Original Article

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Neutrophil to Lymphocyte Ratio as an Early Predictive Marker for Adverse Outcomes in Patients with Acute Pancreatitis

Internal Medicine Section

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ABSTRACT

Introduction: Acute pancreatitis is associated with various complications leading to morbidity and mortality. In inflammation it is common that number and proportion of inflammatory cells vary. In acute pancreatitis it has been observed in various studies that Neutrophil to Lymphocyte Ratio (NLR) can predict prognosis of the disease. Hence, a prospective study was conducted with an aim to determine the clinical significance of NLR in predicting adverse outcomes in acute pancreatitis.

Aim: To compare the NLR at 0 hour, 24 hours and 48 hours between mild and Severe Acute Pancreatitis (SAP) and set an optimal NLR in predicting severity of acute pancreatitis and development of organ failure in acute pancreatitis.

Materials and Methods: A prospective observational study was conducted between September 2017 to August 2019 in a tertiary care teaching institute at Kasturba Medical College and Hospital, Manipal, Karnataka, India. After obtaining Institutional Ethical Committee (IEC) clearance and fulfilling the inclusion and exclusion criteria, 180 patients with age 18 years and above with acute pancreatitis were evaluated. Patient's clinical characteristics, imaging features, biochemical, pathological, microbiological and laboratory parameters were noted. Statistical analysis was done with Statistical Package for the Social Sciences (SPSS) software version 20.0. Unpaired student's t-test was used to compare the mean differences of the two groups. A p-value <0.05 was considered as statistically significant.

Results: In present study, 31-40 years age group was commonly affected with acute pancreatitis. Males were predominantly affected (84%). Among 180 patients, 49 had SAP. Alcohol was the most common cause for acute pancreatitis (69.4%). Mean NLR in Mild Acute Pancreatitis (MAP) at 0, 24, 48 hours of admission to hospital were 9.38, 6.88, 5.15, respectively. In SAP, NLR were 16.27, 12.43, 9.72 at 0, 24, 48 hours, respectively. In MAP, NLR was highest on the day of admission and rapidly came down towards normal value. In SAP, NLR was highest on day 1 and remained higher for a longer duration indicating severe ongoing inflammation.

Conclusion: The NLR at the time of admission has an ability to differentiate between mild and SAP. Patients with NLR >10.80 should be considered as having severe pancreatitis and managed aggressively to treat any potential complications.

Keywords: Inflammation, Inflammatory cells, Mild acute pancreatitis, Organ failure, Severe acute pancreatitis

INTRODUCTION

Acute pancreatitis is defined as an acute inflammation of pancreas [1]. Clinically pancreatitis is diagnosed if patient has two out of three following features- 1) Dull aching pain in the epigastrium which radiates to back; 2) Elevation of serum amylase or lipase which is more than three times the upper limit of the normal; 3) Ultrasound abdomen, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) abdomen showing features suggestive of pancreatitis [2,3]. Various factors precipitate acute pancreatitis, aetiology varies from place to place [4]. Globally, in developed countries gall stones obstructing the pancreatic duct are the most frequent cause of acute pancreatitis [5]. In developing countries and also in India, alcohol consumption is the leading cause of acute pancreatitis. Other predisposing factors include, drugs, hypertriglyceridemia, diabetes mellitus, hypercalcaemia, viral infections like- mumps, leptospirosis, trauma, post Endoscopic Retrograde Cholangiopancreatography (ERCP) etc. Sometimes pancreatitis may be idiopathic or genetic [5]. Inflammation starts within acinar cells of pancreas and then it spreads to surrounding areas and also to distant areas like kidney, lungs and liver [6,7]. Pathological spectrum of acute pancreatitis varies from mild interstitial pancreatitis (uniformly enlarged gland) to severe necrotising pancreatitis (haemorrhage and necrosis within gland) [1,8-10]. This usually correlates with severity of pancreatitis and its clinical severity [2,3].

