

Original Article

# Role of C- Reactive Protein (CRP) and Neutrophil Lymphocyte Ratio (NLR) in detecting severity & Predicting outcome of Acute Pancreatitis patients

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**Abstract:** Acute pancreatitis is an inflammatory disease with varied clinical course. It may vary from mild to severe. Early identification of potentially severe acute pancreatitis is of utmost importance. Acute pancreatitis patients with delayed transfer to intensive care have higher mortality. The severity of the illness can be assessed by some early clinical features, bed side scoring systems, or by the CT severity index. But all these have own disadvantages. So a single and cost effective laboratory test is desired to predict severity of the disease. This study determined the predicting value of C-reactive protein (CRP) and Neutrophil-Lymphocyte ratio (NLR) for the severity of acute pancreatitis of Acute Pancreatitis patients admitted in Chittagong Medical College Hospital. The study followed the observational cross-sectional study design where data has been collected from N=40 patient of department of medicine, Chittagong Medical College Hospital, Chattogram. After obtaining data from clinical examination and laboratory investigations the enrolled patients were grouped into mild and severe pancreatitis using BISAP score. Patients with BISAP score 3 or >3 were grouped as severe and those who scored <3 were grouped as mild pancreatitis. Then quantitative serum CRP and NLR values of each group measured and mean value of each group compared by Chi-square test. After that the values of both CRP and NLR were correlated with severity of acute pancreatitis according to BISAP score by correlation analysis. Finally a cutoff value of CRP and NLR were estimated for predicting severity of acute pancreatitis by receiver operating characteristic (ROC) curve analysis. According to the BISAP score patients of acute pancreatitis were distributed in mild to moderate and severe categories. Among them each categories were distributed according to the CRP level. The result found that most of the severe cases in BISAP score also had CRP level >90 mg/L level (20%), which is statistically significant (P value <0.05). It also found that majority of the mild to moderate cases in BISAP score had CRP level <90 mg/L (72.5%), which is also statistically significant (P value <0.05). The study revealed elevation of CRP and NLR both correlate with the number of BISAP score and thus severity of acute pancreatitis.

