

# **Accuracy of Neutrophil to Lymphocyte Ratio (NLR) as a Predictor of Severe Acute Pancreatitis Keeping Balthazar CT Scan Severity Index Score as Gold Standard**

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## ABSTRACT

**Background:** Acute pancreatitis (AP) is usually a self-limiting process. Scoring systems aim to stratify the severity of the AP, and this in turn guides management with the aim of improving outcomes. Several scoring systems are in use to predict the severity of pancreatitis but none is fool proof. Some are very tedious to perform while others require ICU setting to be monitored. Therefore this study is designed to assess whether a non-expensive and less time consuming tool like NLR ratio can be used to predict severity in patients presenting with acute pancreatitis.

**Objective:** To determine the accuracy of neutrophil to lymphocyte ratio (NLR)  $\geq 4.7$  as a predictor of acute severe pancreatitis keeping Balthazar CT severity index score (7-10) as gold standard for acute severe pancreatitis.

**Setting:** Surgical Unit-5, Civil Hospital, Karachi.

**Duration:** Six months from 30 jan 2019 to 30 july 2019

**Study Design:** Cross sectional study

**Subject and Methods:** A total of 197 patients with acute pancreatitis with an elevated serum amylase or lipase within 24-72 hours within 3 days of start of symptoms were selected in this study. On admission CBC was advised and neutrophil to lymphocyte ratio was calculated. Patients with NLR ratio greater than 4.7 were undergo CT scan abdomen with oral and IV contrast after 1 week to calculate the CT severity index score to assess severity of AP as gold standard. A proforma was used to record.

**Results:** - The average age was  $37.96 \pm 10.98$  years. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of neutrophil to lymphocyte ratio (NLR)  $\geq 4.7$  in prediction of acute severe pancreatitis was 86.1%, 76.8%, 68.1%, 90.6% and 80.02%.

**Conclusion:** Neutrophil to lymphocyte ratio (NLR) can be used as a predictor of severity of acute pancreatitis, right at the time of initial diagnosis.

**Key words:** Acute pancreatitis, Neutrophil, Lymphocyte, NRL ratio.

## INTRODUCTION:

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%.[1] Scoring systems aim to stratify the severity of the AP, and this in turn guides management with the aim of improving outcomes. The scoring system currently regarded as the gold standard for assessment of AP, namely the Acute Physiology and Chronic Health Evaluation (APACHE II), is labor intensive and is not widely adopted for patients with acute pancreatitis outside of the intensive care setting.[2,3] Other scoring systems such as the Sequential Organ Failure Assessment (SOFA) [4,5] have been developed but are still suitable only in the intensive care setting and not for routine use. As such, they are not suitable for stratifying patients at the time of admission or shortly thereafter.[6] Simplified tests using serum markers such as pro-calcitonin, interleukin-6, and interleukin-8 have been said to be able to predict the severity of AP, but these are expensive, non-validated in the clinical arena, and not readily available.[3,7-9] The white cell count (WCC) is a routine serum hematological test that is already incorporated in many of the current AP 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.10 Poor outcome in severe AP is said to be due to an uncontrolled systemic inflammatory response

syndrome (SIRS), with progression to a multi-organ dysfunction syndrome (MODS). Neutrophils propagate SIRS and the inflammatory cascade in AP whereas lymphocyte depletion occurs in severe sepsis, leading to a severe form of AP and subsequent poor outcome.[11-14] An increased neutrophil count with a concomitant decreased lymphocyte count has also previously been associated with severe acute pancreatitis.[11,13] 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 severity and poor outcome in AP.[16-19] In one study,  $NLR \geq 4.7$  predicted severity of acute pancreatitis in terms of ICU admission and LOS >7 days with a sensitivity of 85.2 and 75.0%, specificity of 47.7 and 48.1%, positive predictive value of 14.6 and 24.5%, and negative predictive value of 96.8 and 89.5%, respectively. [20] Also, patients having  $NLR \geq 7.6$  had statistically significant longer average LOS (6.2 vs. 4.2 days,  $p < 0.002$ ) compared  $NLR < 3.6$ . [20]

The rationale of the study is that as it is evident, acute pancreatitis is a multifactorial disease with a varied outcome which might proceed to severe pancreatitis which has varying mortality with morbidity. Lots of scoring systems are in use to predict whether a case will proceed to being severe pancreatitis or not but none is fool proof. Some are very tedious to perform while others require ICU setting to be monitored. Therefore this study is designed to assess whether a non-expensive and less time consuming tool like NLR ratio can be used to predict severity in patients presenting with acute pancreatitis.