Acute pancreatitis can lead to local and systemic complication [6,7]. Local complications include peripancreatic fluid collection, pseudocyst formation, necrotic collection, walled off necrosis. Systemic complications include exacerbations of co-morbidities such as ischaemic heart disease, chronic lung disease, chronic liver disease, new onset organ failure like shock, acute respiratory distress syndrome leading to pulmonary insufficiency. Organ failure may be transient (<48 hours) or persistent (>48 hours) [3]. The SAP has persistent organ failure along with local complications and systemic complications. Laboratory investigations shows increase in amylase and lipase levels in blood atleast three times the normal value [11]. Amylase is most commonly tested but amylase has other source of production like salivary gland, fallopian tube, perforated viscera. Lipase is more specific for pancreatitis and remains elevated for long duration than amylase. In renal failure, lipase will be elevated >2 times the normal value [12,13]. Diabetic patients often have elevated lipase levels.

Among gastrointestinal diseases causing mortalities, acute pancreatitis stands at 14th position [14]. It is the second commonly diagnosed gastrointestinal disease after cholelithiasis and cholecystitis. Hospitalisation due to pancreatitis increases with the increase in age of the patient, more among black race, higher in the males than females. Mild and moderately severe pancreatitis has less mortality rate compared to SAP. But mortality rate due to acute pancreatitis is decreasing worldwide to less than 5% due to advances in the treatment options for acute pancreatitis [15]. Various factors have been considered and severity of acute pancreatitis have been predicted. Revised Atlanta criteria classifies acute pancreatitis into mild, moderately severe and SAP based on presence or absence of organ failure and presence of local or systemic complication [3,16].

The MAP has no organ failure and no systemic or local complication. Moderately, SAP has transient organ failure (less than 48 hours) and has local or systemic complication without persistent organ failure. SAP has persistent organ failure (more than 48 hours either single or multiple organ failure). Other severity predictors are presence or absence of Systemic Inflammatory Response Syndrome (SIRS) at admission and at 48 hours, Ranson's score, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, Bedside Index for Severity in Acute Pancreatitis (BISAP) score [17,18]. Other modalities of diagnosis and severity determination are by imaging like ultrasound abdomen, CT scan, MRI scan of abdomen. Laboratory features like increased Blood Urea Nitrogen (BUN), Haematocrit >44% or rising haematocrit, presence of pleural effusion, pulmonary infiltrates, multiple or extensive extrapancreatic fluid collections favour poor outcome [19].

The NLR has recently gained importance in predicting severity of acute pancreatitis [20]. Neutrophil is the main cell which initiates tissue destruction caused by inflammatory cytokines like Interleukin (IL)-6. Therefore, neutrophilia generated by acute and severe pancreatic tissue damage and inflammation in severe pancreatitis increase NLR. Impaired lymphocyte proliferation due to mitogens in acute pancreatitis also increases the NLR. Neutrophils and lymphocytes reflect better immune response than whole blood count [21,22]. There are several studies which show relationship between peripheral lymphocytopenia and severity of acute pancreatitis [22,23]. It is an inexpensive test and can be performed as a part of routine laboratory investigations. Results can be obtained within hours and if required can be repeated. Numerous studies by Suppiah A et al., Azab B et al., and Zhang Y et al., have shown importance of NLR in predicting severity of acute pancreatitis and its role as an aid in early and aggressive management and decreasing the mortality [9,10,24].

The present study was conducted with an aim to know significance of NLR in acute pancreatitis. The objectives were to compare NLR at 0 hour, 24 hours and 48 hours of admission of patients with mild and SAP, and also to set an optimal NLR in predicting severity of acute pancreatitis, set optimal NLR in predicting organ failure in acute pancreatitis.