**Keywords:** c - reactive protein (CRP), Neutrophil Lymphocyte Ratio (NLR) Pancreatitis patients

## 1. INTRODUCTION

Acute pancreatitis is regarded as one of the medical emergency worldwide. There have been sharp increases in the incidence of acute pancreatitis over the last 30 years in the UK1-3 and in many, but not all, studies of other European or western countries. Acute pancreatitis (AP) caused approximately 275,000 hospitalizations in 20094 (an increase of more than 2-fold since 19885) and is the single most frequent gastrointestinal cause of hospital admissions in the US [1]. The annual incidence of AP6-8 ranges from 13 to 45/100,000 persons, and CP8-9 from 5 to 12/100,000. The incidence of acute pancreatitis is largely increasing and is now estimated to be 70 hospitalization /100000 person annually, resulting in >200000 new case of acute pancreatitis per year in US [2]. It is always associated with acinar cell injury and variable involvement of other regional or remote organ system. It is a dramatic life threatening illness of rapid onset and regarded as medical emergency. Most patients develop mild and self-limiting disease with minimal organ dysfunction – mortality being <5% only. Initial management is similar whatever the cause. The early prediction of severe attack allows appropriate monitoring and intensive care to be in place [3]. The means for severity assessment are usually clinical, multiple scoring and CT severity index. Among them early clinical features have been shown to have poor sensitivity and specificity for prognosis. A number of multiple scoring system can predict the morbidity of acute pancreatitis. Mortality rates correlates with the number of criteria present. The most widely used laboratory tests are estimation of serum amylase and lipase concentration. But they are not 100% sensitive or specific for diagnosis. They have no prognostic value. There is a good need for a reliable, simple and single most biochemical test that consistently predicts severity in patients with acute pancreatitis early. A candidate marker that shows great promise is C-reactive protein (CRP). It is the most popular single laboratory marker for the prediction of severity. However, it is a rather late marker as it requires at least 48-72 hour delay before a useful peak with higher prediction characteristics is reached [3]. Most acute pancreatitis risk scoring systems use total white blood cell counts (WBC) as one of the risk factors. The value of the neutrophil-lymphocyte ratio (NLR) to predict the severity of acute pancreatitis has not been previously evaluated [4]. The neutrophil-lymphocyte ratio (NLR), calculated from the white cell differential count, provides a rapid indication of the extent of an inflammatory process. However, in different diseases like several benign and malignant diseases such as coronary heart disease, esophageal cancer, colorectal cancer and hepatocellular carcinoma, NLR shows more reliable predictor for these [5]. In respect of that, NLR over the total WBC counts might be the important indicator for the acute pancreatitis for the prediction of acute pancreatitis severity. A widely accepting prognostic scoring system, the bedside index for severity in Acute Pancreatitis is BISAP scoring which consists five points including Blood Urea Nitrogen (BUN) >25 mg/dl, Impaired mental status, presence of SIRS, age >60 and pleural effusion [6]. A score of 0-2 is low mortality of less than 2%. A score of 3-5 is associated with a higher mortality of more than 15%. SIRS is defined by the presence of following >2 criteria: Pulse >90beats/min, respiratory rate >20 per min, or PaCO<sub>2</sub> <32mmHg, Temperature >100.4 o F with WBC >12000 or <4000 cells per mm<sup>3</sup>. BISAP score was retrospectively calculated and validated in large population data. Based on BISAP score the study aimed to investigate the prognostic value of the CRP and NLR in Acute pancreatitis (AP) and determine an optimal ratio for severity prediction [7]. The severity of Acute Pancreatitis usually unpredictable for the clinicians. More than 20% cases become severe after the acute attack, which also shows the increasing mortality among the severely attacked patients. Therefore, to assess the severity, multiple scoring systems were used. Among them BISAP scoring is validated and adopted in different studies. To grade the patients as severe or mild pancreatitis, BISAP score might be helpful. However, CRP and NLR also used to detect the AP severity [8]. This study mainly focused on these two (CRP and NLR) based on the BISAP