## **MATERIAL & METHODS**

Setting: Surgical Unit-5, Civil Hospital, Karachi.

Duration: Six months from 30<sup>th</sup> January 2019 to 30<sup>th</sup> July 2019

Sample size: The sample size is calculated using calculator for sensitivity and specificity, university SainMalyasia using confidence interval of 95%, Sensitivity 85.2% [20], specificity 47.7% [20], desired precision 10% and prevalence of 25% [1]. The sample size was 197

Sampling Technique: Non probability consecutive

Study Design: Cross sectional study

## **DATA COLLECTION PROCEDURE:**

After taking approval from ERC & CPSP data was collected. First 197 patients with acute pancreatitis meeting the inclusion criteria, who will present to ER of Dr Ruth K.M Pfau Civil Hospital Karachi, was enrolled in the study. Informed consent was taken from the patients for inclusion in the study after explaining the pros and cons. Patients were evaluated and admitted under a general surgery unit. On admission CBC was advised and neutrophil to lymphocyte ratio was calculated. Patients with NLR ratio greater than 4.7 were undergo CT scan abdomen with oral and IV contrast after 1 week to calculate the CT severity index score to assess severity of AP as gold standard. A proforma was used to record patients demographic data like age, gender and hospital registration number. It included the type of acute pancreatitis i.e. gallstone or non-stone, Balthazar CT scan severity score, duration of symptoms, values of NLR and whether acute severe pancreatitis diagnosed on NLR value (i.e. value of NLR above the reference range of 4.7% was taken as positive while a value within the normal range was taken as negative for acute severe pancreatitis) and acute severe or non-severe pancreatitis on CTSI

score. All data was filled by an independent observer, who was ward’s computer operator, not directly involved in the research process.

**DATA ANALYSIS PROCEDURE:**

Data was analyzed by using SPSS version 22 on computer. Mean and standard deviation was computed for numerical variables like age, duration of symptoms in hours and NLR value whereas Frequency and percentages was employed to assess the categorical variable like gender, gallstone or non-gallstone pancreatitis, CTSI score (acute severe or non-severe pancreatitis) and NLR value for acute severe pancreatitis (present or absent). 2x2 table was used to calculate sensitivity, specificity, positive and negative predictive values and diagnostic accuracy taking CTSI score as gold standard. Stratification was done to control confounding variables like age, gender, duration of symptoms, gallstone or non-gallstone pancreatitis and post stratification. 2x2 table was constructed for computing sensitivity, specificity, positive and negative predictive values and diagnostic accuracy was calculated for NLR using CTSI as gold standard.

**RESULTS**

A total of 197 patients with acute pancreatitis with an elevated serum amylase or lipase within 24-72 hours within 3 days of start of symptoms were selected in this study. Most of the patients were between 21 to 50 years of age. The average age was 37.96±10.98 years. There were 108(54.82%) male and 89(45.18%) female patients. Regarding type of pancreatitis, gallstone was observed in 66.5%. Prevalence was acute severe pancreatitis was 36.5% (72/197) confirmed by balthazar CT severity index score (7-10) which was taken as gold standard for acute severe pancreatitis. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of neutrophil to lymphocyte ratio (NLR) ≥ 4.7 in prediction of acute severe pancreatitis was 86.1%, 76.8%, 68.1%, 90.6% and 80.02%. Stratification analysis was performed and results revealed the accuracy of NRL≥4.7 in prediction of acute severe pancreatitis to be 75% to 80% in all stratified confounding variables as age, gender, type of pancreatitis and duration of symptoms.

