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**Original Research Article**

# Prediction of severity of acute pancreatitis using neutrophil to lymphocyte ratio

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## ABSTRACT

**Background:** Patients with mild acute pancreatitis (AP) have mortality rates of less than 1% which increases up to 10% to 30% in severe AP (SAP). Early prediction of severity helps in complication prevention. Neutrophil lymphocyte ratio (NLR) could be simple, easy and cheap tool for predicting severity of AP in its early course.
**Methods**: This prospective, observational study included forty-five patients admitted over a period of six months from August 2020 to January 2021 with diagnosis of AP at Bir hospital. NLR was performed at the time of admission.
**Results:** The 22.2% patients had SAP with mean age of 45.6±14.73. It was common in male (60%) and the most common cause was gallstone. Etiology, BMI, neutrophilia, lymphopenia, SIRS scores were found to have statistically significant association to severity of AP. A cut off value of 4.49 was calculated for NLR for predicting severity of pancreatitis with sensitivity of 100%, specificity of 97.1%, PPV of 90.9 % and NPV of 100%. Mean NLR was 7.80±1.69 for mortality group.
**Conclusions:** NLR can be used as a simple, easy and inexpensive prognostic marker of severity of AP.

**Keywords:** AP, Severity, NLR

## INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas that starts with local acinar cell injury, resulting in mild self-limiting disease to severe form characterized by variable involvement of other regional tissues or remote organ systems, resulting in infected pancreatic necrosis and multiple organ failure.[1]

Patients with mild AP (MAP) have mortality rates of less than 1% which increases up to 10% to 30% in severe cases. Early detection of severe pancreatitis is therefore essential for limiting its complications.[2,3]

The total leucocyte count (TLC) is a routine test that is easily available even in resource limited settings. An increased neutrophil count and concomitant decreased lymphocyte count has been associated with severe sepsis, bacteremia and surgical stress.[4]

The NLR could be a simple, cheap and easy tool that would help in stratifying severity, almost similar to International standard scoring system, at the time of admission and shortly thereafter and would help in predicting course of AP early on in the disease process.[4]

The main objective of this study is to predict the severity of AP using NLR at the time of admission and also determine the mean NLR in different severity of AP. This study also aims to show association of age, sex, etiology, BMI, TLC as well as other factors with the severity of the AP.

## METHODS

This was a prospective, observational study conducted in Bir hospital, Kathmandu over a duration of six months, from August 2020 to January 2021 after ethical approval from institutional review board (IRB) of national academy of medical sciences, Bir hospital and written informed consent from all the patient involved in the study. This study included all patients admitted with diagnosis of AP. Patients were diagnosed with AP if more than 2 of the following conditions were satisfied: (1) abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum amylase and/or lipase level at least 3 times greater than the upper limit of the normal value; and (3) characteristic manifestation of AP on contrast enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography. AP was categorized into MAP, moderately SAP, and SAP in accordance with the revised Atlanta classification. Patients of age <18 years, pregnant patients, patients with hematological disorders, malignancies, infective and inflammatory diseases, patients on antibiotics prior to presentation, patients on steroids or chemotherapy for any reason and patient not willing to participate in the study were excluded from the study. The sample size of this study was forty-five and patient fulfilling the inclusion and exclusion criteria were sampled using purposive sampling.

Statistical analysis was performed in SPSSv25 (Statistical package for social sciences). Student's t test or ANOVA was used for continuous data and Fischer's exact or chi-square test was used for categorical data, whichever was appropriate. The area under receiver operating curve (ROC) analysis was used to evaluate NLR for predicting severity of AP and optimal cut-off value of NLR for predicting severe pancreatitis was determined by using the trade-off between sensitivity and specificity. A 95% confidence interval was taken, and p value less than 0.05 was termed as statistically significant.