score. The word 'pancreas' comes from the Greek words 'pan' (all) and 'kreas' (flesh). Long assumed to cushion the stomach, its glandular function was unknown. The retroperitoneal pancreas is behind the stomach near the duodenum [9]. It weighs 80 grammes and measures 12-15 cm. It looks like a flattened tongue tissue or the top of a thick walking stick or hook, lying sideways with the handle on the right and the hook turned down. The tail is thinner than the head. Exocrine acinar tissue in lobules makes up 80-90% of the gland. Dispersed throughout the pancreas are 'islets of langerhans', which make up the remaining 10-20% [10]. In addition to glucose homeostasis, they regulate upper gastro intestinal motility and function. Acute pancreatitis is a pancreatic inflammation that may include other tissues or organ systems. Previously normal pancreas is the backdrop of acute pancreatitis [11]. If conservative medical treatment reduces inflammation or removes the aetiology of pancreatitis, the gland normally recovers. After correcting the aetiology, chronic pancreatitis causes ongoing inflammation and irreversible loss of exocrine pancreatic parenchyma. Interstitial, edematous, or mild pancreatitis is acute pancreatitis without parenchymal necrosis. The most frequent pancreatitis. Most cases are modest (80%). Minimal organ impairment and uncomplicated recovery are related. Self-limiting illness improves within 48–72 hours with conservative measures. After treating the problem, the gland can recover, Treatment usually reduces inflammation in 3-7 days. Failure to improve within 48-72 hours of treatment should require pancreatitis complication assessment. The death rate is 30-60% in 25% of patients. Only 5% of acute pancreatitis patients die. Mild acute pancreatitis is self-limiting, while severe causes irreversible exocrine pancreatic tissue loss and death [12]. The initial clinical assessment only detects 50% of severe acute pancreatitis patients. Standard acute pancreatitis diagnostics like serum amylase and lipase don't predict severity either. There are many biochemical indicators for early severity prediction, however further investigations have not consistently supported positive results. CRP levels predict acute pancreatitis severity, levels rise within 24 hours of symptom onset and peak on day 3 or 4. Most investigations have examined CRP's role in acute pancreatitis severity stratification. CRP severity classification cutoffs vary each study, peak CRP >210 mg/L in the first 4 days indicates acute pancreatitis with 80% accuracy, comparable to multiple factor scoring. Others say 150mg to 200mg .Even 100mg/L can predict severe necrotizing pancreatitis beyond 90% [13]. CRP is an 'acute phase protein' or reactant. Its elevation ranges from 50% to 1000 fold. CRP activates the traditional complement pathway. It indicates tissue damage, infection, and inflammation, healthy people have a median CRP value of 1mg/L. This is the best indicator of inflammation. CRP reacts with Streptococcus Pneumonia capsular polysaccharide, hence its name [14]. It is the most sensitive acute phase reactant and dependable inflammatory marker. Hepatocytes generate it predominantly in response to IL-2, IL-6, and TNF. It activates the classical Complement pathway in response to inflammation. CRP induction is fast and its half-life (19 hours) is long enough for repeated measurement. No apparent diurnal fluctuation. Ligand-bound CRP stimulates the traditional compliment pathway, binds to immune cell immunoglobulin receptors, and causes cytokine production and complement-related inflammation [15]. An increase in CRP may indicate systemic inflammation after tissue injury or infection. Within 6 hours of inflammation, the level might rise to 2000 times normal. Due to inflammation or tissue damage, high CRP is connected with poor outcomes. History of CRP first discovered in 1930 when a protein in Streptococci Pneumoniae patients' serum precipitated and bonded to Pneumococcal cell wall C polysaccharide [16]. Tillet and Francis found no CRP in healthy sera in 1930, CRP has long been known to be one of numerous non-specific acute phase reactants raised during inflammation [17]. Macleod and Avery identified this material as a protein and coined the name "acute phase" to describe acute infection serum. After Lofstram showed acute phase response in acute and chronic inflammation, CRP became a nonspecific acute phase protein. The horseshoe crab (limulus

polyphemus), a "living fossil" with large amounts of this protein in its hem fluid, has highly conserved it. Liver hepatocytes produce most CRP in response to IL-1, IL-6, and TNF in kidney, neurons, and alveolar macrophages [18]. Normal serum levels < 6mg/L. Infectious and non-infectious inflammatory disorders increase CRP. The physiological role of CRP is unclear, human CRP is a calcium-dependent ligand-binding protein that aggregates or precipitates cellular, particulate, or molecular complexes containing autologous and extrinsic ligands, specifically phosphocholine (PC) residues. Native and modified plasma lipoproteins, damaged cell membranes, phospholipids, and apoptotic cells are autologous ligands. Glycans, phospholipids, capsular and somatic components, bacteria, fungi, and parasites are extrinsic ligands. Human CRP activates the traditional complement system and promotes opsonization and phagocytosis when ligand bound. Within 24-48 hours of tissue damage, concentrations may increase 1000-fold [19]. While other acute phase components show diurnal change, this one does not. Complete blood count is a cheap, regular, and useful laboratory test that provides essential patient blood content information. Regular peripheral blood counts can diagnose and prognose numerous diseases, including prostate problems. Measure NLR by dividing neutrophils by lymphocytes. NLR may indicate systemic inflammation since neutrophils and lymphocytes are important in tumour immunology and inflammation. Inflammation promotes cancer cell proliferation, angiogenesis, and metastasis, advancing the disease. NLR can indicate chronic and acute inflammatory processes even when white blood cell counts are normal [20].

