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Original Research Article

Novel Inflammatory Score: C-Reactive Protein/Albumin Ratio in Pancreatitis

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Abstract

Background and Objectives: To prevent the complications in pancreatitis, identification of the biomarker at an early stage for screening and prognosis is the need of time. CRP is an easily detectable positive acute-phase protein. A negative acute-phase protein albumin is an indicator of nutritional status. Both independently can be used as prognostic markers. Based on these, combining inflammation and nutritional status, the novel inflammatory prognostic score CAR (CRP/albumin ratio), can be studied in the pancreatitis patients. We planned this study to evaluate the relationship between CAR, amylase, lipase and severity of pancreatitis.

Objectives:

1. To associate CAR score and enzymatic biomarkers.
2. To classify pancreatitis based on pain in abdomen and its association with CAR.

Observation and Results: The result of biochemical parameters like albumin, CRP, amylase, lipase was obtained after processing samples on autoanalyzer in 75 clinically diagnosed cases of pancreatitis. The correlation between the calculated ratio, CAR with biochemical parameters was done along with universal pain symptom severity score. The mean value of CAR was found as 2.204 mg/g. The mean age in yrs was 43.42 yrs, Pain score 0.96, CRP 64.55 mg/L, albumin 3.54 g/dl, amylase 292.468 U/L, lipase 512.36 U/L.CAR was positively correlated with age in yrs, CRP negatively correlated with albumin, amylase, lipase. CAR was found to be highly statistically

significant with CRP and albumin with p value < 0.001. No statistically significant correlation between the universal pain score and CAR, serum albumin, serum amylase and serum lipase was found.

Interpretation and Conclusion: CAR (CRP/albumin ratio) can be used as a novel, promising, easy, repeatable, cost effective, mathematical, inflammatory and comprehensive score as a predictive marker of pancreatitis severity before going for invasive and costly radiological investigations as it is derived from routinely done laboratory parameters.

Keywords: CRP/Albumin ratio, Pancreatitis, Amylase, Lipase, Pain score.

Introduction

The pancreas is an intraabdominal organ secreting several digestive enzymes into the pancreatic ductal system which ultimately empties it into the small bowel. [1] Pancreatitis is the clinical condition characterized by inflammation of pancreatic parenchyma. There are two types: Acute and chronic pancreatitis. Pancreatitis is a disease with high morbidity which affects nearly 0.15% of the world population. Global Burden of Disease study (2015) has reported that there are about 8.9 million cases of Pancreatitis with132,700 deaths worldwide. [2] A South India based tertiary care centre had reported 13.3% rise from 2000-06 to 2007-13. [3]

Acute pancreatitis is sudden inflammation of the pancreas usually manifesting as an upper abdominal pain radiating to the back [1] and of highly variable severity, ranging from mild cases with low mortality to severe cases with high mortality, sometimes life threatening also. [4] Based on the revised Atlanta classification, acute pancreatitis is diagnosed by two of the three criteria: typical belt-like abdominal pain, elevated serum lipase, amylase levels or radiological imaging signs of pancreatitis. [5] The severity can be given as mild when there are no local complications, systemic complications, or organ failure. In moderately severe cases, local or systemic complications or transient organ failure is found. Persistent organ failure is found in severe acute pancreatitis. [1] Mortality ranges from 3 to 17 percent in patients who develop pancreatic necrosis [6].

Chronic pancreatitis is considered as the disease continuum where permanent damage to the pancreas can occur with repeated attacks of acute pancreatitis. Alcohol abuse, smoking, gallstones, hypertriglyceridemia, endoscopic procedures (ERCP) induced cell injury, abdominal trauma, drugs, autoimmune diseases, predisposing genetic mutations, infections, etc. are etiological factors responsible for acute and chronic pancreatitis. [7] Thus it is very important to identify the acute or chronic pancreatitis in an early stage to prevent the complications like pancreatic necrosis, pseudocyst of pancreas, pancreatic cancer, etc.

As pancreatitis is inflammatory in nature, various inflammatory markers like CRP (C-reactive protein), procalcitonin, Tumour necrosis factor, albumin, etc. have been studied with respect to their utility in diagnosis, prognosis and predicting the severity so that the respective preventive, therapeutic roles, and treatment modifications can be studied in these patients. CRP is an easily detectable acute-phase protein synthesized by the liver in response to infection, trauma, etc.so it is

considered as a marker. [8-10] CRP is considered as the gold standard with a cut-off value of 150 mg/ml 48 h after the disease onset to evaluate disease severity and treatment effectiveness. [4]

The most abundant plasma protein, Albumin (ALB), synthesized by the liver, an indicator of human nutritional status, [11] is a negative acute-phase protein showing decreased levels in acute inflammation. It can be used as a prognostic marker in patients with inflammation and infection. [12]

With inflammation and infection, serum CRP increases and albumin decreases. The combination of inflammation and nutritional status can be studied by the novel inflammatory prognostic score, CAR (CRP/albumin ratio) in pancreatitis patients. Mustafa Kaplan (2017) [30] *et al*. studied that the CAR is a novel, promising, easy-to-measure, repeatable and non-invasive inflammation-based prognostic score in acute pancreatitis.