**TABLE 1:**

DIAGNOSTIC ACCURACY OF NLR ≥ 4.7 AS A PREDICTOR OF ACUTE SEVERE PANCREATITIS FOR Balthazar CT scan severity index (CTSI score)								
Acute severe pancreatitis	≤40 years of age	41 to 60 years of age	Male	Female	Gallstone	Non-gallstone	duration of symptoms 1-2days	Duration of symptoms >2days
	CTSI score							

	7- 1 0	< 7	7- 10	< 7	7- 1 0	< 7	7- 1 0	< 7	7- 10	<7	7- 10	<7	7- 10	<7	7- 10	<7
+ve (NLR $\geq$ 4.7)	3 1	20	3 1	9 1	3 1	1 6	3 1	1 3	47	20	15	9	53	25	9	4
-ve (NLR< 4.7)	4	57	6 9	3 9	5 6	5 6	5 0	4	7	57	3	39	7	64	3	32
Total	112		85		108		89		131		66		149		48	

**TABLE 2**

Factors	DIAGNOSTIC ACCURACY OF NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) $\geq$ 4.7 AS A PREDICTOR OF ACUTE SEVERE PANCREATITIS KEEPING BALTHAZAR CT SEVERITY INDEX SCORE (7-10) AS GOLD STANDARD FOR (%)							
	$\leq$ 40 year s of age	41 to 60 year s of age	Mal e	Femal e	Gallston e	Non- gallston e	duration of symptom s 1-2days	Duration of symptom s >2days
SENSITIVITY	88.6	83.8	86.1	86.1	87.0	83.3	88.3	75
SPECIFICITY	74.0	81.3	77.8	75.5	74.0	81.3	71.9	88.9
PPV	60.8	77.5	66.0	70.5	70.1	62.5	67.9	69.2
NPV	93.4	86.7	91.8	88.9	89.1	92.9	90.1	91.4
ACCURACY	78.5	82.4	80.6	79.8	80.1	81.8	78.5	85.4

**DISCUSSION:**

The burden of acute Pancreatitis (AP) is not lower and epidemiological studies observed its incidence is around 5 – 80 per person per 100,000 in a population. The prevalence of AP is quite variable throughout the world and even huge difference can be seen in different areas of a given country. Acute pancreatitis is an acute inflammatory disorder of the pancreas that involves the pancreas and peri-pancreatic tissues but can sometimes affect other organ system too. The rate of complication among these patients varies between 10% and 20% and if not treated immediately the mortality can rise up to 25% but most of the patients resolved spontaneously. [15] Due to varied presentations of acute pancreatitis, multiple severity scoring systems have been designed, to help clinicians in triaging acute pancreatitis patients and predicting their prognosis. Neutrophils, lymphocytes, endothelial cells and macrophages in the pancreatic acini are the main effector cells of AP1 . Simple tests using serum markers, such as white cell count (WCC), hematocrit (HCT), red cell distribution width, high sensitivity C-reactive protein, procalcitonin, interleukin-6 and interleukin-8, have been shown to predict the severity of AP. In the past, only 19% of patients with AP were accurately graded, and only 67% of patients diagnosed with SAP received timely treatment in the ICU. With the development of modern diagnostic technology, and particularly with improvements in scoring systems, such as BISAP, Balthazar CT, Ranson, and APACHE II, the accurate grading rate has increased to 80%. As severity of acute pancreatitis, at the initial stage of manifestation is critical to improve the patient's prognosis. Therefore, there is a need for a simple indicator that can easily predict the patient's prognosis within 24 hours of the manifestation of the disease.[16] 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. In this study to determine the accuracy of neutrophil to lymphocyte ratio (NLR)  $\geq 4.7$  as a predictor of acute severe pancreatitis keeping Balthazar CT severity index score (7-10) as gold standard for acute severe pancreatitis, A total of 197 patients with acute pancreatitis with an elevated serum amylase or lipase within 24-72 hours within 3 days of start of symptoms were selected. Worldwide, the incidence of acute pancreatitis ranges between 5 and 80 per 100,000 population, with the highest incidence recorded in the United States and Finland. When it does cause acute pancreatitis, it is usually in young people (approximately age 40 years) who also suffer from inflammatory bowel disease. The median age at onset depends on the etiology. In our study, most of the patients were between 21 to 50 years of age patients and the average age was  $37.96 \pm 10.98$  years. [17] Generally, acute pancreatitis affects males more often than females. In males, the etiology is more often related to alcohol; in females, it is more often related to biliary tract disease. Idiopathic pancreatitis has no clear predilection for either sex. There were 108(54.82%) male and 89(45.18%) females in our study. Determination of underlying etiologies which causes the development of acute pancreatitis is crucial and has a great importance on assessing the prognosis at the time of presentation and during hospitalization. Different studies have documented the prognosis of acute pancreatitis patients in relation to underlying etiological factors; every study has shown different statistics in their region. Developed countries like USA, UK, Japan, and china where alcohol consumption is higher than the developing countries are also linked to higher mortality rates in alcohol associated pancreatitis because chronic consumption of alcohol predispose the patients with liver cirrhosis and pancreatitis which affects the outcome in these patients and leads to poor