## 2. MATERIALS AND METHODS

This was a cross sectional observational study conducted in the department of Medicine, Chittagong Medical College Hospital. Sample size determination depends on time and resources. Prevalence of Acute pancreatitis is 0.05% worldwide (Range from 20-80 per 100,000 estimated people). So estimated population was calculated by using the following statistical formula:

$$n = z^2 p (1-p) / d^2$$

Where n= the desired sample size, Z=the standard normal deviate, usually set at 1.96 at 5 % level which corresponds to 95% confidence level. P means prevalence = 0.05 (50% approximately).

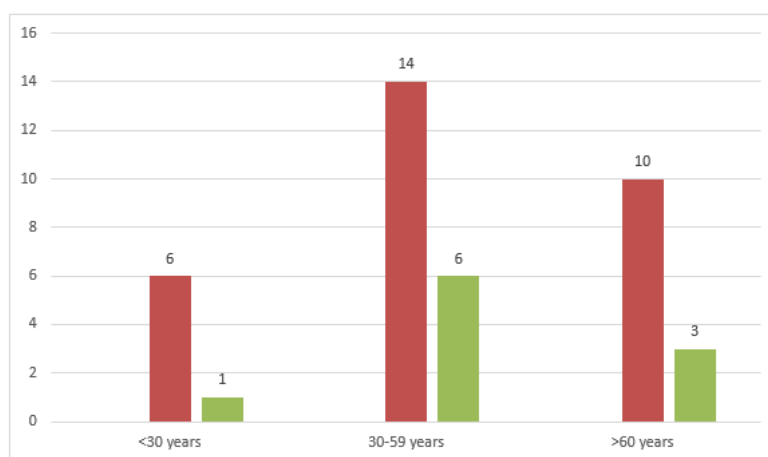
The degree of accuracy or precision level is d which is considered at 5%.The higher value of d will yield lower sample size and smaller value of d will yield higher sample size. Z statistic is 1.96, which corresponds to the 95% confidence level, d is the level of accuracy that is considered 0.05 (5%).

$$\begin{aligned}
 &= \frac{Z^2 p (1-p)}{(d)^2} \\
 &= \frac{(1.96)^2 \times 0.05 (1-0.05)}{(0.05)^2} \\
 &= \frac{3.8416 \times 0.05 \times 0.95}{(0.05)^2} \\
 &= \frac{0.282742}{0.0025} \\
 &= 73
 \end{aligned}$$

Due to time constrain, less hospital admission and pandemic situation sample size was reduced to 40. Sample selection was done by purposive sampling. Proper counseling was done to all participants. Then patients were provided a consent form that was prepared previously. The questionnaire was prepared as mentioned in the appendix. Statistical analysis was carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The quantitative observations were indicated by frequencies and percentages. Chi square test was used for categorical variables. P values <0.05 was considered as statistically significant.

### 3. RESULTS AND DISCUSSION

According to the distribution of the study is respect of age and sex, most of the cases were male (75%). However, majority of the cases were from 30 to 59 years of age (50%). In respect to every age group Male patients were more than female. Red portion of the bar represents male population where green portion represents female population. This diagram shows admitted patients with acute pancreatitis are mostly adult population. Number of male patients were more than female patients.



**Figure 01:** Bar Diagram showing distribution of Acute Pancreatitis among male and female population.

The table shows, Attending patients with acute Pancreatitis were mostly male (75%). Total 22.5% presented with severe acute pancreatitis. Among them majority (17.5%) patients were male.

**Table 01:** Relationship between Gender and Severity of Acute Pancreatitis

In respect to the occupational distribution of the cases, majority of the cases were day labor or worker

Severity of Pancreatitis	Gender distribution		Total N (%)
	Male n (%)	Female n (%)	
Mild to Moderate	23 (57.5%)	8 (20%)	31 (77.5%)
Severe	7 (17.5%)	2(5%)	9 (22.5%)
Total	30 (75%)	10 (25%)	40 (100%)

(30%). House wives (22.5%) and Service holders (20%) were common too. Among the participants, most

of them were day laborer industrial worker (38%) while 27% house wife, 13% were service holder. According to the categorization of acute pancreatitis patients from BISAP score, 77.5% cases were mild to moderate however, 22.5% cases were identified as severe.

