establishing prognosis. Radiology. 1990;174(2):331-336.

8. Chatzicostas C, Roussomoustakaki M, Vardas E, Romanos J, Kouroumalis EA. Balthazar computed tomography severity index is superior to Ranson criteria and APACHE II and III scoring systems in predicting acute pancreatfis outcome. J Cun Gastroenterol. 2003;36(3):253–260.

9. Garcea G, Jackson B, Pattenden CJ, Sutton CD, Neal CP, Dennison AR et al. Early warning scores predict outcome in acute pancreatifis. J Gastrointest Surg. 2006;10(7):1008-1010.

10. Corfield AP, Cooper MJ, Williamson RC, Mayer AD, McMahon MJ, Dickson AP, et al. Prediction of severity in acute pancreatitis: Prospective comparison of three prognostic indices. Lancet. 1985;326 (8452): 403–407.

11. Triester SL, Kowdley KV. Prognostic factors in acute pancreatitis. J Clin Gastroenterol. 2002; 34(2):167-176.

12. Aoun E, Chen J, Reighard D, Gleeson FC, Whitcomb DC, Papachristou GI. Diagnostic accuracy of interleukin-6 and interleukin-8 in predicting severe acute pancreatitis: A meta-analysis. Pancreatology. 2009;9(6): 777–785.

13. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care. 2010;14(5): R192.

14. Pezzilli R, Billi P, Beltrandi E, Casadei Maldini M, Mancini R. Impaired lymphocyte proliferation in human acute pancreatitis. Digestion. 1997; 58(5): 431–436.

15. Wyllie DH, Bowler IC, Peto TE. Relation between lymphopenia and bacteraemia in UK adults with medical emergencies. J Clin Pathol. 2004; 57(9): 950–955.

16. Halazun KJ, Hardy MA, Rana AA, Woodland DC, Luyten EJ, Mahadev S et al. Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. Ann Surg. 2009;250(1): 141–151.

17. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005;91(3): 181–184.

18. Azab B, Jaglall N, Atallah JP, Lamet A, Raja-Surya V, Farah B, et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. Pancreatology. 2011;11(4): 445–452.

19. Suppiah A, Malde D, Arab T, Hamed M, Allgar V, Smith AM. The Prognostic Value of the Neutrophil-Lymphocyte Ratio (NLR) in Acute Pancreatitis: Ientification of an Optimal NLR. J Gastrointest Surg. 2013;17(4):675-681.

20. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified early warning score in medical admissions. QJM. 2001;94(10):521–526.