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Study on neutrophil-lymphocyte ratio (NLR) as a prognostic marker in acute pancreatitis

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Abstract
Acute pancreatitis is an inflammatory disease of the pancreas. The etiology and pathogenesis of acute pancreatitis have been intensively investigated for centuries worldwide. It can be initiated by several factors, including gallstones, alcohol, trauma, infections and hereditary factors. About 75% of pancreatitis is caused by gallstones or alcohol. Acute pancreatitis (AP) is usually a self-limiting process; however, 25 % of patients present with or subsequently develop a severe form of the disease that is associated with a mortality of up to 50 %. The neutrophil–lymphocyte ratio (NLR) is a measure of the divergence of these two WCC (white cell count) components (lymphocytes and neutrophils), which may be more accurate than the total WCC or individual neutrophil/lymphocyte counts in predicting poor outcome in patients with acute pancreatitis. The reported annual incidence is 35-40 per lakh population worldwide. The incidence of acute pancreatitis in India and in the West has increased by 28% over the past decade. The WBC count is correlated with poor prognosis as a compositional element of Ranson's criteria, Glasgow score, Acute Physiology and Chronic Health Evaluation-II (APACHE-II), and Bedside Index of Severity in Acute Pancreatitis (BISAP), which are the prognostic scoring systems of acute pancreatitis. The objective of the study is to investigate the validity of NLR in predicting outcome, and to determine an optimal cut-off value that would allow division of patients into mild (MAP) and severe acute pancreatitis (SAP) groups based on NLRs within the first 48h of hospitalization.

Keywords: SAP- severe acute pancreatitis, MAP- mild acute pancreatitis, NLR – neutrophil lymphocyte ratio, WBC- white blood cell

Introduction

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. Neutrophils and lymphocytes reflect the immune response better than the total WBC count. In particular, studies have demonstrated the correlation between peripheral lymphocytopenia and the severity of acute pancreatitis. In addition, one study established the superiority of the NLR over the total WBC counts in predicting the severity of acute pancreatitis. Patients are diagnosed with acute pancreatitis if more than 2 of the following conditions were satisfied: (1) abdominal pain consistent with acute pancreatitis (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 acute pancreatitis on contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography.1,15 Acute pancreatitis was categorized into mild acute pancreatitis (MAP), moderately severe acute pancreatitis, and severe acute pancreatitis (SAP) in accordance with the revised Atlanta classification.16,43 for the purpose of analysis, we grouped the moderately severe pancreatitis cases with the SAP cases. Consequently, SAP was considered to be the presence of transient (less than 48 h) or persistent (over 48 h) organ failure and/or local or systemic complications.16 Local complications included an acute peripancreatic fluid collection, a pancreatic pseudocyst, an acute necrotic collection, and a walled-off necrosis. Through this study, we evaluated the usefulness of the NLR as an early predictive marker for development of SAP and organ failure in acute pancreatitis. Although the total WBC count is a compositional element of Ranson's criteria, Glasgow score, APACHE-II, and BISAP (scoring systems for evaluation of the prognosis of acute pancreatitis), the total WBC count itself, unlike CRP or blood urea nitrogen, is not assessed as an independent marker for the prediction of the prognosis of acute pancreatitis. However, the NLR was identified by several existing studies as an index that reflects the prognosis of various benign inflammatory or malignant diseases. This study demonstrated that the NLR was elevated in patients presenting with acute pancreatitis and that NLR can allow providers to classify patients according to disease severity and the presence of organ failure. Therefore, there is a need for a simple indicator that can easily predict the patient's prognosis within 24 h of the manifestation of the disease. Prognostic scoring systems such as the Ranson's criteria, APACHE-II, and sequential organ failure assessment (SOFA) 11 score have limitations in actual application since they are complex and contain data not routinely ordered or collected during hospitalization at the current time.4 However, 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. 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.8, 12 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 6.3,5,6,7

Materials & Methods

The present study will be carried out in all the inpatients diagnosed to have acute pancreatitis in the Department of General Medicine and Department of General Surgery, at Dr. B. R. Ambedkar Medical College, Bengaluru, Karnataka.

Sample Size: 50 cases

Collection of Data

Sequential patients admitted with a confirmed diagnosis of AP. Acute pancreatitis was defined as clinical findings consistent with a diagnosis of pancreatitis together with an elevation in serum amylase/lipase of three times the upper limit of normal. The white cell differential count was analyzed and the NLR determined by calculating the ratio between the absolute neutrophil and lymphocyte counts at 0, 24h. The present study was carried out in all the inpatients diagnosed to have acute pancreatitis in the Department of General Medicine and Department of General Surgery, at Dr. B. R. Ambedkar Medical College, Bengaluru, Karnataka. The white cell differential count was analyzed and the NLR determined by calculating the ratio between the absolute neutrophil and lymphocyte counts at 0, 24h AND 48h respectively. The sensitivity and specificity of the NLR for the identification of patients with severe AP were calculated on admission, and 24h and 48h.

