ORIGINAL ARTICLE

Role of Neutrophil-Lymphocyte Ratio (NLR) in predicting development of organ failure in Acute Pancreatitis

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Abstract

Background: Different modalities are available for predicting development of organ failure in Acute Pancreatitis. A single marker with high sensitivity and specificity is yet to be identified. This study intends to find out the utility of Neutrophil Lymphocyte Ratio (NLR) in predicting development of organ failure in Acute Pancreatitis. Methods: A total of 117 patients admitted with acute pancreatitis were included. Clinical parameters and biochemical tests were recorded on admission and on day 3 & day 5 of admission. CT scan was performed in all patients. NLRwas calculated using these data.Every patient was followed regularly for identification of organ failure. Statistical analysis was done with SPSS V22. Results: Among 117 patients, 67(57.3%) were male and 50(42.73%) were female with a mean age of 47.99±15. Among the patients the etiology was found to be biliary, hypertriglyceridemia, alcohol, malignancy and post-ERCP complications in 25(21.4%),23(19.7%),8(6.8%),3(2.6%),2(1.7%) cases respectively. In 53(45.3%) cases no definite etiology could be found. 83(70.9%) patients had mild,15(12.8%) had moderately severe and 19(16.2%) had severe acute pancreatitis. 23 (19.65%) patients developed complication, whereas 94 (80.34%) developed no complication.Organ failure was present in 34(29.06%) cases among total 117 cases.Those patients who developed organ failure had a mean NLR of 6.25±0.96, in contrast to a mean of 3.64±0.50 in those who didn't developed organ failure.ROC curve evaluating the role of NLR in predicting development of organ failure in acute pancreatitis showed an AUC of 0.984. ROC curve revealed a cutoff point of 5.04 with highest sensitivity (97.1%) & specificity (97.6%) with a PPV & NPV of 94.3% & 98.8% respectively. Conclusion: Calculating NLR is simple, it is readily available, easy to assess and cost-effective. It can be used as a new simple & cost-effective marker for the prediction of development of organ failure in Acute Pancreatitis.

Key words: Neutrophil-Lymphocyte Ratio (NLR), Predictor, Organ failure, Acute pancreatitis.

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Introduction

Acute pancreatitis accounts for 3% of all cases of abdominal pain admitted to hospital.1 The incidence of acute pancreatitis appears to be increasing.2 As the population is becoming increasingly overweight, the incidence of gallstones, the most common cause of acute pancreatitis, is rising. Whereas gallstones and alcohol appear to be the cause of acute pancreatitis in the majority of cases, many other conditions like hypertriglyceridemia predispose to acute pancreatitis to varying degrees.3 About 80% of all cases are mild and have a favorable outcome. Of the rest 20% of patients with severe disease, almost all (98%) die within the first week, usually from multiorgan failure. After this time the majority of deaths result from sepsis, especially that complicating infected necrosis. On admission it is possible to predict patients at risk of this complication.1 Predicting severity of pancreatitis early in the course of disease is critical to maximize therapy and to prevent and minimize organ dysfunction and complications. Unfortunately, the management of patients with acute pancreatitis is complicated by the inability to distinguish mild from severe disease during the early stages.3

Severe acute pancreatitis has a poor prognosis and early prediction of development of organ failure in Acute Pancreatitis helps us in taking appropriate steps to halt the disease progression and to reduce development of complications. Several predictors (biochemical parameters, clinico-biochemical scores and radiological scores) have been used to predict the development of organ failure in Acute Pancreatitis. But a simple, inexpensive, routinely available and highly accurate predictor is however not yet available. A lot of scoring systems, such as Ranson Glasgow, APACHE II, bedside index for severity in acute pancreatitis (BISAP), are there to predict the development of organ failure in acute pancreatitis. These scoring systems either take more than 48 hours to evaluate (Ranson, computed tomography severity index) or are difficult to memorize and cumbersome (APACHE II) or are costly and not widely available (Creactive protein [CRP], trypsinogen activation peptide [TAP]).