## RESULTS

Total 45 patients were included in the study among which 22.2% patients presented with SAP with mortality rate of 4.4%. Mean age for SAP was 45.6±14.73. AP was more common in male (60%) with gallstone (71.10%) as the commonest etiology of AP (Table 1). There was statistically significant association between etiology, BMI, increasing neutrophil count, decreasing lymphocyte count, NLR, SIRS and severity of pancreatitis (Table 1). There was no statistically significant association between age, gender, TLC and severity of pancreatitis (Table 1). A ROC was generated for NLR at admission for predicting SAP (Figure 1), which yielded an area under curve (AUC) of 0.99 (Table 2).

Coordinates in ROC curve was analyzed (Table 3) and NLR of 4.49 was taken as a cut off for diagnosis of SAP with true positive rate of 100% and false positive rate of 2.9%. NLR ≥4.49 predicted the occurrence of severe pancreatitis with sensitivity of 100%, specificity of 97.1%, PPV of 90.9 % and NPV of 100% (Table 4). Mortality group had higher mean NLR (7.80±1.69) and it was statistically significant (Table 5).

**Table 1: Factors influencing severity of acute pancreatitis.**

| SAP | | Mild | Moderate | Severe | Percent (%) | P value | Statistical test |
|---|---|---|---|---|---|---|---|
| **Mean age (in years)** | | 46.37±14.64 | 40.60±21.89 | 45.60±14.73 | | 0.74 | ANOVA |
| **Gender** | Male | 37.8% | 6.7% | 15.6% | 60 | 0.75 | Chi-square test |
| | Female | 28.9% | 4.4% | 6.7% | 40 | | |
| | | 66.7% | 11.1% | 22.2% | 100 | | |
| **Etiology** | Gallstone | 55.6% | 0% | 15.6% | 71.1 | 0.001 | Chi-square test |
| | Alcohol | 8.9% | 6.7% | 6.7% | 22.2 | | |
| | Others | 2.2% | 4.4% | 0% | 6.7 | | |
| | | 66.7% | 11.1% | 22.2% | 100 | | |
| **Mean BMI** | | 23.34±2.05 | 22.38±2.36 | 30.58±1.58 | | 0.001 | ANOVA |
| **Mean TLC** | | 9930±4057.87 | 8340±2680.11 | 10290±4704.95 | | 0.67 | ANOVA |
| **Neutrophilia** | | 70.90±7.20 | 71.60±5.07 | 83.60±5.71 | | 0.001 | ANOVA |
| **Lymphocytopenia** | | 24.87±7.07 | 24±3.80 | 12.4±3.4 | | 0.001 | ANOVA |
| **NLR** | | 3.12±0.93 | 3.05±0.63 | 7.34±2.55 | | 0.001 | ANOVA |
| **SIRS** | | 0.57±0.67 | 0.80±0.83 | 2.10±0.73 | | 0.001 | ANOVA |

**Table 2: Area under the curve (AUC) and significance (SAP).**

| Area | Std. error[a] | Asymptotic sig.[b] | Asymptotic 95% confidence interval | |
|---|---|---|---|---|
| | | | Lower bound | Upper bound |
| **0.990** | 0.012 | 0.000 | 0.967 | 1.000 |

The test result variable(s): NLR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. a. Under the nonparametric assumption. b. Null hypothesis: true area=0.5