prognosis. On the other hand, some of the studies also observed that pancreatitis caused by gallstones has more severe and insidious onset and is associated with higher mortality than alcohol induced AP. While, there are studies which has shown no difference among these two etiologies.[18] In the Pakistan, the most common etiology of acute pancreatitis is gallstones and to some extent less common is excessive alcohol consumption while drug induced AP is rarely observed in daily routine practice. This is in accordance to our observation. In our study regarding type of pancreatitis, gallstone was observed in 66.5% cases. Among the available scoring systems currently used, Balthazar and the early warning score (EWS) use CT and physical exam findings, respectively. Although the Balthazar score is superior to other scoring systems in the prediction of the extent of pancreatic necrosis, it was found inferior to the Ranson and APACHE systems in the prediction of organ failure and other adverse outcomes during hospitalization [19]. In our study the prevalence of acute severe pancreatitis was 36.5% (72/197) confirmed by balthazar CT severity index score (7-10) which was gold standard for acute severe pancreatitis. Studies have confirmed that the NLR, which was determined by calculating the ratio of the absolute neutrophil and lymphocyte counts, could be an independent prognostic factor for AP using a cut-off value of  $\geq 10.6$ . In our study the tool to diagnose acute severe pancreatitis was NLR value (i.e. value of NLR to diagnose acute severe pancreatitis was the reference range of 4.7% taken as positive while a value within the normal range was taken as negative for acute severe pancreatitis) and acute severe or non-severe pancreatitis on CTSI score. Although the NLR can predict the prognosis of AP more accurately compared with other markers [20], it was also turned out with controversial results . Our study verified the validity of the NLR using the above recommended cut-off value, and obtained a sensitivity of 86.1%, specificity of 76.8%, positive predictive value 68.1%, negative predictive value 90.6% and accuracy 80.02%. Our results are in accordance with the study done by Xiuzhong Qi, who in their retrospective study verified the validity of the NLR using the cut-off value of  $\geq 10.6$ , and obtained a sensitivity of 80.4%, specificity of 51.1%, +LR of 1.644, and -LR of 0.384. The results also showed that the lymphocyte maybe the main effector cell of the inflammatory response in AP compared with the neutrophil. Other studies have also shown an association between lower peripheral lymphocyte counts and the severity of cases of acute pancreatitis [21]. Such decline in lymphocyte count in acute pancreatitis was attributed to apoptosis and was also associated with lymphocyte dysfunction . Additionally, prior studies have shown that a low lymphocyte count, together with a high neutrophil count, is associated with adverse outcomes in various other medical and surgical conditions [22] . Researchers worldwide have suggested that we should focus on the ratios of components in the WCC, including neutrophils and ymphocytes, rather than the absolute values of white blood cells (WBCs) and their components. The absolute lymphocyte count has been assessed as an important part of the immune system and showed good prognostic value. Azab has reported that the neutrophil-lymphocyte ratio (NLR) is also clearly related to a patient's condition [23], but turned out with controversial results. Neutrophil is also an important component of WBCs. It propagates inflammation and tissue destruction in AP by activating a cascade of inflammatory cytokines (including IL-6, IL-8 and TNF- $\alpha$ ); proteolytic enzymes (including myeloperoxidase, elastase, collagenase and  $\beta$ glucuronidase); and oxygen free radicals [24] . Our study demonstrated that the NLR was elevated in patients presenting with acute pancreatitis and that NLR can be used to classify patients according to disease severity and the presence of organ failure. NLR is

predictive and can be assessed at the early stages which is repeatable, easily accessible and inexpensive. [25]

## CONCLUSION:

To conclude Neutrophil to Lymphocyte ratio (NLR) can be used as a predictor of severity of acute pancreatitis, right at the time of initial diagnosis. Further it may be predictive of risk of adverse outcomes, need for ICU care as well as length of hospital stay. NLR can be used as a tool to refer at risk patients to tertiary center needing ICU admission.