MATERIALS AND METHODS

A prospective observational study was conducted between September 2017 to August 2019 in the Department of General Medicine and Gastroenterology at Kasturba Medical College and Hospital, Karnataka, India, a tertiary care teaching hospital in Southern India. A total of 180 patients who were aged 18 years and above with acute pancreatitis after screening for inclusion and exclusion criteria were evaluated for clinical, laboratory and imaging features to obtain data. Clinical details and investigations were collected as per standard proforma. IEC clearance was obtained prior to the study (IEC: 698/2017). Patients were selected after obtaining informed consent. Patient's confidentiality was maintained.

Inclusion criteria: Patients were included in the study if they had any two of the following features: 1) Acute abdominal pain which was severe, persistent, epigastric in location radiating to back consistent with acute pancreatitis; 2) Elevation in the serum amylase or lipase more than three times the upper limit of normal; 3) Ultrasonography abdomen or Contrast Enhanced Computed Tomography (CECT) abdomen was suggestive of features consistent with acute pancreatitis [3].

Exclusion criteria: Patients were excluded from the study if they had: 1) Chronic pancreatitis; 2) Acute on chronic pancreatitis; 3) Acute pancreatitis with underlying autoimmune disorders, haematological malignancy, or those on immunotherapy; 4) Post ERCP pancreatitis.

Acute pancreatitis was categorised into mild, moderately severe and SAP in accordance with revised Atlanta classification [3,16]. For statistical convenience moderately severe and SAP were grouped together as SAP. MAP is characterised as without a local and systemic complications.

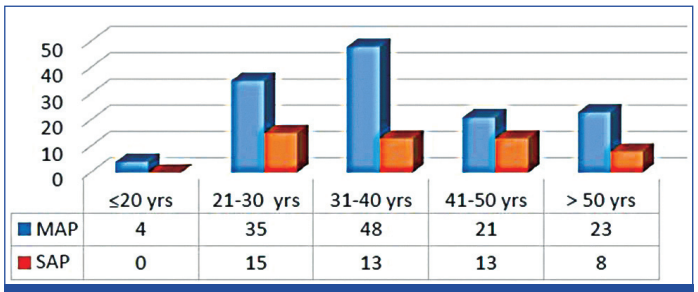
The SAP is characterised by presence of transient (<48 hours) or persistent (>48 hours) organ failure or local or systemic complications. Local complications include peripancreatic fluid collection, pseudocyst of pancreas, necrotic collection, walled off necrosis. Organ failure is characterised by shock (systolic BP <90 mmHg), Pulmonary insufficiency (arterial PaO_2 <60 mmHg or PaO_2/fiO_2 <300), Renal failure (serum creatine >1.5 mg/dL). The NLR was calculated based on absolute neutrophil count and absolute lymphocyte count which was available in complete blood count done as a routine haematological laboratory test at admission, at 24 hours and at 48 hours. Patients were followed-up till they were either discharged or deceased.

STATISTICAL ANALYSIS

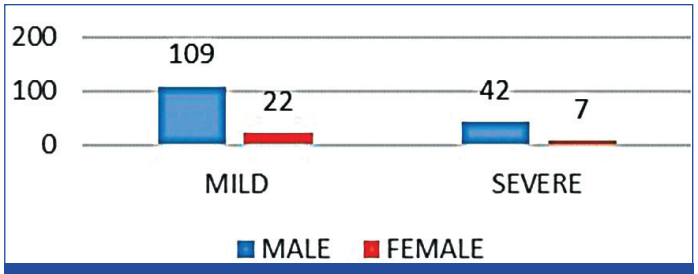
Data were entered in a standard proforma and further entry was done on Microsoft Excel 2013. Frequency and percentages were used to summarise categorical variables. Statistical anlaysis was done using SPSS version 20.0. Continuous variables were presented as mean±Standard Deviation (SD) for normally distributed data and categorical variables as percentages. Unpaired student's t-test was used to compare mean differences of the two groups. A p-value of <0.05 was considered statistically significant. The optimal cut-off value of NLR was computed by using the trade-off between sensitivity and specificity on the Receiver Operating Characteristic (ROC) curves, and the accuracy of prediction of the NLR was estimated using the area under the receiver-operating curve (AUC).

