Original research article

Study on Neutrophil-Lymphocyte Ratio (NLR) As a Prognostic Marker In Acute Pancreatitis

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Abstract

Background: 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. **Material and methods**: The present study will be carried out in all the in patients diagnosed to have acute pancreatitis in the Department of Medicine and Department of General Surgery, at All India institute of medical sciences, New Delhi. and 50 cases will be studied. Study duration of between Aug 2019 To June 2022.**Conclusion:** The Acute pancreatitis is one of the more commonly encountered etiologies in the emergency setting and its incidence is rising. Presentations range from a mild self- limiting condition (MAP) which usually responds to conservative management,to one with significant morbidity and mortality in its most severe forms (SAP).
Keywords: Acute Pancreatitis, NLR, Neutrophlia, and Lymphopenia, CRP.

Introduction

Acute pancreatitis (AP) is usually a self-limiting process; however, 25 % of patientspresent with or subsequently develop a severe form of the disease that is associated with a mortality of up to 50 %.[1] Acute pancreatitis is an inflammatory disease of thepancreas. 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. Ethanol compromises fuel and energy metabolism, thereby resulting in decreased serum glucose levels with elevated levels of lipids due to increased production and decreased utilization of energy sources. Alcohol can aggravate HTG and the liberated free fatty acid esters can promote calcium influx which leads to calcium- mediated pancreatic necrosis. Nutritional deficiencies, including hypoglycemia, activated counterregulatory mechanisms and reduced cofactor availability reduce or inhibit insulin secretion, thus further compromising energy metabolism and exacerbating hyperlipidemia. An acute inflammatory process of the pancreas thatstarts with local acinar cell injury with variable involvement of other regional tissuesor remote organ systems. Although the majority of acute pancreatitis cases are mild and self-limiting, severe

cases can be accompanied by complications such as necrosis or organ failure in approximately 25% of patients. In such severe acute pancreatitis (SAP), high mortality rates of up to 50% have been reported. The severity of acute pancreatitis isrelated to extrapancreatic organ failure secondary to the patient's systemic inflammatory response, and a poor prognosis of SAP is thought to be the result of uncontrolled systemic inflammatory response syndrome or multi-organ dysfunction syndrome. White blood cell (WBC) counts and C-reactive protein (CRP) levels are non-specific markers of systemic inflammation that can be measured using routine serum hematological tests. , 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.[2,3] However,the total WBC count can fluctuate based on various physiological and pathological conditions including hydration status, stress, and pregnancy in addition to how the blood specimen is handled. 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] 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] Therefore, neutrophilia generated by the acute and severe pancreatic tissue damage and inflammation in SAP increases the NLR. As evidenced by few 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. In the literature review, elevation of the NLR in early phase of SAP was estimated to be abnormalities in cellular immunity due to early apoptosis of lymphocytes and delay of neutrophil apoptosis.[8,9,10,11]

Objectives

To use NLR as a predictor of prognostic outcome in patients with acute pancreatitis. To determine its sensitivity and specificity on admission, 24hrs and 48hrs.

Review of Literature

The pancreas is perhaps the most unforgiving organ in the human body. Situated deep in the center of the abdomen, the pancreas is surrounded by numerous important structures and major blood vessels.The pancreas is a retroperitoneal organthat lies in an oblique position, sloping upward from the C-loop of the duodenum tothe splenic hilum. In an adult, the pancreas weighs 75 to 100g and is about 15 to 20 cm long. The fact that the pancreas is situated so deeply in the abdomen and is sealed in the retroperitoneum explains the poorly localized and sometimes ill-defined nature with which pancreatic pathology presents. The head of the pancreas is nestled in the C-loop of the duodenum and is posterior tothe transverse mesocolon.Most of the pancreas drains through the duct of Wirsung, or main pancreatic duct, into the common channel formed from the bile duct and pancreatic duct. The length of the common channel is variable. In about one third of patients, the bile duct and pancreatic duct remain distinct to the end of the papilla, the two ducts merge at the end of the papilla in another one third, and in the remaining one third, a true common channel is present for a distance of several millimeters. The main pancreatic duct is usually only 2 to 3 mm in diameter and runs midway between the superior and inferior borders of the pancreas, usually closer to the posterior than to the anterior surface. Pressure inside the pancreatic duct is about twice that in the common bile duct, which is thought to prevent reflux of bile into the pancreatic duct. The main pancreatic duct joins with the common bile duct and empties at the ampulla of Vater or major papilla, which is located on the medial aspect of the second portion of the duodenum. The muscle fibers around the ampulla

