Evaluation of Neutrophil-Lymphocyte Ratio in Early Diagnosis of Severe Acute Pancreatitis using the Computed Tomography Severity Index as Reference Standard

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ABSTRACT

Objective: To evaluate the Neutrophil-Lymphocyte ratio (NLR) in the early diagnosis of severe acute pancreatitis (SAP) and to assess the disease severity as determined by Computed Tomography Severity Index (CTSI).

Study Design: Cross-sectional study

Place and Duration of Study: Surgery department of Combined Military Hospital, Rawalpindi, Pakistan, from Jan to Jul 2021.

Methodology: A total of 107 patients diagnosed with acute pancreatitis, aged 18-70 years of either gender, were included. Patients with diseases such as chronic pancreatitis, diabetes, cardiovascular diseases, trauma, ERCP (iatrogenic), hypertriglyceridemia, alcohol, and end-stage renal and hepatic diseases were excluded. Laboratory investigations included CBC, LFT, serum amylase, serum lipase, and abdominal ultrasound. Amylase and lipase levels greater than three times normal, and ultrasonographic evidence of cholelithiasis, were reviewed by a surgical specialist to confirm the diagnosis of acute biliary pancreatitis.

Results: Out of 107 participants, 41(38.31%) came out to be true positives and 7(6.54%) false positive respectively in the positive NLR group. Out of 59(55.14%) who were NLR below cut-off, 55(55.40%) were true negatives and 4(3.73%) false negatives. The positive predictive value was 85.42% whereas the negative predictive value was 93.22%. Sensitivity and specificity were 91.11% and 88.71% respectively.

Conclusion: It is concluded that NLR remains a highly effective, minimally invasive, and reproducible method in predicting the outcome of acute pancreatitis, especially in the first few hours of presentation.

Keywords: Acute pancreatitis, neutrophil-lymphocyte ratio, sensitivity

INTRODUCTION

Acute pancreatitis is an acute inflammatory process affecting the pancreas with variable involvement of local tissues and remote organs.[1] The disease process and pathology lie in the fact that highly activated substances, especially protein-breaking enzymes, are released into the pancreas, therefore, causing autolysis and destruction .[2] The resultant sequelae can range from simple peripancreatic fluid collections (PFC) to pancreatic necrosis and abscesses.[3] The correct and timely recognition of this disease is of utmost importance. Not only do the surgeons find its diagnosis challenging owing to its presentation mimicking other diseases like Myocardial Infarction (MI) and visceral perforation, but also the intensivist struggles when managing the complications and end-organ damage.[2] The end organ damage can greatly reduce life expectancy, increase hospital stay, and bear a cost

burden on hospitals. The recognized clinical course has 2 phases. This starts from weeks 1 and 2, where intense efforts from the body to maintain hemostasis result in systemic inflammatory response syndrome (SIRS) and end-organ dysfunction.[3]

Clinicians have experimented with various modules to identify high-risk patients for complicated pancreatitis and predict end-organ damage. No single module is perfect, and the combination of different methods confuses the surgeon in properly managing the disease.[4]

A variety of extrapolative scoring systems are used to evaluate severe acute pancreatitis (SAP) like Ranson, the Acute Physiology and Chronic Health Evaluation (APACHE-II) system, and the Bedside Index for Severity in Acute Pancreatitis (BISAP) score.[5] Although the newer assessment tool, like BISAP, is easier to use and has a great predictive ability in terms of recognizing mortality and end-organ damage, it has the disadvantage that it can be calculated at the end of twenty-four hours and not in the early phase of the disease.[6] Therefore, there was a need to introduce a

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newer tool that can be used in the first few hours of presentation and thus help surgeons timely incorporate at-risk patients into intensive care programs.

Neutrophil-lymphocyte ratio (NLR) can predict poor outcomes in several conditions. These include benign and malignant diseases of the gastrointestinal and cardiopulmonary systems.[7] The optimal cut-off value of NLR remains debatable among authors. Cho et al stated 7.8 to be the optimal cut-off NLR value with sensitivity 88.9% and specificity 41.1%.[5] Another study found 4.76 as an optimal cutoff value with sensitivity 68.6% and specificity 50.5%.[2] Considering that there is no common consensus among authors on a cutoff value of NLR,[7,8] will be taken as the optimal cutoff value as it shows good sensitivity and specificity of 88.9% and 41.1% respectively.[8]

In Pakistan, most hospitals routinely order neutrophil and lymphocyte levels as part of a complete blood count (CBC). Therefore, we aim to establish the diagnostic accuracy of NLR and hence establish the fact that it is an effective and pragmatic index and can be used in the early stages of diagnosis.

METHODOLOGY

This cross-sectional study was carried out at Combined Military Hospital, Rawalpindi, Pakistan, from Jan to Jul 2021. Using non-probability consecutive sampling, a total of 107 patients met the inclusion criteria. After approval from the hospital Ethics and Research Committee (Certificate No. 450), patients were selected from the emergency department of Combined Military Hospital (CMH).

