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Original Article

Role of Neutrophil to Lymphocyte Ratio (NLR) and C-Reactive Protein to Albumin Ratio (CAR) as Early Predictors of Severity in Acute Pancreatitis

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Abstract:

Background: *Acute pancreatitis (AP) is a life-threatening disease caused by a variety of factors, and once it progresses to severe acute pancreatitis, the prognosis is poor. Different modalities are available for predicting severity in acute pancreatitis. A single, cheap, widely available marker with high sensitivity and specificity is yet to be identified.*

Aims and objectives: *The present study was aimed to determine the relation of the neutrophil-lymphocyte ratio (NLR) and CRP-Albumin ratio (CAR) in early prediction of severity in acute pancreatitis.*

Materials and methods: *This cross-sectional study was conducted at the Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General Hospital, Shahbagh, Dhaka, Bangladesh, from April, 2020 to March, 2022. Diagnosis of acute pancreatitis was made by clinical findings, serum amylase and lipase levels (>3 times the upper limit of normal values), evidences of acute pancreatitis by ultrasonography and computed tomography (CT). Severity of acute pancreatitis was classified according to the revised version of Atlanta classification. Data collection was done through a structured questionnaire. Data were analyzed by SPSS 23. Receiver operating characteristic (ROC) curve was constructed to estimate the sensitivity and specificity of NLR and CAR.*

Results: *A total of 120 patients with acute pancreatitis were enrolled in this study. Age of the patients was 45.20±13.93 (mean ±SD) years, male predominance was observed (54.2%). Majority of the cases were mild 52.5% (n=63) compared to moderate 28.3% (n=34) and severe 19.2% (n=23). The NLR was 6.63±3.344 (Mean ± SD) with a range of 1.32 to 18.75. The CAR was 3.20±2.23 (Mean ±SD) with range of 0.14-7.20. The area under the curve (AUC) of NLR and CAR were 0.865 and 0.949 for severity of AP respectively. Sensitivity, specificity, PPV, NPV and accuracy of NLR at cut-off ≥5.72 were 80.7%, 76.2%, 75.4%, 81.4% & 78.3% and that of CAR at cut-off ≥2.07 were 96.5%, 76.2%, 78.6%, 96.0% & 85.8%.*

Conclusion: *This study revealed that NLR and CAR are good predictors in the assessment of severity of AP. These easily accessible and low-cost inflammatory markers can be used for the management of acute pancreatitis.*

Key words: *Acute Pancreatitis, Neutrophil to Lymphocyte Ratio and C-Reactive Protein to Albumin Ratio.*

Introduction

Acute pancreatitis (AP) is an inflammatory process in which local pancreatic injury leads to systemic inflammation by activating cytokine cascades.[1]The reported annual incidence of acute pancreatitis is 13 to 45 per 100,000 populations in different countries of the world.[2]Acute pancreatitis is categorized into mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) according to revised Atlanta classification 2012.Mild acute pancreatitis (MAP) is the commonest form, has no organ failure, no local or systemic complications, and usually resolves within the first week. Moderately severe acute pancreatitis (MSAP) is defined by transient organ failure (duration <48h) and/or local or systemic complications. Severe acute pancreatitis (SAP) is manifested by persistent organ failure (duration >48 h).[1]

The management of patient with acute pancreatitis is determined by an accurate assessment of the severity of the disease. Although most cases of AP are self-limiting, 25 % cases present with or subsequently develop a severe form of the disease that is associated with a mortality of up to 50 %.[3]Predicting severity of acute pancreatitis early in the course of disease is critical to maximize therapy and to prevent and minimize organ dysfunction and complications. The severity of acute pancreatitis is related to extra-pancreatic 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 (SIRS) or multi-organ dysfunction syndrome (MODS).[1,3,4]