RESULTS

Out of total 180 patients, 131 (73%) had MAP and 49 (27%) had SAP. Out of 180 patients, 31-40 year was the most common age group affected by both mild and SAP, with males (n=151, 84%) affected more than females (n=29, 16%). Out of 131 MAP, 109 were males and 22 are females. Out of 49 SAP, 42 were males and seven were females [Table/Fig-1,2].

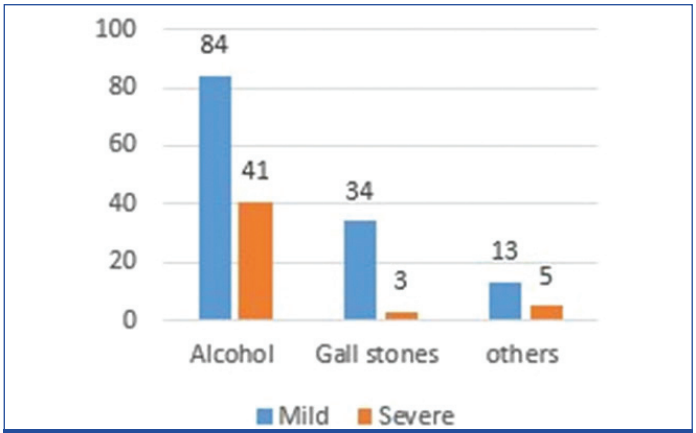


[Table/Fig-1]: Age distribution of patients with acute pancreatitis.
X axis is age group (years); Y axis is numbers



[Table/Fig-2]: Gender distribution of patients with acute pancreatitis.
X axis is severity gender wise; Y axis numbers

In the present study, alcohol (n=125) was the most common cause in both mild (n=84) and severe (n=41) acute pancreatitis. Gall stone (n=37) was the second most common cause in mild (n=34) and severe (n=3) acute pancreatitis. About 18 patients were having different causes, out of which 16 had no definite cause and one each had hypercalcaemia and hypertriglyceridemia [Table/Fig-3].



[Table/Fig-3]: Aetiology of acute pancreatitis.

Mean NLR in MAP at 0 hour 9.38, at 24 hour was 6.88 and at 48 hour were 5.15. In SAP NLR was 16.27 at admission, 12.43 at 24 hour and 9.72 at 48 hours. Two groups were compared at 0 hour, 24 hour and 48 hours following admission and there were statistically significant differences between the MAP and SAP groups (p-0.001). No significant changes were observed in age in MAP and SAP groups. Pulse rate, respiratory rate, Haemoglobin, haematocrit, creatinine and calcium levels revealed a statistically significant difference [Table/Fig-4].

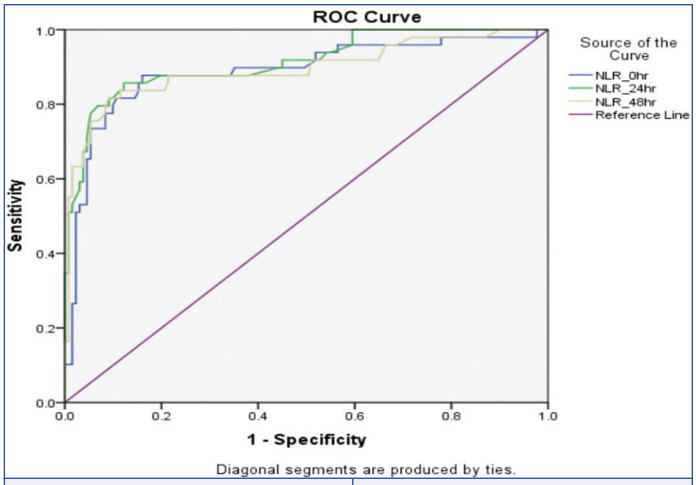
Variables	MAP (131) mean±SD	SAP (49) mean±SD	p-value*
Age (years)	38.89±12.9	39.37±10.7	0.80
Pulse rate (per minute)	85.13±6.6	101.4±12.1	0.01
Respiratory rate (per minute)	17±1.1	23±4.2	0.02
Haemoglobin (gm/dL)	14.3±2.55	15.6±2.99	0.008
Haematocrit (%)	42.51±7.10	44.6±8.73	0.02
Creatinine (mg%)	0.87±0.37	1.9±1.34	0.01
Calcium (mg%)	8.86±0.8	7.89±0.95	0.01
NLR 0 hr	9.38±2.74	16.27±6.87	0.001
NLR 24 hr	6.88±1.26	12.43±5.43	0.001
NLR 48 hr	5.15±1.13	9.72±6.28	0.001