Inclusion Criteria: Patients diagnosed with Acute pancreatitis who have gallstones visible on ultrasound of the abdomen, aged 18 to 70 years, and presenting to the emergency department within the first twenty-four hours of symptom onset.

Exclusion Criteria: Patients who presented more than twenty-four hours after the onset of symptoms, as well as those with conditions such as chronic pancreatitis, diabetes, cardiovascular diseases, trauma, ERCP (iatrogenic), hypertriglyceridemia, alcohol use, and end-stage renal and hepatic diseases, were excluded from the study.

Sample estimation was done by the WHO Calculator of sensitivity and specificity of NLR, which were taken as 88.9% and 41.1% respectively. Confidence level was set at 95% and precision was taken as 0.10 for both sensitivity and specificity. The

sample size was calculated as 110, and the study included 107 participants as per the inclusion criteria.

After a complete history and examination, laboratory investigations were ordered on admission, i.e., on day [1]. These included CBC, liver function tests (LFT), serum amylase, serum lipase levels, and an ultrasound of the abdomen to confirm cholelithiasis. All labs and radiologic studies were sent to the Armed Forces Institute of Pathology and Radiology, respectively. Patients with levels more than three times the normal (normal range 30-110 U/L) and ultrasonographic confirmation of gallstones were reviewed by a surgical specialist to confirm the diagnosis of acute biliary pancreatitis. Patients were informed about their diagnosis and their participation in this research project, and informed consent was obtained. All patients received treatment for acute pancreatitis. Seventy-two hours after admission, all patients underwent a CT scan to determine the severity index (CTSI) and diagnose severe acute pancreatitis (SAP). The CT scan was performed by a consultant radiologist at the Armed Forces Institute of Radiology, where the severity was reported.

The data, recorded on proforma, was analyzed through descriptive statistics with qualitative and quantitative variables. Qualitative variables like gender and CTSI were measured by frequency or percentage. Quantitative variables like age, Serum amylase, lipase, and NLR were presented as mean ± standard deviation (SD). Sensitivity was calculated by (TP/TP+FN)/100, Specificity by (TN/TN+FP)/100, Positive predictive value by (TP/TP+FP)/100, and Negative predictive value by (TN/TN+FN)/100. p-value of ≤ 0.05 was taken as significant. NLR was estimated by calculating the ratio of absolute neutrophil count and lymphocyte count, taking 7.8 as an optimal cutoff value.

RESULTS

In our study, a total of 107 patients were included in the study protocol as per the inclusion criteria. The mean age of the patients was 44.55 ± 10.19 years. Among them, 58 patients (54.21%) were categorized within the 18-45 years age group, while 49 patients (45.79%) belonged to the 46-70 years age group. Gender distribution revealed 64 (59.81%) males and 43(40.19%) females. The baseline characteristics along with different means are shown in Table-I. NLR and CTSI diagnosed SAP in 48(44.86 %) and 45(42.06%) patients, respectively. Table-II represents sensitivity and specificity between both groups. Overall,

sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the neutrophil-lymphocyte ratio, in predicting the severity of acute pancreatitis in the early diagnostic phase, taking CTSI as the gold standard, were 91.11%, 88.71%, 85.42%, 93.22% and 89.71% respectively.

Table-I: Demographic Variables (n=107)

Demographic Data	Group(n=107)
Mean Age (Years)	44.55±10.19
Gender (Male/Female)	
Male	64(59.81%)
Female	43(40.19%)
Mean Serum Lipase (U/L)	136.33±17.89
Mean Serum Amylase (U/L)	114.00±12.82
Mean NLR	7.22±3.36

NLR – Neutrophil-Lymphocyte Ratio

Table-2: Sensitivity and Specificity Between NLR and CTSI Groups (n=107)

	NLR Positive	NLR Negative
CTSI Positive	41(38.31%) True Positive	4(3.73%) False Negative
CTSI Negative	7(6.54%) False Positive	55 (51.40%) True Negative

*Sensitivity= TP/(TP+FN)=41/(41+4)*100=91.1%*
*Specificity= TN/(TN+FP)=55/(55+7)*100=88.7%*
*Positive Predictive Value= TP/(TP+FP)*100=41/(41+7)= 85.4%*
*Negative Predictive Value= TN/(TN+FN)*100=55/(55+4)= 93.2%*
*Diagnostic Accuracy=(TP+TN)/All patients*100 = (41+55)/58=89.7%*

NLR – Neutrophil-Lymphocyte Ratio
CTSI - Computed Tomography Severity Index

DISCUSSION

This research was conducted to determine the diagnostic accuracy of the NLR for severe AP at initial presentation in the emergency room, taking CTSI as the gold standard. Neutrophil-lymphocyte ratio supported the diagnosis of severe acute pancreatitis in 48(44.86%) patients. CTSI findings confirmed severe acute pancreatitis in 45(42.06%) cases. In NLR-positive patients, 41(38.31%) were True Positive and 07(6.54%) were False Positive. Among 59(55.14%) NLR-negative patients, 04(3.73%) were False Negative, whereas 55(51.40%) were True Negative. Overall sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the neutrophil-lymphocyte ratio, in predicting the severity of acute pancreatitis in the early diagnostic phase, taking CTSI as the gold standard, were 91.11%, 88.71%, 85.42%, 93.22%, and 89.71% respectively.