Different scoring systems, such as Ranson's,Glasgow score, Acute Physiology and Chronic Health Evaluation (APACHE), bedside index for severity in acute pancreatitis (BISAP) have been developed to assess severity of AP. Some of these scoring systems require more than 48 hours to be completed (Ranson's, Glasgow score, computed tomography severity index) while APACHE II score is complex and difficult to apply outside intensive care setting. Simplified tests using serum markers such as procalcitonin, TNF-alpha, interleukin-6, and interleukin-8 have been applied to predict the severity of AP, but they are expensive, not readily

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available, and cannot adequately predict the severity of AP.[4,5]

Many direct or combined markers of systemic inflammation are based on routine, inexpensive and readily available laboratory tests, including the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and red-cell distribution width (RDW).[5] Complete blood count (CBC) is a routine test for emergency patients available even in the resource limited center. A rapid and sustained increase in neutrophils indicates the development of systemic inflammatory response syndrome (SIRS) and multi organ dysfunction syndrome (MODS) which are indicators of severe form of AP.[6] Studies have also shown that there is an association between peripheral lymphocytopenia and the severity of acute pancreatitis.[7] Elevation of NLR during the first 48 hour of hospital admission is significantly associated with severe form of AP and is an important negative prognostic indicator in AP.[5]

NLR was found to be a better predictor of ICU admission or mortality in AP than was total WBC count or individual neutrophil and lymphocyte counts.[8]In a retrospective study, identified that the NLR is significantly higher in the group that had died than in the group that had survived from AP.[9]

The C-reactive protein /albumin ratio (CAR), currently a popular marker, was the second marker to be examined as part of this study's objective. C- reactive protein (CRP) is a positive acute-phase reactant synthesized by the liver, and its level in blood increases within hours in response to inflammation and infection. Albumin is a negative acute-phase reactant synthesized by the liver, and its level in the blood decreases during inflammation. The CRP/albumin ratio is determined by dividing the CRP by the albumin measurement and is an established scoring system used to determine the degree and activity of inflammatory disease, which is considered to be a more useful indicator of the status of inflammation than CRP or albumin alone.[10] It has been shown that it can be used in predicting patient outcomes in many diseases, such as sepsis, hepatocellular carcinoma, small cell lung, pancreatic and esophageal cancer, inflammatory bowel disease etc.[10-15] However, there are relatively few studies conducted in AP. Kaplan et al. analyzed the Ranson's and Atlanta scores, as well as the effects of CAR in severity and prognosis of AP. They observed an increase in severity and poor prognosis with increased CAR value.[16]A study found that CAR values are significantly higher in the severe pancreatitis group compared with moderate group.[17]

Study evaluating the role of NLR and CAR in the prediction of severity and adverse outcome of AP is scarce in our country. The aim of this study was to demonstrate the usefulness of NLR and CAR independently in predicting severity of acute pancreatitis at the early stage of the disease.

Materials And Methods

This was a cross sectional study carried out at the department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General Hospital, Dhaka from April, 2020 to March, 2022.Purposive type of non-probability sampling technique was applied to enroll the patients with acute pancreatitis admitted within 72 hours of onset of symptoms in the department of GHPD.

Inclusion criteria were all patients diagnosed with acute pancreatitis based on clinical, laboratory and imaging modalities as per revised Atlanta criteria, age ≥18 years. Exclusion criteria were onset abdominal pain to hospital admission ≥72 h, AP induced by trauma or pregnancy, known case of chronic pancreatitis, chronic kidney disease, cirrhosis.Patients on antibiotics, steroids or chemotherapy, suffering from serious infection or inflammation of any other organ system.