## REFERENCES

1. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, et al. Comparison of BISAP, ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol.* 2010;105(2):435–41.
2. 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):959–70.
3. Pavlidis TE, Pavlidis ET, Sakantamis AK. Advances in prognostic factors in acute pancreatitis: a mini-review. *Hepatobiliary Pancreat Dis Int.* 2014;9(5):482-6.
4. Suppiah A, Malde D, Arab T, Hamed M, Allgar V, Smith AM, et al. The prognostic value of the neutrophil lymphocyte Ratio (NLR) in acute pancreatitis: identification of an optimal NLR. *J Gastrointest Surg.* 2013;17(4):675.
5. Qi X, Yang F, Huang H, Du Y, Chen Y, Wang M et al. A reduced lymphocyte ratio as an early marker for predicting acute pancreatitis. *Scient Rep.* 2017;7(6):54-8.
5. 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): R161.
6. 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. *Pancreat.* 2009;9(6):777-85.
7. Mofidi R, Suttie SA, Patil PV, Ogston S, Parks RW. The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: systematic review. *J Surg.* 2009;146(1):72-81.
8. Pezzilli R, Billi P, Miniero R, Fiocchi M, Cappelletti O, MorselliLabate AM, et al. Serum interleukin-6, interleukin-8, and beta 2- microglobulin in early assessment of severity of acute pancreatitis. Comparison with serum C-reactive protein. *Dig Dis Sci.* 1995;40(11):2341-8.
9. Jones MJ, Neal CP, Ngu WS, Dennison AR, Garcea G. Examination of the prognostic value of leucocyte subsets and neutrophil-to-lymphocyte ratio in patients with acute pancreatitis. *Pancreat.* 2014;14(3):S63.
10. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophillymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. *Crit Care.* 2010;14(5):R192.
11. Le Tulzo Y, Pangault C, Gacouin A, Guilloux V, Tribut O, Amiot L, et al. Early circulating lymphocyte apoptosis in human septic shock is associated with poor outcome. *Shock.* 2002;18(6):487-94.



12. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy*. 2001;102(1): 5–14.
13. Pezzilli R, Billi P, Beltrandi E, Casadei Maldini M, Mancini R. Impaired lymphocyte proliferation in human acute pancreatitis. *Digestion*. 1997;58(5):431-36.
14. Wyllie DH, Bowler IC, Peto TE. Relation between lymphopenia and bacteraemia in UK adults with medical emergencies. *J Clin Pathol*. 2004;57(9):950–5.
15. 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):141-51.
16. 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):181-4.
17. Jeon TJ, Park JY. Clinical significance of the neutrophillymphocyte ratio as an early predictive marker for adverse outcomes in patients with acute pancreatitis. *World Journal of Gastroenterology*. 2017; 23(21):3883.
18. Arima K, Okabe H, Hashimoto D, Chikamoto A, Tsuji A, Yamamura K, et al. The diagnostic role of the neutrophil-to-lymphocyte ratio in predicting pancreatic ductal adenocarcinoma in patients with pancreatic diseases. *Int J Clin Oncol*. 2016;21(5):940-5. 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. *Pancreatol*. 2011;11(4):445-52.
19. Banks PA. Epidemiology, natural history, and predictors of disease outcome in acute and chronic pancreatitis. *Gastrointest Endosc*. 2002;56(6):S226-30.
20. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible?. *Pancreas*. 2010;39(1):5-8.
21. Singla A, Csikesz NG, Simons JP. National hospital volume in acute pancreatitis: analysis of the Nationwide Inpatient Sample 1998- 2006. *HPB (Oxford)*. 2009;11(5):391-7.
22. Ho UC, Mu CF, Hsu CY. Ethnic differences in risk factors of acute pancreatitis. *Ethn Health* 2018;23(3):321-8.
23. Bonfrate L, Wang DQ, Garruti G, Portincasa P. Obesity and the risk and prognosis of gallstone disease and pancreatitis. *Best Pract Res Clin Gastroenterol* 2014;28(4):623-35.
24. McNabb-Baltar J, Ravi P, Isabwe GA, Suleiman SL, Yaghoobi M, Trinh QD, et al. A population-based assessment of the burden of acute pancreatitis in the United States. *Pancreas*. 2014;43(5):687-91.
25. Chatzicostas C, Roussomoustakaki M, Var-das E, Romanos J, Kouroumalis EA: Baltha-zar computed tomography severity index is superior to Ranson criteria and APACHE II and III scoring systems in predicting acute pancreatitis outcome. *J Clin Gastroenterol*. 2003;36:253–60.