**Table 3: Coordinate points on the ROC curve for NLR (Severe).**

| Positive if greater than or equal to A* | Sensitivity | 1-Specificity |
|---|---|---|
| **0.0800** | 1.000 | 1.000 |
| **1.2650** | 1.000 | 0.971 |
| **1.5350** | 1.000 | 0.943 |
| **1.8600** | 1.000 | 0.914 |
| **2.1100** | 1.000 | 0.886 |
| **2.1600** | 1.000 | 0.857 |
| **2.2150** | 1.000 | 0.800 |
| **2.4150** | 1.000 | 0.771 |
| **2.6400** | 1.000 | 0.743 |
| **2.7200** | 1.000 | 0.714 |
| **2.7800** | 1.000 | 0.686 |
| **2.8150** | 1.000 | 0.629 |
| **2.9150** | 1.000 | 0.600 |
| **3.0900** | 1.000 | 0.543 |
| **3.1900** | 1.000 | 0.514 |
| **3.2500** | 1.000 | 0.486 |
| **3.3200** | 1.000 | 0.400 |
| **3.3700** | 1.000 | 0.371 |
| **3.4500** | 1.000 | 0.343 |
| **3.6250** | 1.000 | 0.314 |
| **3.8000** | 1.000 | 0.257 |
| **3.8750** | 1.000 | 0.229 |
| **4.0000** | 1.000 | 0.114 |
| **4.2000** | 1.000 | 0.086 |
| **4.3500** | 1.000 | 0.057 |
| **4.4900** | 1.000 | 0.029 |
| **4.7250** | 0.900 | 0.029 |
| **5.0350** | 0.700 | 0.029 |
| **5.9000** | 0.600 | 0.000 |
| **6.9500** | 0.500 | 0.000 |
| **8.0500** | 0.400 | 0.000 |
| **8.9000** | 0.300 | 0.000 |
| **9.8750** | 0.200 | 0.000 |
| **11.1250** | 0.100 | 0.000 |
| **12.5000** | 0.000 | 0.000 |

The test result variable(s): NLR has at least one tie between the positive actual state group and the negative actual state group. *A. The smallest cut off value is the minimum observed test value minus 1, and the largest cut off value is the maximum observed test value plus 1. All the other cut off values are the averages of two consecutive ordered observed test values.

**Table 4: Comparison of sensitivity, specificity, PPV and NPV of NLR in predicting severity of AP.**

| SAP | NLR (>4.49) |
|---|---|
| **Sensitivity** | 100% |
| **Specificity** | 97.1% |
| **PPV** | 90.9% |
| **NPV** | 100% |

**Table 5: Mean NLR in mortality versus no-mortality group.**

| Group | Mean NLR | P (Independent t test) |
|---|---|---|
| **Mortality** | 7.80±1.69 | 0.015 |
| **No-mortality** | 3.87±2.14 | |