Diagnosis of acute pancreatitis was made based on clinical, laboratory and imaging finding based on revised Atlanta criteria. From the acute pancreatitis patients who fulfil the inclusion and exclusion criteria were considered primarily for study. Informed written consent was taken from each patient. Particulars of the patient, relevant history was taken and detailed clinical examination was done and recorded in predesigned structured data collection sheet. All relevant laboratory investigations were done.Complete blood count, CRP (Reference: <6 mg/L), serum albumin (Reference: 34-50 g/L) were performed on a blood sample obtained immediately after hospitalization before giving antibiotics and fluid management. CBC was measured in an automated hematology analyzer. Serumalbumin and CRP were measured with ARCHITECT using albumin BCG 7D53 reagent and BNII/BN Prospec system using cardio phasehs CRP reagent respectively. The neutrophil to lymphocyte ratio (NLR) was calculated as a ratio of differential count of neutrophil to lymphocytes. The c-reactive protein to albumin ratio (CAR) was calculated as the ratio of CRP to albumin level. Chest

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x-ray and ultrasonogram of abdomen were done in all patients. Computed tomography (CT) scan was also performed after 72 hours of abdominal painif needed. Attacks of acute pancreatitis were classified as mild, moderately severe and severe according to revised Atlanta criteria and with the help of modified Marshall scoring system for organ failure.

After collection of information data were checked, verified for consistency & edited for finalized result. After editing & coding, the coded data were entered into the computer by using the SPSS (Statistical Package for Social Sciences) version 23.0 software. Data cleaning validation &analysis was performed using the SPSS software. Receiver-operating characteristic (ROC) curves were used to determine the cut-off value of neutrophil to lymphocyte ratio (NLR) and CRP/albumin ratio. Diagnostic accuracy was measured by calculating sensitivity, specificity, positive predictive value, negative predictive value and accuracy. Statistical association was determined by using an appropriate statistical tool like unpaired sample t-test for continuous variables. The result was presented in tables as mean, standard deviation (SD), frequency, and percentages. Statistical significance was set at 0.05 level and confidence interval at 95% level.Ethical clearance was obtained from the Institutional Review Board, BIRDEM.

RESULTS

This cross-sectional study was carried out in the Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders, BIRDEM General Hospital, Dhaka. After fulfilling inclusion and exclusion criteria 120 patients of acute pancreatitis were selected for the study. The purpose of this study was to investigate the diagnostic value of the NLR and CAR for predicting the early severity of acute pancreatitis. The results are described by following tables and figures.

Majority of the patients were in 40-49 years of age (27.5%) followed by 50-59 and ≥60 years (19.2%), 30-39 years (18.3%) and 18-29 years (15.8%). Mean age was 45.2 ±13.93 years. Male predominance (54.2%) was seen and male to female ratio was 1.18:1. About 49 (40.8%) cases were due to unknown etiology, 41 (34.2%) cases were due to hypertriglyceridemia, 28 (23.3%) cases were due to gallstone, 2 (1.7%) cases were due to alcohol.All the patients had abdominal pain followed by nausea or vomiting 95.8%, fever 32.5% and jaundice 18.3%. (Table I).

Out of 120 patients 78 (65.0%) had diabetes, 20 (16.7%) were smoker, 23 (19.2%) were obese, 6 (5.0%) had history of taking diuretics, 63 (52.5%) had no complications and 57 (47.5%) had different complications. (Table II).

According to the revised Atlanta classification, 63 (52.5%) patients had mild acute pancreatitis, 34 (28.3%) patients had moderately severe acute pancreatitis and 23 (19.2%) patients had severe acute pancreatitis (Figure 1).

Statistically significant difference was found with NLR and CAR between mild acute pancreatitis and moderate-severe acute pancreatitis. (Table III).

Sensitivity, specificity, PPV, NPV and accuracy at different cut-off values of NLR in predicting moderate-severe AP is tabulated above. NLR at a cut-off value of ≥5.72 showed sensitivity, specificity, PPV, NPV and accuracy as 80.7%, 76.2%, 75.4%, 81.4% and 78.3%. (Table V and Figure 2).

Fifty-seven patients had moderate-severe acute pancreatitis, among them NLR (Cut-off value ≥5.72) could detect 46 cases and among 63 patients of mild acute pancreatitis, NLR (<5.72) could detect 48 cases. (Table VI) and (Figure 3).