[Table/Fig-4]: Characteristics among mild and Severe Acute Pancreatitis (SAP). Data presented as mean±SD and unpaired student t-test was used to compare mean differences of two groups; *p-value <0.05 is considered significant

This demonstrates that in MAP the NLR was highest on the day of admission and fell rapidly towards normal value over the subsequent 48 hours indicating resolution of the inflammatory process. In SAP, the NLR peaked on day 1 and then started to fall but remained higher on day 2 than the baseline score in MAP group indicating significant ongoing inflammation.

Optimal NLR for severity of pancreatitis was generated by using ROC and corresponding AUC analysis [Table/Fig-5]. [Table/Fig-6] demonstrates cut-off value of NLR for acute pancreatitis at 0 hour of 10.8 had high sensitivity (77.5%) and specificity (90%) in differentiating between MAP and SAP. NLR cut-off values demonstrated nearly 80% of accuracy at 0 hour. Positive Predictive Value (PPV) value remained high at 75% and NPV was 90% at admission. Thirty eight people with SAP had NLR >10.8 compared to 13 patients with MAP. Out of 180 patients in this study, 34 patients (19%) had organ failure and 146 (81%) did not have organ failure. Acute Kidney Injury (AKI), ARDS, shock were the most commonly encountered organ failures in the present study. Out of 34 patients with organ failure 33 patients suffered with AKI, 27 patients were in need of ventilator support for Acute Respiratory Distress Syndrome (ARDS), 19 patients were required to be supported by ionotropes for shock. Ten patients among these had both AKI and ARDS, three patients had both AKI and shock, 16 patients suffered from all three i.e., AKI, ARDS and shock.

The optimal NLR for organ failure was generated by using ROC and corresponding AUC analysis [Table/Fig-7]. [Table/Fig-8] demonstrates



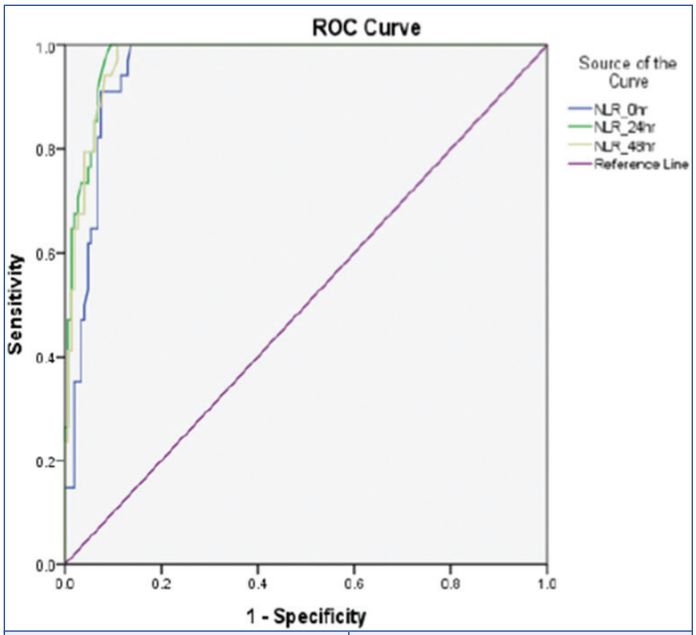
	Cut-off value
NLR at 0 hr	>10.80
NLR at 24 hr	>7.43
NLR at 48 hr	>6.34

[Table/Fig-5]: ROC curve for severity of acute pancreatitis.