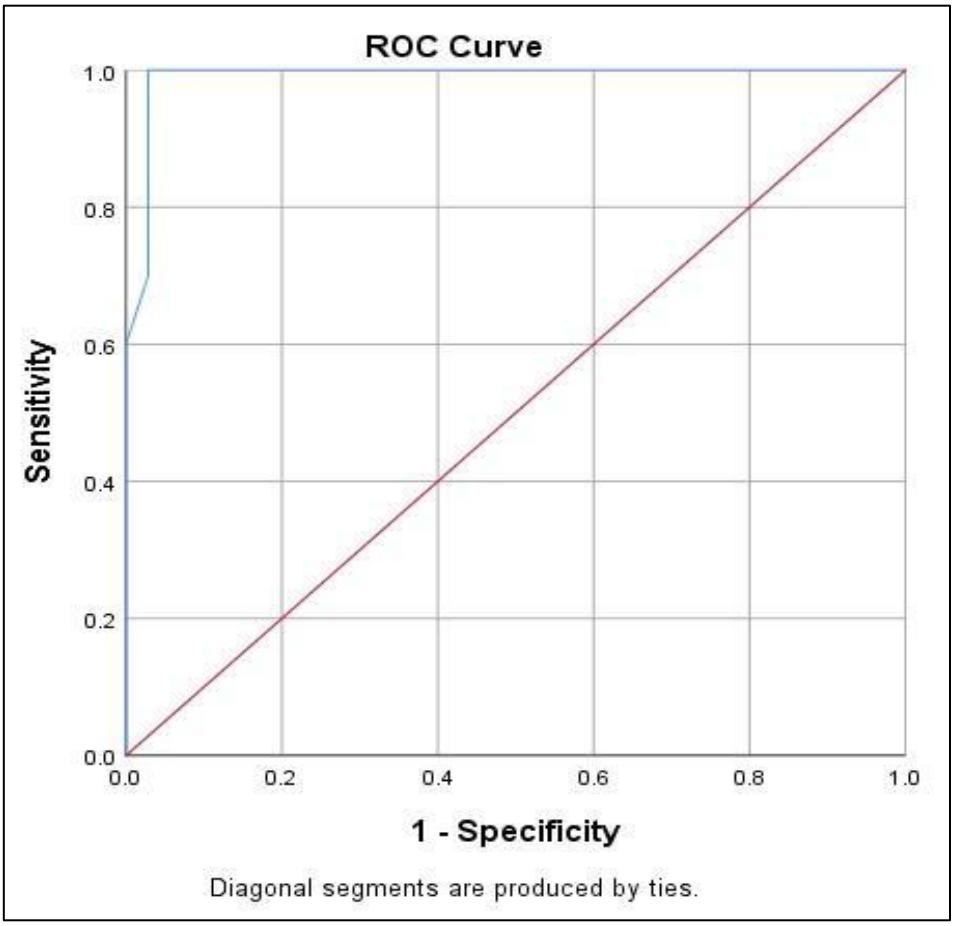


**Figure 1: ROC for NLR at admission.**

## DISCUSSION

AP is a dynamic disease process characterized by inflammation of the pancreas, elevated pancreatic enzymes, and abdominal pain. Its incidence is 4.5-35/100000.[5] The most common cause is gallstone followed by alcohol.[6,7] Other causes include smoking, invasive procedures such as endoscopic retrograde cholangiopancreatography (ERCP), hyperlipidemia, hypercalcemia, biliary system anomalies, abdominal trauma, drugs, bacterial or viral infection and idiopathic causes.[8-11] It is more common in male and age above 55 years increases the risk of developing severe pancreatitis by almost twofold.[12-14]

AP starts with local acinar injury and although majority of AP cases are mild and self-limiting, severity may change rapidly during the course of the disease.[15,16] Severe cases accompanied by complications such as pancreatic necrosis, pancreatic abscess, pancreatic pseudocyst, splenic vein thrombosis and multiple organ failure can occur in approximately 25% of patients. In such cases, high mortality rates of up to 50% have been reported.[12,17] Two peaks of mortality have been recognized in AP i.e. early and late phase. Mortality in early phase is due to SIRS, whereas complication due to sepsis, infected pancreatic necrosis, MODS are the major causes of mortality in late phase.[18,19]

Multiple severity scoring systems have been designed to help clinicians in triaging patients and predicting prognosis. The Ranson score, the acute physiologic assessment and chronic health evaluation II (APACHE II) score, the bedside index for severity in AP (BISAP) score, and the Glasgow-Imrie criteria are currently in wide use. However, these systems are time-consuming, unsuitable for evaluation of patients at the time of admission or shortly thereafter and difficult to apply to patients outside of intensive care settings.[12] Simplified serum markers such as c reactive protein (CRP), procalcitonin, interleukin-6, and interleukin-8 can be used to predict the prognosis or severity of AP, but they are expensive and not readily available.[20] NLR is a cost effective and simple tool for prediction of prognosis which can be calculated and serially monitored at any level of health care without additional economic burden to patients.[13]

White cell count is a marker of infection and inflammation and is part of many AP prognostic scoring systems including Ranson, Imrie, APACHE II, and the simplified acute physiology score (SAPS II). Neutrophils and lymphocytes are important components of white cell

count. Neutrophils are the initial cells that are activated and they propagate inflammation and tissue destruction via activation of a cascade of inflammatory cytokines (IL-6, IL-8, and TNF-α), proteolytic enzymes (myeloperoxidase, elastase, collagenase, and β-glucoronidase), and oxygen free radicals.[10,21] An increase in neutrophil number corresponds and mediates subsequent inflammatory response. Hence, the traditional view is that neutrophilia is the primary cause of an elevated NLR, SIRS, and poor prognosis, while lymphocyte count remains static.[10,21] The lymphocytic immune response occurs later and its main function is to mediate and resolve the preceding nonspecific inflammatory process. In case of uncontrolled inflammation, lymphopenia occurs by lymphocyte redistribution, lymphocyte dysfunction and accelerated apoptosis.[22,23] Persistent lymphopenia is hence considered as much a contributor to increased NLR and poor prognosis as neutrophilia.[4,24] The predictive superiority of NLR is attributed to the alterations of WBC by various physiological and pathological conditions (e.g. hydration status, stress, pregnancy), as well as the inconsistency associated with drawing and handling of blood specimens. While these variables can change the absolute WBC and its individual subtypes, NLR remains more stable.[21,25] In our study, neutrophilia, lymphocytopenia and increasing NLR had statistically significant association with severity of AP.