form the sphincter of Oddi, which controls the flow of pancreatic and biliary secretions into the duodenum. The risk of the occurrence of inflammatory changes is connected with the papillarystenosis of the smaller duodenal papilla. According to estimations, approximately 3% of the cases of acute pancreatitis, described in literature, is caused by a tumour on the pancreas or duodenal papillae (Fan et al., 1993). It may cause the oedema of the papillae of Vater, the regurgitation of duodenal contents into the pancreatic ducts and increase in the permeability of the pancreaticducts. Ethyl alcohol exerts cytotoxic influence as well because it form the ethyl esters of fat acids, which damage the cells of the pancreas, causing acute alcohol- related pancreatitis (Golub et al., 1998; Schenker & Montalvo, 1998).[12] Genetic research has differentiated a disease of the genetically-conditioned mechanism of development: *hereditary pancreatitis* – acute pancreatitis occurring within the family. The research suggests the existence of mutation N34S in the generesponsible for coding a pancreatic inhibitor, trypsin, defined as PSTI (*pancreatic secrectory trypsin inhibitor*) or SPINK1 (*serine peptidase inhibitor, Kasal type 1*). This polypeptide constitutes one of the barriers, safeguarding against self-digestion of the cells of the pancreas. The mutation of the gene results in the earlier activationof trypsinogen inside the cell and its destruction (Karczowski, 2002; Swaroop et al., 2004). The premature activation of the pancreatic pro-enzymes is still regarded as the essential pathomechanism of self-digestion of the pancreatic gland which occursin the severe form of acute pancreatitis. In the pancreatic tissue, besides enzymatic activation, and acinar cells production of TNF-α, macrophages and monocytes are the main inflammatory cells involved in the pathogenesis of local and systemic inflammation. The production of proinflammatory substances by these cells results in amplification of the inflammation to distant organs as liver, lungs kidneys intestines and might result inmulti organs failure.[17,18] Absolute lymphocytopenia can be used in the prediction of infectious emergency admissions. Moreover, the ratio of neutrophil and lymphocyte counts - referred to as the NLR - has even higher value in predicting bacteremia.

Material and methods

The Prospective and Observational Study will be carried out in all the in patients diagnosed to have acute pancreatitis in the Department of Medicine and Department of General Surgery, at All India institute of medical sciences, New Delhi. and 50 cases will be studied. Study duration of between Aug 2019 To June 2022. 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.

Patient outcome is to be classified to mild (MAP) and severe acute pancreatitis (SAP) using the APACHE II score. SAP was defined as objective evidence of organ failure (circulatory shock, acute renal failure, and acute pulmonary failure) and/or local complications of necrosis, abscess of pseudocyst. High dependency admission is defined as patients requiring invasive monitoring (central venous and/or arterial catheter), inotropic or renal support requirement, or patients developing respiratory complications.

Inclusion criteria

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

Exclusion criteria

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

Results

Age and Gender Distribution among study Patients			
Variable	Category	n	%
Age (in Yrs)	21-30 yrs	9	18%
	31-40 yrs	17	34%
	41-50 yrs	13	26%
	51-60 yrs	8	16%
	> 60 yrs	3	6%
Gender	Males	40	80%
	Females	10	20%

Descriptive table showing Age and Gender Distribution among studyPatients

Distribution of study patients based on the Acute PancreatitisGrades			
Variables	Grades	n	%
AP GRADE	MAP	31	62%
	SAP	19	38%

Distribution of study patients based on the Acute Pancreatitis Grades 31 out of the 50 cases (62%) had mild acute pancreatitis while the remaining 19(38%) had severe acute pancreatitis. The ratio of MAP to SAP was 1.63: 1. 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% and4 cases; 21.1% respectively. There was no significant statistical difference between any cause of acute pancreatitis among the study population (χ2=11.255; P=0.08), indicating that therewas a relatively high incidence of less common causes of acute pancreatitis amongstudy population. Comparison of Mean Neutrophil count, Lymphocyte Count & NLR at different time Intervals between MAP & SAP using Mann Whitney Test Among the cases of mild acute pancreatitis, mean neutrophil count was 67.23 ± 6.63% at baseline, rose to 69.87 ± 6.02% at the end of 24 hours and then dropped to 60.29 ± 4.79% at the end of 48 hours. Mean lymphocyte count was 9.87 ± 1.86% atbaseline, rose to 14.58 ± 5.19% at the end of 24 hours and further rose to 22.16 ± 6.96% at the end of 48 hours. The mean neutrophil to lymphocyte ratio at baseline was 7.01 ± 1.33; dropped to 5.37 ± 1.78 at the end of 24 hours and further dropped to 3.00 ± 0.96 at the end of 48 hours. Among the cases of severe acute pancreatitis, mean neutrophil count was 81.26 ± 4.77% at baseline, dropped to 70.11 ± 7.10% at the end of 24 hours and then remained 70.11 ± 5.27% at the end of 48 hours. Mean lymphocyte count was 11.47 ± 2.89% at baseline, rose to13.68 ± 3.76% at the end of 24 hours and further rose to 17.47 ± 3.72 at the end of 48 hours. The mean neutrophil to lymphocyte ratio at baseline was 7.54 ± 1.88; dropped to 5.47 ± 1.51 at the end of 24 hours and furtherdropped to 4.21 ± 1.11at the end of 48 hours. Mean difference between neutrophil count of MAP and SAP was statistically significant at baseline and at the end of 48 hours; that between lymphocyte count ofboth entities was statistically significant at baseline and at the end of 48 hours. The mean difference of NLR ratios of both entities was statistically significant at theend of 48 hours. Dyslipidemia was the most prevalent comorbidity among both grades of acute pancreatitis (13 out of 50 cases; 26%), followed by diabetes mellitus (8 out of50 cases; 16%). However, among cases of severe acute pancreatitis, diabetes mellitus was the commonest comorbidity (5 out of 19 cases; 26.3%). There was no significant statistical difference between different comorbidities (χ^2=7.427; P=0.28), indicating that comorbidities were more or less evenly distributed among the study population.