Complete blood count, particularly leukocyte count, is a key initial investigation in surgical trauma centers. White blood cell and differential counts are used to evaluate scoring systems for diagnosing acute pancreatitis. An increase in leukocytosis may indicate disease severity. The distinction between mild and severe acute pancreatitis lies in the widespread cytokine response in the latter, which impacts multiple organs, including the respiratory and renal systems.[9]

Considering this fact, Jager et al. have included leukocyte count in the diagnosis of sepsis. The rise and fall patterns of the differential count are predictable. An increase is observed in the early phase of inflammation, while a decrease occurs in the late phase. Nonetheless, fluctuations indicate a worse prognosis.[10] The reason for these changes is due to the overactivation of the body's immune system caused by bacteria entering the bloodstream, leading to overproduction and eventual depletion of leukocytes as explained by Le Tulzo et al.[11] This concept was also used by Zahorec et al. and Pezilli et al., determining that NLR is used to evaluate the severity of AP in the early phase of the disease.[12,13] There is no doubt that the pattern of rising and falling differential cell counts, characteristic of severe illness and incorporated into the NLR, makes it more reliable and accurate compared to the total count.[14]

The utilization of the ratio of neutrophils to lymphocytes, particularly in pancreatitis, was first reported by a Azab et al. It was observed that NLR was far more accurate and predictive of poor outcomes compared to the total count of patients admitted to the intensive care units. It was shown that a ratio greater than 4.7 was associated with high morbidity and longer hospital stay.[15]

Suppiah et al and Binnetoğlu et al., NLR in the early phase i.e., the first forty-eight hours. They showed that it was even more accurate when used in the early period and can predict the group of patients likely to develop the severe form of the disease. But the study was confined to a limited number of patients (n=146). The small sample size and difficulty in ascertaining the onset of pain in trauma centers were the major limitations. However, NLR remains a poor predictor of mortality, especially in AP.[16,17]

Regarding end organ involvement, Gülen et al., found the ratio to be significantly higher (median, 7.09 vs 4.85; ROC AUC 0.984; 95% CI) in patients receiving treatment for multi-organ dysfunction. After a ratio of 5.4, NLR showed a sensitivity of 97.1% and a specificity of 97.6%, with a PPV of 94.3% and an NPV of 98.8%.[18]

Another research by Kara *et al.,* found the NLR ratio to be higher in SAP; it is not different in pancreatitis due to gallstones and other causes.[19] Huang *et al.,* established that utilization of NLR is far more statistically significant than total leukocyte count, where severe pancreatitis is concerned.[20] When compared with Abayli *et al.,* the ratio is far easier, hands-on, useful, and pragmatic in predicting the end-organ damage caused by inflammation of the pancreas.[21] Among C-Reactive protein and red cell diffusion, NLR was far superior in terms of predicting prognosis and endpoint mortality in acute biliary pancreatitis, as studied by Li *et al.* A rise in the ratio also indicates a five times chance of intensive care admittance.[22] An increased NLR is strongly associated with local and systemic complications of pancreatitis, like ARDS and DIC. This concept was given by O'Connell *et al.*[23]

No research has yet compared the Neutrophil-to-Lymphocyte Ratio (NLR) with the revised edition of the Atlanta classification. A higher NLR has prompted researchers to develop new cell therapies aimed at mitigating the body's response to infection and inflammation. This helps reduce cytokine release and the potential for organ damage. Surgeons are now able to identify high-risk groups who are more likely to develop severe forms of the disease. They have established protocols to ensure timely admission of these patients under the care of an intensivist, allowing for early treatment and necessary arrangements in case of any organ damage.

RECOMMENDATIONS

The study recommends that the neutrophil-lymphocyte ratio should be used routinely in predicting the severity of acute pancreatitis in the early diagnostic phase which will result in proper pre-operative planning for these patients to reduce morbidity and mortality.

CONCLUSION

The neutrophil-lymphocyte ratio is a sensitive and precise non-invasive method in predicting the severity of acute pancreatitis in the early diagnostic phase and has not only dramatically improved our ability to accurately detect the severity of acute pancreatitis but also improved patient care by pre-operatively planning the proper management of patients. So, it is recommended that the neutrophil-lymphocyte ratio should be used routinely in predicting the severity of acute pancreatitis in the early diagnostic phase which will result in proper pre-operative planning for these patients to reduce morbidity and mortality.

LIMITATION OF STUDY

The limitations are that the study is single-center only. A multi-center study would result in a wider demographic area with more conclusive results. Further studies may need to be done for these groups of patients.

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