In an effort to define a suggested NLR cutoff value for predicting SAP, it is believed that sensitivity is of more clinical importance than specificity as conservative and supportive management is the initial standard of care for patients presenting with AP. Hence, a ROC was generated for NLR at admission for predicting SAP, which yielded an AUC of 0.99. Coordinates in ROC curve was analysed and NLR of 4.49 was taken as a cut off for diagnosis of SAP with true positive rate of 100% and false positive rate of 2.9%. NLR≥4.49 predicted the occurrence of severe pancreatitis with sensitivity of 100%, specificity of 97.1%, PPV of 90.9 % and NPV of 100%. Azab et al recommended an NLR of 4.7 as a cut-off for predicting severity in terms of ICU admission and length of hospital stay more than 7 days with sensitivity of 85.2% and 75%, specificity of 47.7% and 48.1%, PPV of 14.6 and 24.5% and NPV of 96.8 and 89.5% respectively.[21] In a study conducted by Jeon et al optimal cut-off value of baseline NLR for predicting SAP was 4.76 with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of 63.6, 56.7, 21.2, 89.5, and 57.7% respectively.[12]

BMI is considered as a risk factor for severity of AP at admission.[26] In a study done by Brown et al BMI of >30 kg/m$^2$ predicted SAP with sensitivity of 71%, specificity of 92%, PPV of 63% and NPV of 94%.[27] Patients with severe pancreatitis were significantly more obese than those with mild disease and the mortality rate of obese patients was significantly higher.[28] In our study, the severity of AP increased with increase in BMI, with mean BMI of 30.58±1.58 in SAP, and it was found to be statistically significant.

Patients with higher systemic inflammatory response syndrome score at admission had an increased risk for SAP.[29] In this study, severity of pancreatitis increased with increase in SIRS score and it was statistically significant.

The relationship between mortality and NLR value in AP has been reported in several studies.[30] In this study, there was a mortality rate of 4.4% and the mean NLR was 7.80±1.69 in mortality group while the mean NLR was 3.87±2.14 in non-mortality group, which was statistically significant. In a retrospective study by Li et al the NLR was reported to be independently related to mortality in AP.[31]

Limitations of the study: This was single-centred study with small sample size conducted over a short period of six months. Hence, the results might not accurately reflect the impact of NLR measurement on predicting SAP and could have overestimated or underestimated the predictive value of NLR. This study was performed in a tertiary care centre which could have resulted in selection bias with disproportional inclusion of patients with severe disease status. Also, serial measurement of NLR was not done after admission and during course of treatment. Hence, we could not evaluate the variations in NLR with time. Continuous NLR monitoring could have provided us with a dynamic reflection of the variable course of AP, with optimal NLRs varying with change in patient status. This study focused on sensitivity of the test but since poor specificity and PPV are the weaknesses of current AP scoring systems, we should aim to develop a tool with acceptable sensitivity but greater specificity. The incorporation of a variable with high specificity would enhance current scoring systems rather than one with high sensitivity but low specificity.

## CONCLUSION

AP is a common cause of pain abdomen in patients presenting in emergency department. Early detection of possible severe course of the disease is essential for limiting adverse outcomes. NLR can be used as a prognostic marker of severity of AP. Though this will not replace the currently accepted scoring systems; because of its convenience in assessing repeatedly without any further cost and discomfort, it can be used routinely as a simple, cheap and easy tool in every case of AP to assess its severity and predict complications.

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