Sensitivity, specificity, PPV, NPV and accuracy at different cut-off values of CAR in predicting moderate-severe AP is tabulated above. A cut-off value of CAR ≥2.07 predicts moderate-severe AP with sensitivity, specificity, PPV, NPV and accuracy as 96.5%, 76.2%, 78.6%, 96.0% and 85.8% respectively (Table VIII).

Fifty-seven patients had moderate-severe acute pancreatitis among them CAR (Cut-off value ≥2.07) could detect 55 cases and among 63 patients of mild acute pancreatitis, CAR (<2.07) could detect 48 cases (Table IX).

Table I: Distribution of study population by demographic profile (N=120)

Characteristics		n (%)
Age (Mean±SD)		45.20±13.93
Age group		
	18-29 years	19(15.8)
	30-39 years	22(18.3)
	40-49 years	33(27.5)
	50-59 years	23(19.2)
	≥60 years	23(19.2)
Sex		
	Male	65(54.2)
	Female	55(45.8)
Etiology		
	Unknown	49(40.8)
	Hypertriglyceridemia	41 (34.2)
	Gallstone	28 (23.3)
	Alcohol	2(1.7)
Clinical features		
	Abdominal pain	120(100.0)
	Nausea and or vomiting	115(95.8)
	Fever	39(32.5)
	Jaundice	22(18.3)

Table II: Distribution of study population according to contributing factors and complications (N=120)

Characteristics		n (%)
Contributing factors		
	DM	78(65.0)
	Smoking	20(16.7)
	Obesity	23(19.2)
	Diuretics	6(5.0)
Complication		
	Without complications	63(52.5)
	With complications*	57(47.5)

* Peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, pleural effusion, ascites, renal failure, respiratory failure, shock, hypocalcemia etc.

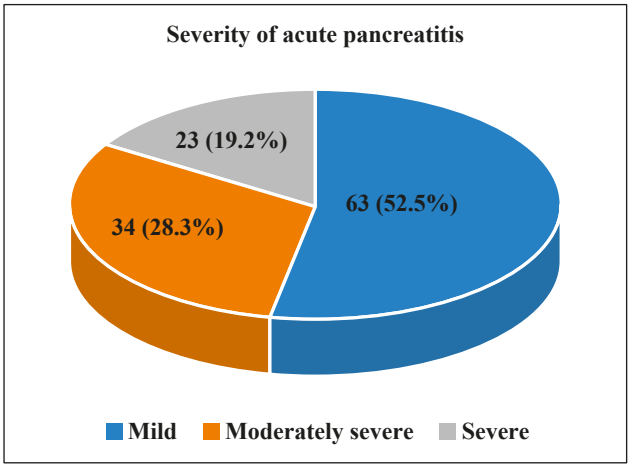

Figure 1: Distribution of study population according to severity based on revised Atlanta classification (N=120)

Table III: Association of NLR and CAR between mild and moderate-severe acute pancreatitis (N=120)

Score	Total	Mild AP (n=63)	Moderate severe AP (n=57)	P value*
NLR	6.63±3.34	**4.70±1.73**	**8.78±3.40**	<0.001
CAR	3.20±2.23	**1.51±1.34**	**5.09±1.31**	<0.001

NLR: Neutrophil to lymphocyte ratio; **CAR:** CRP to albumin ratio

*P value was determined by unpaired t-test.

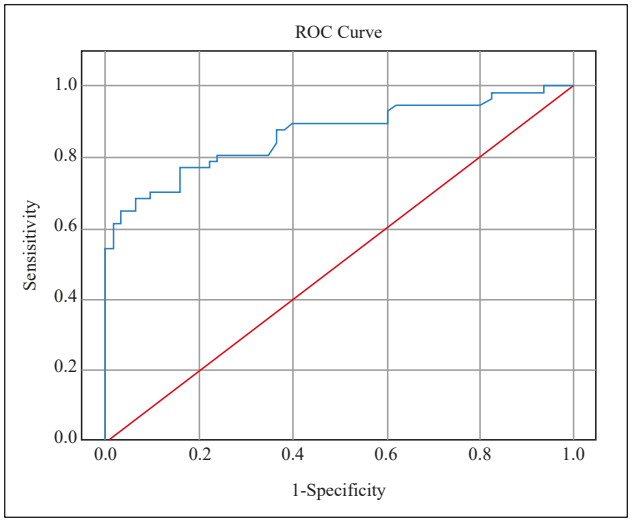

Figure 2: ROC curve analysis of NLR for predicting moderate-severe acute pancreatitis.