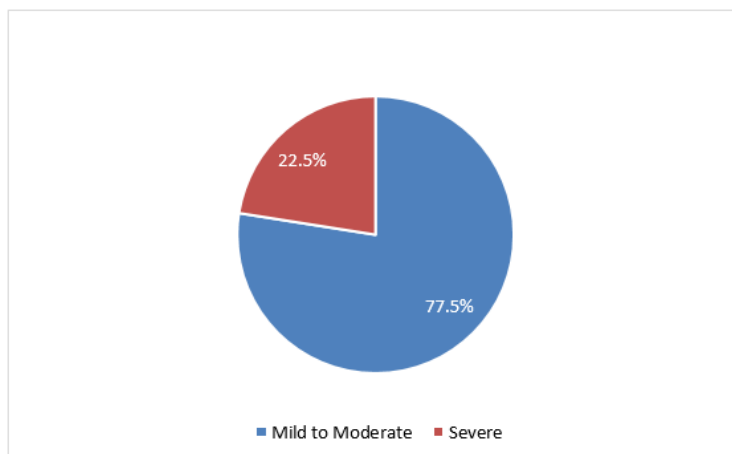
**Table 02:** Occupation distribution of the acute pancreatitis patients

Occupation	Numbers	Percentage
Service	8	20%
Business	4	10%
Students	3	7.5%
Day labour/ Workers	12	30%
Housewife	9	22.5%
Others	4	10%
Total	40	100%

According to the BISAP score patients of acute pancreatitis were distributed in mild to moderate and severe categories. Among them each categories were distributed according to the CRP level. We found most of the severe cases in BISAP score had also  $>90$  mg/L level (20%), which is statistically significant (P value  $<0.05$ ). We also found Majority of the mild to moderate cases in BISAP score were also  $<90$  mg/L CRP level (72.5%), which is statistically significant as well (P value  $<0.05$ ).

**Table 03:** Distribution of C-reactive protein level and BISAP score in acute pancreatitis patients

BISAP Score	CRP Level	Numbers (%)	P Value
0-2	$\geq 90$ mg/L	2 (5%)	$<0.05$
	$<90$ mg/L	29 (72.5%)	
$\geq 3$	$\geq 90$ mg/L	8 (20%)	$<0.05$
	$<90$ mg/L	1 (2.5%)	

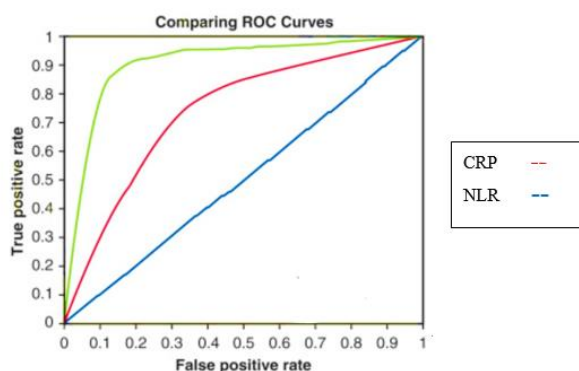


**Figure 02:** Pie chart on Acute pancreatitis severity (BISAP score)

According to the BISAP score patients of acute pancreatitis were distributed in mild to moderate and severe categories. Among them each categories were distributed according to the Neutrophil Lymphocyte Ratio. We found most of the severe cases in BISAP score ( $\geq 3$ ) had  $\geq 7$  (15%) as well as 20% mild to moderate cases in BISAP score had also NLR  $\geq 7$ . We calculate the P value and found it statistically insignificant (P value  $>0.05$ ). In compare to that, we also found Majority of the mild to moderate cases in BISAP score had NLR value  $<7$  (52.5%), which is statistically significant (P value  $<0.05$ ).