Discussion

Acute pancreatitis was defined as clinical findings consistent with a diagnosis of pancreatitis together with an elevation in serum amylase of three times the upper limit of normal. Patient outcomes was classified to mild (MAP) and severe acute pancreatitis (SAP) using the APACHE II score. SAP was defined as objective evidence of organ failure (circulatory shock, acute renal failure, and acute pulmonary failure) and/or local complications of necrosis, abscess of pseudocyst. Patients with mild pancreatitis did not have none of these complications. High dependency admission is defined as patients requiring invasive monitoring (central venous and/or arterial catheter), inotropic or renal support requirement, or patients developing respiratory complications. 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. In a study conducted by Azab B et al[13](Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis). They found that NLR was a better predictor of ICU admission or prolonged hospitalization in AP than was total WBC count and suggested a cutoff value of < 4.7 as a predictor of a poor outcome. In-Hospital mortality was extremely low in that study and the investigators failed to assess records of organ failure. Suppiah et al. revealed an association between NLR measured in the first 48 h and the risk of AP developing into a more severe form. However, that study was limited by a small sample size ($n = 146$), and the AP cases included were mostly mild, with no local/systemic complications or organ failure. Recently, Gulen et al[16]**.** Investigated the association between NLR and early mortality and argued that NLR is not a significant independent prognostic factor**.** Zhang et al[16]**.** Demonstrated that elevated NLR is associated with POF, ICU stay longer than > 7 days, and increased in-hospital mortality in a Chinese population. 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. Clinical profile of patients with acute pancreatitis by Prasad H L et al showed that alcohol induced pancreatitis was more common, followed by biliary etiology in males, in our study, it is consistent that alcohol induced acute pancreatitis is more common i.e. 19 patients (consuming more than 21 units of alcohol per week) than gall stone associated acute pancreatitis in 9 patients. Though universally gall bladder associated pancreatitis is the most common etiology, especially in developed countries, Lankisch PG et al Acute pancreatitis: does gender matter? , and Spanier BW et al, [15] aetiology and outcome of acute and chronic pancreatitis: An update. Our study, in comparison, showed a higher incidence of AP in alcoholics, due to the geographical area of our teaching institute, which is centred around plenty of construction buildings and masonry, unemployment on the rise, thereby contributing to majority of the patients who visit our centre are not financially secure. Kandasam et all reported that 78% of males the predominant etiology is alcoholis, and 77% of females the most common etiology of AP is biliary etiology. In our study, out of 26 patients of alcoholic pancreatitis, 24 patients were males and 2 were females i.e. 92% were males. Out of 10 patients of gall bladder associated pancreatitis, 5 patients were females and 5 were males (50%). In our study, number of diabetic patients were 17 out of 50 (34%), as opposed to study conducted by Kandasam P et al reported 62.5% diabetics, implying that many of the diabetic patients in our sample study did not undergo screening of diabetes in the initial period as most of the patients who were suffering from AP, and who were screened for diabetes, 12 out of 17 patients, had random sugars above 200mg/dl, with 2 patients in DKA status (diabetic ketoacidosis). An increased serum level of alanine aminotransferase (>48 IU/L) is associated

with a high probability of gallstone pancreatitis (positive predictive value 80-90%). In our study, comparison of mean values of SGOT levels in the 2 groups revealed that patients with SAP had a higher mean SGOT/AST (280U/L) and a mean of (140U/L) in MAP group. In our study of 50 patients, 12 patients (24%) had gallstone related pancreatitis with a correspondingly high level of SGOT.

Conclusion

Acute pancreatitis is an inflammatory disease of the pancreas. The etiology and pathogenesis of acute pancreatitis have been intensively investigated forcenturies 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. Disease severity is best predicted from a number of clinical scoring systemswhich can be applied at diagnosis in association with repeated clinical assessment as we have utilised the NLR ratio to predict the severity of pancreatitis, as a less cumbersome, cost effective screening and diagnosing method of acute pancreatitis.

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