Table IV:Area under the curve of NLR for predictingmoderate-severe acute pancreatitis.

AUC	Std. Error	*P* value	95% CI Lower Bound	95% CI Upper Bound
0.865	0.034	**<0.001**	0.798	0.933

Table V: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy at different cut off values of NLRfor prediction of moderate-severe AP (N=120).

Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
≥5.44	84.2	63.5	67.6	81.6	73.3
≥5.65	80.7	73.2	73.0	80.7	76.7
≥5.72	**80.7**	**76.2**	**75.4**	**81.4**	**78.3**
≥5.90	78.9	77.8	76.3	80.3	78.3
≥6.01	77.2	77.8	77.2	77.8	77.5

PPV: Positive predictive value; **NPV:** Negative predictive value.

Table VI: Cross tabulation of moderate-severe acute pancreatitis with NLR based on derived cut off value (N=120)

NLR	Moderate-severe AP	Mild AP	Total
≥5.72	46	15	61
<5.72	11	48	59
	57	63	120

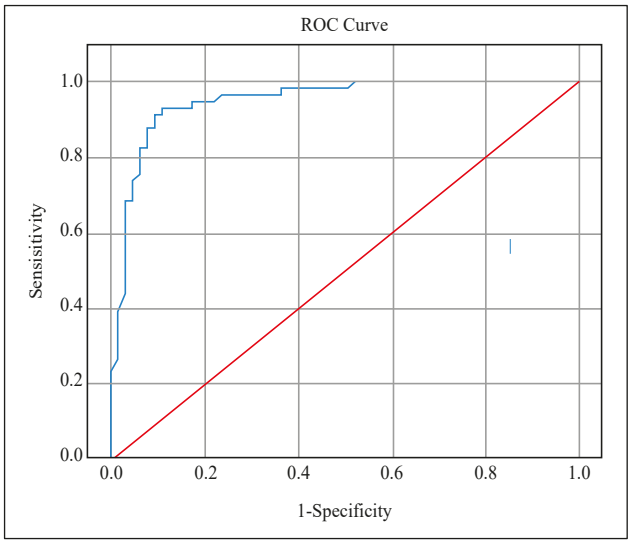

Figure 3: ROC curve analysis of CAR for predicting moderate-severe acute pancreatitis.

Table VII: Area under the curve of CAR for predicting moderate-severe acute pancreatitis

AUC	Std. Error	*P* value	95% CI Lower Bound	Upper Bound
0.949	0.020	<0.001	0.910	0.988

Table VIII: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy at different cut off values of CAR for prediction of moderate-severe AP (N=120).

Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
≥1.67	98.3	63.5	70.9	97.6	80.0
≥1.95	96.5	68.3	73.3	95.6	81.7
≥2.07	**96.5**	**76.2**	**78.6**	**96.0**	**85.8**
≥2.34	94.7	82.5	83.1	94.6	88.3
≥2.50	93.0	82.5	92.9	82.5	87.5

PPV: Positive predictive value; **NPV:** Negative predictive value.

Table IX: Cross tabulation of moderate-severe acute pancreatitis with CAR based on derived cut off value (N=120)

CAR	Moderate-severe AP	Mild AP	Total
≥2.07	55	15	70
<2.07	2	48	50
	57	63	120

DISCUSSION

Acute pancreatitis is an inflammatory process in which local pancreatic injury leads to systemic inflammation through cytokine cascade activation.[19] The severity of acute pancreatitis is related to extra pancreatic 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 (SIRS) or multi-organ dysfunction syndrome (MODS).[1,3,4,20] The aim of this study was to evaluate the role of NLR and CAR for early prediction severity in AP.