**Table 04:** Distribution of Neutrophil Lymphocyte Ratio and BISAP score in acute pancreatitis patients

BISAP Score	CRP Level	Numbers (%)	P Value
0-2	$<7$	24 (60%)	$<0.05$
	$\geq 7$	7 (17.5%)	
$\geq 3$	$<7$	4 (10%)	$>0.05$
	$\geq 7$	5 (12.5%)	



**Figure 03:** Comparative Receiver Operating Curve for acute pancreatitis patients for CRP and NLR

According to this receiver operating curve (ROC), it is visible that the more true positivity were found in CRP level in compare to NLR. More false positive were found in NLR. Acute pancreatitis patients in BISAP score were more sensitive with CRP rather than NLR.

**Table 05:** Time of arrival to the hospital and outcome of acute pancreatitis patients

Time of arrival for treatment	Outcome	N (%)
≤24 hours	Cured	32 (80%)
	Death	0
>24 hours	Cured	6 (15%)
	Death	2 (5%)

According to the arrival time of the cases in the hospital for treatment shows that, all the patients who came within 24 hours were cured. However, those who were came after 24 hours, death occurred (5%) among them.

### 3.1 Discussion

Comparing this study to relevant ones, 31 (77.5%) of 40 patients got moderate acute pancreatitis and 9 (22.5%) became severe, a study identified 72% mild and 28% severe acute pancreatitis [21]. A study reported 76% and 24% of patients suffered mild and severe acute illness. The outcome matches other investigations. Of 40 hospitalised patients, 7 (17%) were 15-29 years old, 20 (50%) were 30-59, and 13 (33%) were above 60. This reveals that middle-aged people are more likely than old and young people to have acute pancreatitis, indicating a statistically significant age effect [22]. Acute pancreatitis is more common in 30-59-year-old adults, out of 40 patients, 30 (75%) were male and 10 (25%) were female [23]. Other research disagree with this outcome, male acute pancreatitis rates were slightly higher than female