The neutrophil-lymphocyte ratio (NLR) has been identified as a more reliable predictor of adverse outcomes in several benign and malignant diseases, such as coronary heart disease, esophageal cancer, colorectal cancer, and hepatocellular carcinoma, when compared with the WBC count.4-9 Neutrophils and lymphocytes reflect the immune response better than the total WBC count.4-6 In particular, studies have demonstrated the correlation between peripheral lymphocytopenia and the severity of acute pancreatitis.10,11 In addition, one study established the superiority of the NLR over the total WBC counts in predicting the severity of acute pancreatitis.12

The NLR was computed by calculating the ratio of the absolute neutrophil and lymphocyte counts, and the analysis was conducted using the NLR values on the day of hospitalization.The aim of this study was to demonstrate the usefulness of the NLR in predicting the development of organ failure in the early stages in patients with acute pancreatitis. In addition, this study examined the optimal cut-off value of the NLR in predicting organ failure in patients with acute pancreatitis.

Materials and methods

This prospective and observational study was done in the department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), Square

Hospitals Ltd, Dhaka, Bangladesh from January, 2018 to June, 2019. Patients aged more than 18 years, admitted with abdominal pain and fulfilling the diagnostic criteria of acute pancreatitis by clinical history, physical examination, biochemical tests and different imaging modalities were included in this study. Patients attending after 72 hours after the onset of abdominal pain, patients having chronic pancreatitis, chronic kidney disease, serious co-morbid conditions like COPD, heart failure and patients suffering from severe infection or inflammation of any other organ system were excluded from the study. Patients unwilling to give voluntary consent to participate in the study were also excluded. Consecutive type of non-probability sampling technique was applied to enroll the patients. Prior to the commencement of this study, the research protocol was approved by the Ethical Review Committee (ERC) of the institution.The aims and objective of the study along with its procedure, alternative diagnostic methods, risk and benefits were explained to the patients in easily understandable local language and then informed consent was taken from each patient.

A predesigned structured questionnaire was used for recording all the data. To detect etiology of acute pancreatitis, liver function test, fasting lipid profile, USG of abdomen were done in all cases. Demographic data like age, sex, BMI; clinical data like presence of abdominal pain, severity and radiation of abdominal pain, abdominal lump, anemia, fever, GCS score, vital parameters were recorded. Laboratory data like hemoglobin, white blood cell count, platelet count, FBS, HbA1c, blood urea, BUN, serum creatinine, serum amylase, serum lipase, serum procalcitonin, serum bilirubin, serum albumin, AST, ALT, alkaline phosphatase, serum LDH, fasting lipid profile, ABG, CA 19.9, USG and CT scan of upper abdomen findings were recorded. Laboratory tests were done on admission and CBC, serum creatinine, BUN, ABG were repeated on day 3 and on day 5 of admission to follow up the patient. Computedtomography (CT) scan was performed in all patientsafter 72 hours of admission for detectionof the development of fluid collections, the extentof inflammation, and necrotic changes. Serum procalcitonin levels were done on admission. NLR,Glasgow score, Ranson score and BISAP score was calculated using the data available within the first24 hours after admission. Attacks of acute pancreatitis were classified as mild, moderately severe and severe according to revised Atlanta criteria and with the help of modified Marshall scoring system for organ failure. Every patient was followed regularly for identification of organ failure or any other complication. Data were analyzed by computer analysis method using SPSS version 22.

Statistics
Statistical analyses were carried out by using the Statistical Package for Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean, standard deviation, and categorical variables as frequencies and percentages. The NLR was treated as a continuous variable, and organ failure distribution were treated as categorical variables. ROC curve was plotted for assessing the performance of NLR in predicting development of organ failure in acute pancreatitis. The optimal cut-off value of NLR was computed by using the trade-off between sensitivity and specificity on the receiver-operating characteristic (ROC) curves, and the accuracy of prediction of the NLR was

estimated using the area under the receiveroperating curve (AUC). Performance of NLR was further analyzed by chi-square (X2) test. Correlations between variables were measured by Spearman correlation coefficient test. A p-value <0.05 was considered as significant.

Results

A prospective observational study was carried out to evaluate the role of NLRin predicting development of organ failure in acute pancreatitis. Total 117 patients with acute pancreatitis, who fulfilled the inclusion criteria, were included in this study. The result of the study is presented in following tables and diagrams.

Table 01: Demographic, clinical and biochemical characteristics of the study population (n=117)

Parameters	Result
Age (years)	47.99±15.90
Sex (Male)	67(57.3)
Contributing factor	
Smoking	36(30.8)
Alcohol	10(8.5)
Tea/ coffee	93(79.5)
OCP	3(2.6)
DM	82(70.1)
BMI	25.36±3.4
Clinical features	
Abdominal pain	117(100.0)
Nausea and / orvomiting	109(93.2)
Fever	24(20.5)
Duration of hospital stay	8.04±4.26
HCT	37.23±4.80
Blood urea nitrogen	17.40±9.61
CRP	60.61± 81.2

Values are expressed as mean±SD & Number (%). Values within the bracket are expressed as percentage.