Study Design: Prospective and Observational Study

Duration: November 2016 - June 2018

Inclusion Criteria

1. Patients admitted with acute pancreatitis due to varied etiology (alcohol, gallstones, idiopathic, hypercalcemia, hereditary, malnutrution, autoimmune, infections etc) i.e. medical and surgical causes.
2. Patients fulfilling APACHE 2 criteria on admission.

Exclusion Criteria

1. Patients not fulfilling APACHE 2 criteria on admission.
2. Chronic pancreatitis.

Statistical Tools

Data will be summarized by mean, standard deviation and percentage, sensitivity and specificity and other statistical tests, like Chi Square and ANOVA test was employed to plot the ROC curve and Mann Whitney test was used for the comparison of mean NLR ratio.

Estimation of Sample Size

Sample Size for Percents

1. Best estimate of the population size.
2. Best estimate of the rate in the population (%): Best estimate of what the actual percent of the survey characteristic is. This is based on the null hypothesis. If it is not known, this value is arbitrarily taken as 50%
3. Maximum acceptable difference (%): This is the maximum percent difference that is acceptable between the true population rate and the sample rate. Typically taken as 5%
4. Desired confidence level (%): Level at which the true population rate falls within the acceptable difference; the same as the desired confidence in the findings of the study

Hence

1. Best estimate of the population size: 6400 (as per incidence of pancreatitis in Southern India as per recent studies)
2. Best estimate of the rate in the population (%): 50%
3. Maximum acceptable difference (%): 5%
4. Desired confidence level (%): 95%
5. Confidence interval for confidence level of 95%: 13.81

$$\text{Sample Size} = \frac{Z^2 * (p) * (1-p)}{c^2}$$

Where:
Z = Z value (e.g. 1.96 for 95% confidence level)
p = percentage picking a choice, expressed as decimal (.5 used for sample size needed)
c = confidence interval, expressed as decimal (e.g. 04 = ±4)

Correction for finite population size (pop):

$$\text{New sample size (ss)} = \frac{ss}{1+\frac{(ss-1)}{pop}}$$

Required sample size is hence 50.

Among cases of both mild and severe acute pancreatitis, excessive alcohol consumption was the commonest cause (14 cases; 45.2% and 12 cases; 63.2% respectively) followed by the presence of obstructive gallstones (8 cases; 25.8% and 4 cases; 21.1% respectively. There was no significant statistical difference between any cause of acute pancreatitis among the study population ($\chi 2$=11.255; P=0.08), indicating that there was a relatively high incidence of less common causes of acute pancreatitis among study population. The mean alcohol intake among cases with severe acute pancreatitis due to excessive alcohol consumption was 31.00 ± 9.79 units/week; nearly double that of cases with mild acute pancreatitis (15.88 ± 6.72 units/week). The Mann-Whitney U Test revealed a Z value of -3.846 and a two-tailed P value of <0.001; which implies that a randomly selected case among cases with severe acute pancreatitis due to excessive alcohol consumption was very likely to have a higher weekly alcohol consumption than a randomly selected case among those having mild acute pancreatitis. The mean alcohol intake among cases with severe acute pancreatitis due to excessive alcohol consumption was 31.00 ± 9.79 units/week; nearly double that of cases with mild acute pancreatitis (15.88 ± 6.72 units/week). The Mann-Whitney U Test revealed a Z value of -3.846 and a two-tailed P value of <0.001; which implies that a randomly selected case among cases with severe acute pancreatitis due to excessive alcohol consumption was very likely to have a higher weekly alcohol consumption than a randomly selected case among those having mild acute pancreatitis.

Conclusion

In our study, 80% were males and 20% were females, similar to study conducted by Dr. K Vengadakrishnan *et al* at Sri Ramachandra Medical College and Research Institute, where there were 83 males and 27 females in their study population of 110 subjects, and a similar prospective analytical study conducted at Mysore medical college by Prasad H L *et al* where there were 22 males and 18 females in their study of 40 patients of acute pancreatitis. In our study of 50 patients, the NLR of 3.45 at 48hrs was arrived at, which was proven to be statistically significant (p value of <0.001) and a ratio beyond this value (3.45 at 48hrs) indicated poor outcomes. The NLR at 48hrs had a overall sensitivity and specificity of 68.4% and 71% respectively. The NLR cut off at baseline and 24hrs was found to be 7.65 and 5.62 respectively. Acute pancreatitis is an inflammatory disease of the pancreas. The etiology and pathogenesis of acute pancreatitis have been intensively investigated for centuries worldwide. It can be initiated by several factors, including gallstones, alcohol, trauma, infections and hereditary factors. About 75% of pancreatitis is caused by gallstones or alcohol. 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. 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. To date, only one paper has investigated the role of NLR in AP. Azab *et al*. reported the NLR to be superior to the total WCC or individual neutrophil and lymphocyte counts in predicting ICU admission and death in patients with AP. Therefore, there is a need for a simple indicator that can easily predict the patient's prognosis within hours of manifestation of the disease. The NLR is a simple, inexpensive, and easy to carry out prognostic tool to predict adverse outcomes in patients with acute pancreatitis.

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