Total 120 patients with acute pancreatitis, who fulfilled the inclusion criteria, were taken for the study. Most of the patients were in 40-49 years of age (27.5%) followed by 50-59 (19.2%) and ≥60 years (19.2%), 30-39 years (18.3%) and 18-29 years (15.8%). Mean age was 45.2 ±13.93 years ranging from 19 to 75 years of age. Study conducted by Mukherjee et al and Datta et Al., found mean age of their study acute pancreatitis cases 44.40±10.80 years and 44.25±2.70 years respectively.[2],Another study conducted by Hasan and associates found majority of their study cases were in 5th and 4th decades.[20] All these findings are nearly consistent to the findings of this study.

Majority of the study subjects were male 65 (54.2%) with 1.18:1 male female ratio. Hasan et al, Haque et al and Rahman et al also found maximum of their study cases were male.[21,22,23]

In this study, all the patients had abdominal pain (100.0%), 96.79 % had nausea or vomiting, 32.5% had fever, 18.3% had jaundice.

Majority of, 49 (40.8%) cases were due to unknown etiology, 41 (34.2%) cases were due to hypertriglyceridemia, 28 (23.3%) cases were due to gallstone, 2 (1.7%) cases were due to alcohol. In many studies show that alcohol is the leading cause of acute pancreatitis, but socio-cultural & religious factor discourage alcohol consumption in our society.

According to revised Atlanta classification, 63 (52.5%) patients had mild acute pancreatitis, 34 (28.3%) patients had moderately severe acute pancreatitis and 23 (19.2%) patients had severe acute pancreatitis. In a previous study by Borges et al. observed 76.0% patients had mild acute pancreatitis, 12.0% had moderate acute pancreatitis and 12.0% patients had severe acute pancreatitis.[24] Another study by Barad et al. observed among 60 patients 31 patients were having mild form of acute pancreatitis whereas 29 patients were having moderately severe or severe form of the disease.[25] In a study by Bhanou et al. 47.7% had mild pancreatitis, 22.4% moderate and 29.9% severe pancreatitis.[18]

The NLR is a simple test that is inexpensive, routinely performed during the initial evaluation of patients, not affected by the volume status of the patient, and can be repeated easily.[4,26] In current study, mean value of NLR was 4.70±1.73 for mild acute pancreatitis and 8.78±3.40 for moderate to severe acute pancreatitis with statistical significance (p<0.001). A ROC curve analysis was performed to determine the cut-off value of the NLR in order to

distinguish mild and moderate acute pancreatitis according to revised Atlanta classification. The area under the ROC curve (AUC) of NLR was 0.865. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at different cut off values of NLR were calculated. At a cutoff value ≥5.44 were 84.2%, 63.5%, 67.6%, and 81.6%; at ≥5.65 were 80.7%, 73.2%, 73.0% and 80.7%; at ≥5.72 were 80.7%, 76.2%, 75.4% and 81.4%; at ≥5.90 were 78.9%, 77.8%, 76.3% and 80.3%; at ≥6.01 were 77.2%, 77.8%, 77.2%, 77.8% and 77.5% respectively for predicting moderate-severe AP.NLR was 4.804±5.79 and 8.54±3.49 for mild and moderate-severe acute pancreatitis which was also statistically significant found in the study.[30]Kokulu et al. showed NLR at 48 hours for mild acute pancreatitis was 2.42±2.0 and moderate-severe pancreatitis was 12.0±7.24 and the difference was statistically significance (p<0.001).[27] In ROC curve analysis for predicting moderate to severe pancreatitis showed an AUC 0.865 with p value<0.001. Among different cut-off values, for predicting moderate to severe pancreatitis value NLR at a cutoff value ≥5.72 had sensitivity 80.7% and specificity of 76.2% which was similar with Azab et al. (≥4.7) but lower than Jeon and Park (≥ 6.14).[28]However, Kaplan et al. reported a cut-off value of >13.64 for predicting SAP.[29] Further, Kokulu et al. reported sensitivity and specificity were 87.50% and 69.05%, respectively, when the NLR cut-off value was >7.13 and a 48-hour value of >6.2 with an AUC of 0.93.[27]In this study, at a cutoff point of 5.72 sensitivity (80.7%) & specificity (76.2%) with a PPV (75.4%) & NPV (81.4%). Jeon et al. in their study found that the ROC for the NLR predicting organ failure yielded an AUC of 0.62 (95% CI: 0.51-0.72). They demonstrated an optimal baseline NLR of 5.03 with sensitivity, specificity, PPV & NPV of 64.3%, 53.1%, 18.5% & 95.6% respectively for predicting development of organ failure.[30] ROC curve analysis results for NLR by Ilhan et al. showed that there was a significant prediction power of NLR for AP (R^2=0.842; P<0.001). For NLR parameter, if cut-off value is chosen to be 4.10, then sensitivity is 71.4% and specificity is 100 % in their findings.[31]