Table 02: Association of NLR with development of organ failure in acute pancreatitis (n=117).

Development of organ failure in acute pancreatitis	n(%)	NLR (Mean±SD)	p value
Absent	83(70.94)	3.64±0.50	<0.001
Present	34(29.06)	6.25±0.96	

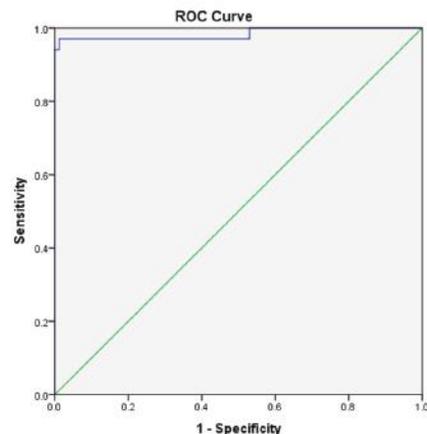Unpaired T-test was done to measure the level of significance (95% CI)

Figure 01: ROC curve showing test accuracy of NLR in the prediction of development of organ failure in acute pancreatitis (AUC=0.984, p<0.001).

Table 03: Evaluation of different cutoff points of NLR as a predictor of development of organ failure in acute pancreatitis (n=117)

Cutoff points for NLR	Sensitivity (%)	Specificity (%)
4.00	97.1	81.9
4.53	97.1	94.0
5.04	97.1	97.6
5.19	94.1	98.8

Table 04: Performance test of NLR as a predictor of organ failure in acute pancreatitis (n=117)

NLR	Organ failure		Total	p-value
	Present	Absent		
≥ 5.04	33 (97.1)	2 (2.4)	35 (29.9)	<0.001
< 5.04	1 (2.9)	81 (97.6)	82 (70.1)	
Total	34 (100.0)	83 (100.0)	117 (100.0)	

Chi-square (X2) test was done to measure the level of significance

Table 05: Correlation of NLR with Glasgow, Ranson and BISAP score.

Marker	r value	p value
NLR	1.0	<0.001
Glasgow score	0.524	<0.001
Ranson score	0.487	<0.001
BISAP score	0.515	<0.001

Spearman test was done to measure the level of significance

Table 06: Correlation among NLR, Hematocrit (HCT), CRP and Blood Urea Nitrogen (BUN).

Marker	r value	p value
NLR	1.0	<0.001
Hematocrit (HCT)	0.429	<0.001
CRP	0.442	<0.001
Blood Urea Nitrogen (BUN)	0.491	<0.001

Spearman test was done to measure the level of significance

Discussion

A prospective observational study was carried out to evaluate the role of NLR in predicting development of organ failure in acute pancreatitis. Total 117 patients with acute pancreatitis, who fulfilled the inclusion criteria, were included in this study. Among the patients, 67 (57.3%) patients were male and 50 (42.73%) patients were female. Mean age of the study population was 47.99±15.90 (mean± SD) with minimum age 18 years and maximum age 95 years. In a study by Albulushi et al.13 found the mean age of acute pancreatitis of 47 years among which 55 % were male and 45% were female. The mean age and sex difference of the above study correlate with this study.

Out of 117 patients, 36(30.8%) were smoker and 10 (8.5%) were alcoholic. 55(47%) patients were overweight and 12 (10.3%) patients were obese. Mean BMI was 25.36±3.4. Haque MM14 found that mean BMI was 25.88±2.95.Mean hematocrit on admission was 37.23±4.80. Mean blood urea nitrogen was 17.40±9.61 and mean HbA1c was 7.97±1.70. Average duration of hospital stay was 8.04±4.26 days. Haque MM14, in his study also found that mean HCT was 32.9±7.5, mean BUN was 21.7±7.2, mean HbA1c was 7.8±1.7 and average duration of hospital stay was 7.8±2.5 days. All of which is almost similar to these study results.