NLR	SAP	MAP	Total
>10.8	38 (77.5%)	13 (10%)	51
<10.8	11 (22.5%)	118 (90%)	129
Total	49 (100%)	131 (100%)	180

[Table/Fig-6]: NLR at admission and severity of acute pancreatitis.

an optimal NLR cut-off value 12.19 had a high sensitivity (88.2%) and a high specificity (88.4%) in predicting organ failure in patients with acute pancreatitis. Positive predictive value was 63% and negative predictive value was 96% with an accuracy rate 86.6%. This suggests that those with acute pancreatitis with NLR >12.9 are likely to develop significant organ failure.



	Cut-off value
NLR at 0 hour	>12.19
NLR at 24 hour	>9.11
NLR at 48 hour	>6.97

[Table/Fig-7]: ROC curve for organ failure in acute pancreatitis.

NLR	With organ failure	Without organ failure	Total
>12.19	30 (88.2%)	17 (11.6%)	47
<12.19	4 (11.8%)	129 (88.4%)	133
Total	34 (100%)	146 (100%)	180

[Table/Fig-8]: Organ failure vs NLR at 0 hour.

DISCUSSION

Acute pancreatitis is described as process of inflammation that begins as acinar cell injury and this process can spread and tends to involve surrounding tissues and various organs ultimately leading to organ failure [1]. However, most of pancreatitis cases are mild and resolve on their own, but severe cases are associated with organ dysfunction and necrosis of pancreas, which accounts for about 25% [8-10]. Mortality in these patients can reach upto 50% of those affected, due to unregulated inflammation resulting in multiple organ dysfunction and finally into failure [6]. Serum levels of White Blood Cell (WBC) counts and C-Reactive Protein (CRP) which are measured as a part of routine haematological evaluation are of low significance in predicting severity of illness. Hence, there is a need for diagnostic tool to predict the severity of acute pancreatitis at the time of admission, so that adverse outcomes can be picked up at earliest and managed accordingly and decrease mortality. Few studies have been done on NLR vs WBC in pancreatitis but more research is needed in this area. In a study by Li Y et al., authors compared parameters like Red-cell Distribution Width (RDW), Lymphocyte to Monocyte Ratio (LMR), Prognostic Nutritional Index (PNI), NLR among those patients who survived and those who died of acute pancreatitis. In that study, NLR was the most powerful marker of overall survival in that series [25]. NLR has emerged as a powerful indicator of severity in various inflammatory conditions [26]. In the present study, out of 180 patients, there were mild (n=131, 73%) and severe (n=49, 27%) acute pancreatitis cases. Similar results with (mild 72% and severe 28%) with 76 cases of acute pancreatitis were observed in Indian population based study done by Negi N et al., [23]. Also, similar results were observed in other worldwide studies like Suppiah A et al., and Azab B et al., who concluded that most of acute pancreatitis are mild in nature [9,10].

In the present study males (n=151, 84%) outnumbered females (n=29, 16%), with ratio of male to female was 5:1. Gender distribution in the present study was similar to previous studies like Suppiah A et al., and Azab B et al., [9,10]. The probable explanation for male predominance in all studies were being their lifestyle and activities. Similar findings were noted by Negi N et al., in Indian population [23]. The overall mean age of pancreatitis was 38 years in mild and 39 in SAP group in the present study. Most common age group affected was 31-40 years in both groups. Age groups included in this study ranged from 18-80 years. Similar results were observed in studies done by Negi N et al., group in which 42 years was the mean age affected [23]. However, studies like Suppiah A et al., and Azab B et al., has found that mean age affected was 54 years, slightly higher than the present study age group [9,10]. Thereby, it can be concluded that there is no age predilection for pancreatitis illness.