(52.3% vs. 47.7%), male and 49.4% female in 13110 patients. Social, economic, financial, gender discrimination, occupation, alcohol consumption, and narcotics may affect its distribution approx. 23 male patients (57.5%) had mild disease, whereas 7 (17.5%) had severe disease. Mild to severe illness ratio in men was 0.77: 0.23. From 10 female patients, 8 (20%) got mild disease and 2 (5%), severe disease [24]. The study reveals that severe acute pancreatitis is more common in men, gender affects acute pancreatitis severity. Males had 44% and 38% greater chances of gastrointestinal bleeding (aOR 1.44, 95% CI 1.18–1.76) and other major complications (aOR 1.38, 95% CI 1.05–1.82) [25]. A study reveals men have more severe acute pancreatitis than women, most patients in our study were low-income (38% day labourers, 27% housewives, 13% service holders). Univariable logistic regression analysis revealed high ASI in older age groups (OR 1.06 per year;  $P < 0.001$ ) and high deprivation areas (OR 2.40;  $P < 0.001$ ), with the latter primarily linked to alcoholic aetiology (OR 6.50 (95 per cent confidence interval 3.90 to 10.84)) [26]. Alcoholic aetiology explained the association between socioeconomic hardship and acute pancreatitis in that study. However its predominance in low-socioeconomic groups may be due to eating habits, lifestyle, alcohol consumption, and infection. A study divided 40 patients into two groups in this investigation, BISAP score 0-2 indicates mild to moderate acute pancreatitis, while  $\geq 3$  indicates severe acute pancreatitis. Category distribution was based on CRP. It discovered the greatest sensitivity and specificity around 92.4 AUC when we placed CRP data in receptor operating curve [27]. Most patients with BISAP score 0-2 had CRP levels  $< 90$ , identified 31 mild-to-moderate acute pancreatitis patients. Out of 31 patients, 29 had a CRP level  $< 90$ . Only 2 patients had CRP  $> 90$ . Of the 9 severe acute pancreatitis patients (BISAP score  $\geq 3$ ), only one had a CRP level  $< 90$ . Comparing these values revealed significant results ( $P < 0.05$ ). Out of 9 severe acute pancreatitis patients (BISAP score  $\geq 3$ ), 8 had CRP levels  $> 90$ , while only 2 mild to moderate patients (BISAP score 0-2) had CRP levels  $> 90$ . Comparing these values revealed significant results ( $P < 0.05$ ) [28]. Interval CRP is equal to absolute CRP in AP severity prognosis, it reveals a rise of  $> 90$  mg/dL from admission best predicts severe illness. CRP levels above 83mg/dl increase recovery time ( $R > 7D$ ,  $p = 0.004$ ) [29]. A study found that is more reliable in detecting acute pancreatitis severity than other markers. Admission CRP cut-off was 90, which is comparable with other research. It assessed NLR values of acute pancreatitis patients and arranged them by BISAP severity [30]. The severe group had a statistically larger NLR at admission 5 than the mild AP group. The emergency department NLR cut-off value was determined using receiver operating characteristic (ROC) curve analysis to differentiate AP patients with and without systemic problems. Area under the ROC curve was 0.81. When the NLR cut-off was  $> 7.13$ , sensitivity was 87.50% and specificity 69.05% [31]. This study sorted patient NLR results by BISAP score, 24 (60%) of 31 patients with BISAP scores 0-2 had NLR values  $< 7$ . However, 4 severe acute pancreatitis patients had an NLR value  $< 7$ . A statistical comparison revealed significant results ( $P$  value  $< 0.5$ ). Out of 9 patients with BISAP score  $\geq 3$ , only 5 had NLR  $> 7$ , while 7 individuals with mild to moderate pancreatitis (BISAP score 0-2) had NLR  $> 7$ . We observed no statistical significance and  $P$  value  $> 0.05$  [32]. NLR values  $< 7$  are more accurately related with mild to moderate acute pancreatitis than those  $> 7$  with severe acute pancreatitis. It compared with result to similar studies. One meta-analysis [33] found that 'NLR has a moderately good diagnostic value in predicting the severity of acute pancreatitis, 54 Another 5.55 comparison. Another study disputed NLR's early prediction of acute pancreatitis severity, where as our sample was limited. Patients presented in emergency at various times, and many received antibiotics and anti-inflammatories before hospitalisation. All of these factors may have contributed to our study's difference from others. The study also assessed these 40 patients' hospital staying outcomes. It found 32 (80%) of 40 patients presented within 24 hours of symptom onset [34]. Disease complications killed 02(5%) people in this group, hospitalisation before 24 hours

improves outcomes, it found that delayed hospital presentation of acute pancreatitis is associated with multi-organ failure, sepsis, and other comorbidities, requiring greater ICU admission [35].

#### 4. CONCLUSIONS

Acute pancreatitis is an inflammatory disease with varied clinical course. It may vary from mild to severe. Early identification of potentially severe acute pancreatitis is of utmost importance. Acute pancreatitis patients with delayed transfer to intensive care have higher mortality. The severity of the illness can be assessed by some early clinical features, bed side scoring systems, or by the CT severity index. But all these have own disadvantages. So a single and cost effective laboratory test is desired to predict severity of the disease. Data obtained from this study reveals, Elevation of CRP and NLR both correlate with the number of BISAP score and thus severity of acute pancreatitis. Between these two marker CRP is more accurate and it can predict the severity and thus probable outcome of acute pancreatitis than NLR. NLR also correlates with the BISAP score grading but not as accurate as CRP. Thus it becomes a less reliable tool to determine severity and thus early prediction of acute pancreatitis than CRP. Large scale multi centered studies carried out over prolong period of time involving large number populations of different socioeconomic background may provide more precise information.

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