In this study, 25 (21.4%) cases were gall stone pancreatitis, 23 (19.7%) cases were due to hypertriglyceridemia, 8 (6.8%) cases were due to alcohol, 3 (2.6%) cases were due to malignancy, 2 (1.7%) cases due to post ERCP complications, 2 (1.7%) cases were due to gall stones and hypertriglyceridemia and 1 (0.9%) cases were due to hyper triglyceridaemia and alcohol (figure 1). In 53(45.3%) cases no definite etiology could be found. Al-Karawi et al.15 found

found that 67.5% cases of acute pancreatitis were due to biliary cause; alcohol was responsible in 1.8% of cases and 17% cases were due to unknown cause. In another study, Chang et al.16 found gall stone as etiology in 34.1% of cases and alcohol in 33.6% cases and hyper triglyceridaemia in 12.3% of cases.

High prevalence of hypertriglyceridemia in this study could be explained by increased prevalence of DM, obesity and metabolic syndrome among the study population. And the low prevalence of alcohol as etiology of acute pancreatitis could be due to social custom as well as religious belief.

Out of 117 patients 83 (70.9%) had mild acute pancreatitis according to revised Atlanta criteria, 15 (12.8%) patients had moderately severe acute pancreatitis and 19 (16.2%) patients had severe acute pancreatitis (Figure 02). Cho et al.17 found 13% cases as severe acute pancreatitis, 8% cases as moderately severe and 79% cases as mild acute pancreatitis in their study which is similar to present study. This study showed that, 94 (80.34%) patients did not develop any kind of complications from acute pancreatitis, on the other hand 23 (19.65%) patients developed complications. Albulushi et al.13 found 32% patients that developed complication of acute pancreatitis in their study. Haque MM14 in his study found that 17 (23.9%) developed complication whereas 54 (76.1%) developed no complication, which is similar to this study.

The NLR is a simple test that is inexpensive, routinely performed during the initial evaluation of patients, not affected by the volume status of the patient, and can be repeated easily. 12,18 In particular, since neutrophilia and lymphopenia are indexes of systemic inflammation and physiological stress,

they can better reflect complications such as necrosis or organ failure.10-12,18. The neutrophil, as a major cell associated with the active inflammation response, is the main initiator of tissue destruction caused by several inflammatory cytokines such as interleukin 1 and interleukin 6.12,18 Therefore, neutrophilia generated by the acute and severe pancreatic tissue damage and inflammation in SAP increases the NLR.12,18 On the other hand, there was a decreased number of peripheral total and lymphocyte subsets measured within 48 h after admission in patients with acute pancreatitis.12,18 As evidenced by existing studies, patients with SAP had a significantly lower number of lymphocytes in comparison with patients having the mild form of the disease, thereby further increasing the NLR. It is probably due to an impaired lymphocyte proliferative response to mitogens in acute pancreatitis patients.10-12,18 Similar to other published studies by Azab and Suppiah12,18, this study investigated the predicting value of the NLR for development of organ failure.

Organ failure was present in 34 (29.06%) cases among total 117 cases. Those patients who developed organ failure had a mean NLR of 6.25±0.96, in contrast to a mean of 3.64±0.50 in those who didn't developed organ failure. Jeon TJ et al.19 in their study found that the NLR was significantly higher in the group of patients with organ failure than in the group of patients without organ failure (median, 7.09 vs 4.85). ROC curve evaluating the role of NLR in predicting development of organ failure in acute pancreatitis showed an AUC of 0.984 (95%CI). ROC curve revealed a cutoff point of 5.04 with highest sensitivity (97.1%) & specificity (97.6%) with a PPV & NPV of 94.3% & 98.8% respectively. Jeon TJ et al.19 in their study found

thatthe ROC for the NLR predicting organ failure yielded an AUC of 0.62 (95%CI: 0.51-0.72). They demonstrated an optimal baseline NLR of 5.03 withsensitivity, specificity, PPV & NPV of 64.3%, 53.1%, 8.3% & 95.6% respectivelyfor predicting development of organ failure. This cutoff point of 5.04 was further evaluated by Chi-X2 test, which revealed a Chi-X2 statistic of 103.06. Spearman rank correlation test showed a positive correlation between NLR, Glasgow score, Ranson score & BISAP score. Moreover, NLR had positive correlation with CRP, HCT & BUN, as revealed by Spearman rank correlation test.

Conclusion

The ultimate objective of any scoring system or marker is to predict the patients with severe attack early in the course of disease and initiate prompt management. Prediction of development of organ failure in pancreatitis helps in better outcome of the patient in terms of morbidity and mortality.Various markershave been established to predict the development of organ failure and each one has its own advantages & disadvantages. NLR is one of the better systems because it is simple, easy to assess, available at every healthcare center, and cost effective compared to other markers and hence can be used in peripheral centers for early referral.

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