In present study, alcohol (n=125, 69.4%) was the most common cause of both mild as well as severe pancreatitis, followed by gallstones (n=37, 20.55%). Similar results were observed in an Indian based study by Negi N et al., where 73% cases affected by alcohol and 40% were affected with gallstones. However, in a study done by Suppiah A et al., gallstones aetiology of pancreatitis were about 59%, followed by 27% due to alcohol [9].

The majority of NLR studies till date have divided study populations into tertiles and each tertile group was a categorical variable used to predict poor outcome. Present study did not divide the population into tertiles, as the study aimed to determine an optimal NLR cut-off value. Instead, present study used ROC analysis to define the optimal NLR cut-off using NLR as a continuous variable. This optimal NLR was then compared with other potential cut-off values. In the present study cut-off value for predicting severity of acute pancreatitis was taken as 10.80, and value was similar to cut-off value as in Suppiah A et al., [9] study [Table/Fig-9]. Present study had got good sensitivity (77.5%) and equally good specificity (90%) when compared to other two studies i.e., Suppiah A et al., and Azab B et al., [9,10]. However, no such data is available in Indian studies on pancreatitis.

Parameters	Azab B et al., study [10]	Suppiah A et al., study [9]	Present study
Cut-off value of NLR at 0 hour	4.7	10.6	10.8
Sensitivity	60-70%	63-90%	77.5%
Specificity	40-50%	50-57%	90%

[Table/Fig-9]: Optimal NLR in predicting severity of acute pancreatitis in various studies [9,10].

Present study investigated the predicting value of the NLR for development of organ failure which was not done in earlier studies. Cut-off value of NLR at 0 hour of 12.9 had a sensitivity of 88.2% and specificity of 85% in predicting organ failure. In this study, baseline NLR predicted the development of organ failure with a slightly higher accuracy rate than it predicted SAP with an AUC of 0.95 and 0.89, respectively. This is because the NLR represents the patients' inflammatory response and organ failure, which occurs because of a systemic inflammatory response. In the present study, acute kidney injury (n=33, 97%) was the most common organ affected in acute pancreatitis followed by ARDS (n=27, 79%) and Shock (n=19, 55%). All three organs were involved in about 16 (47%) patients. So, it can be predicted that those organs which depend on good perfusion were commonly affected which occurred due to loss of effective circulatory volume due to loss of fluids into third spaces. In the present study, patients with SAP had median length of ICU stay of 6-8 days and maximum days of ICU stay were 12 days. It can be predicted that hospital stay increases as severity increases. Similar results were observed in Negi N et al., in an Indian population study [23]. This was also observed in other studies like Suppiah A et al., and Azab B et al., studies [9,10]. In a study by Zhang Y et al., NLR was found to be an independent risk factor for persistent organ failure, prolonged ICU stay and increased in hospital mortality following acute pancreatitis [24]. In the present study, 16 patients had expired and all were from SAP group. There was 50% mortality in the present study compared to 30% in Negi N et al., study in SAP group [23]. A meta-analysis done by Kong W et al., found that NLR had moderate to high predictive value for severity of acute pancreatitis which can be used as tool to guide clinical management of patients with acute pancreatitis [27].

Limitation(s)

Only patients from medical departments were included in the present study, hence many surgical aetiologies may be missed. Prognostic value of NLR was not compared with currently used scoring systems of acute pancreatitis. Future studies including a larger number of patients across both sub-groups of acute pancreatitis should be performed to further compare the differences between NLR.

CONCLUSION(S)

The NLR at 0 hour has an ability to differentiate between mild and severe acute pancreatitis. Patients with NLR >10.80 at 0 hour are categorised into SAP and hence they are to be managed aggressively to prevent adverse outcomes. Sequential changes in the NLR over time seems to reflect the progress and therapeutic response. The NLR is a simple, inexpensive test that can be used to classify patients according to disease severity or presence of organ failure. Thus by delineating between mild and SAP, NLR can aid in predicting adverse outcomes and requirement of intense monitoring of those patients with acute pancreatitis and helps to reduce mortality.

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