The novel inflammation-based score, the CRP/albumin ratio is believed to be a more useful indicator of the inflammatory status than CRP or albumin alone.[10] In this study, CAR (CRP/albumin ratio) was 1.51±1.34 (mean± SD) for mild acute pancreatitis and 5.09 ±1.314 (mean± SD) for moderate to severe acute pancreatitis which was also statistically significant (p<0.001).ROC curve evaluating the role of CAR in predicting severity of acute pancreatitis showed an AUC of 0.949 (95%CI ,0.910-0.988). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at different cut off values of CAR were calculated. At a cutoff value ≥1.67 were 98.3%, 63.5%, 70.9% & 97.6%; at ≥1.95 were 96.5%, 68.3% & 73.3%; at ≥2.07 were 96.5%, 76.2%, 78.6% & 96.0% and at ≥2.34 were 94.7%, 82.5%, 83.1% & 94.6%; at ≥2.50 were 93.0%, 82.5%, 92.9%, 82.5%, 87.5% respectively for predicting moderate-severe AP. ROC curve revealed a cutoff point of ≥2.07 with highest sensitivity (96.5%) & specificity (76.2 %). Kutlu and Gokden reported that, CRP/albumin ratio had significant moderate correlation with Ranson, Atlanta and Baltahazar scores and hospitalization period in AP patients.[32] Similar with our results, Yilmaz et al reported that patients diagnosed with AP, CRP/albumin values value was significantly different between mild, moderate or severe AP groups.[17] Kaplan et al. reported that CAR ratio was a significant marker in predicting mortality.[16]Although the data regarding the CRP/albumin ratio in AP is limited, there are some studies regarding the CRP or albumin values in AP. C-reactive protein on 2nd day after disease onset is still considered to be one of the most commonly used biomarkers to predict the severity in acute pancreatitis.[33]A one-unit rise in the CRP/albumin ratio was shown to result in a 1.52-fold increase in mortality risk. Patients with a CRP/albumin ratio of >1.63 had a higher Ranson and Atlanta categorization than those with a CRP/albumin ratio of 1.63. Patients with a CRP/albumin ratio greater than 1.63 had a 19.3-fold increased risk of mortality.[16]

Conclusion

In this study, patients with moderate-severe acute pancreatitis had significantly higher level of NLR and CAR. Diagnostic accuracy of CAR was relatively higher than NLR (AUC:0.949vs 0.865). These easily accessible and low-cost inflammatory markers can be used as good predictors for severity assessment, managementand referral of risk patients to tertiary center.

Statement:

This work was carried out during the period of November 2019 to September 2021 as a thesis work for the partial fulfillment of Doctor of Medicine in Gastroenterology under Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. It was examined by appropriate board of examiners and declared passed.

Conflicts of interest: Nothing to declare

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