There are very few studies which have studied the relationship between CAR and amylase, lipase levels and the severity of pancreatitis. Thus, to address this need we thought of planning this prospective study.

Aim and Objectives: To evaluate the relationship between CAR (CRP/albumin ratio) and enzymatic biomarkers (amylase, lipase) in adults diagnosed with pancreatitis by revised Atlanta guidelines in a tertiary care Hospital.

Objectives

1. To measure the enzymatic biomarkers (amylase and lipase) in adults diagnosed with pancreatitis.
2. To estimate and calculate CAR (CRP/albumin ratio) in adults diagnosed with pancreatitis.
3. To study the association between the CAR (CRP/albumin ratio) and enzymatic biomarkers (amylase and lipase)
4. To classify diagnosed pancreatitis cases as mild, moderate, and severe based on pain in abdomen
5. To study the association between the CAR (CRP/albumin ratio) and with symptom severity.

Material and Methods

Study Design:

The study was conducted in the department of Biochemistry, Medicine, Surgery and Gastroenterology, tertiary care Hospital. Study type was prospective, cross sectional, observational, hospital based, single centre study. The study duration was of 5 months from May 2022 to September 2022.Study Population included the participants visiting the OPD and IPD sections of the Department of Medicine, Surgery and Gastroenterology, tertiary care centre.

Study Methodology

The written informed consent was taken. The inclusion and exclusion criteria were adhered. The participants had undergone the detailed history taking and the physical examination.

The approval was taken from the institutional ethics committee before starting the actual research work. (with a reference letter no. BVDTUMC/IEC/27, dated 25.4.2022)

Diagnosed cases of pancreatitis with (age ≥18 years) of either gender by revised Atlanta guidelines [(5)] following below mentioned two out of three criteria, were included the study.

1. Typical belt-like abdominal pain,

2. Elevated serum lipase, amylase levels

3. Radiological imaging signs of pancreatitis

Participants were classified based on symptom severity i.e. pain in abdomen into mild, moderate and severe.

Inclusion Criteria: Clinically diagnosed cases of pancreatitis of both genders with age more than 18 years were included in the study.

Exclusion Criteria: Known cases of Malignancy, severe systemic disorders (cardiac, hepatic, gastrointestinal, neurological, or renal), autoimmune disorders, endocrine disorders, women with pregnancy were excluded from the study.

Sample Size:

SD was estimated using the range of CRP/ALB ratio [34] which is 0.8825 using the formula

SD=Range /4

Absolute Difference =0.2, Confidence Interval=95%, SD=0.8825

Using 95% of confidence interval, minimum sample size was obtained as **Sample Size=75**

Clinical Examination: All the participants had undergone the detailed clinical examination. Blood sample was collected for biochemical investigations. All the biochemical investigations were performed after quality control run for the parameters under study as per routine QC schedules of the laboratory.

Sample Collection

Under all aseptic precautions,2 ml of the blood sample was collected from the antecubital vein without occlusion in plain vacutainers and was used for the following biochemical investigations.

Table 1

Sr No	Parameter	Method/Technique	Instrument Name
1	Serum Amylase total	Enzymatic (CNPG3 Substrate)	Abbott Alinity ci Integrated Platform (Automated Biochemistry Analyser)
2	Serum Lipase	Enzymatic Kinetic Colorimetric	
3	Serum CRP	Immunoturbidimetry	
4	Serum Albumin	Bromocresol Green (BCG)	

Amylase: The Principle of the procedure: α-Amylase hydrolyzes the 2-chloro-4-nitrophenyl-α-D-maltotrioside (CNPG3) to release 2- chloro-4-nitrophenol (CPNP) and form 2-chloro-4-nitrophenyl-α-D-maltoside (CNPG2), maltotriose, and glucose. The rate of formation of the 2-chloro-4-nitrophenol can be detected spectrophotometrically at 404 nm wavelength to give a direct measurement of α-amylase activity in the sample.

Methodology: Enzymatic (CNPG3 Substrate) [35]

Lipase: The Principle of the procedure: The method for the determination of lipase is based on the cleavage of specific chromogenic lipase substrate 1,2-O-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin)-ester emulsified in stabilized microparticles. In the presence of specific activators of pancreatic lipase as colipase, calcium ions and bile acids, the substrate is converted in 1,2-O-dilauryl-rac-glycerol and glutaric acid-6'-methylresorufin-ester which decomposes spontaneously in glutaric acid and methylresorufin. The increase of absorbance, due to methylresorufin formation, is proportional to the activity of lipase in the sample.

Methodology: Kinetic colorimetric [35]

C-Reactive Protein (CRP): The Principle of the procedure: An antigen-antibody reaction occurs between CRP in the sample and anti CRP antibody which has been adsorbed to latex particles, agglutination results. This agglutination is detected as an absorbance (572 nm wavelength), with the rate of change being proportional to the quantity of CRP in the sample.

Methodology:
Turbidimetric/Immunoturbidimetric [36]

Albumin: The Principle of the procedure: The Albumin BCG procedure is based on the binding of bromocresol green specifically with albumin to produce a coloured complex. The absorbance of the complex at 628 nm wavelength is directly proportional to the albumin concentration in the sample. Methodology: Bromocresol Green (BCG) [35] We calculated the CRP/ALB ratio (CAR) as dividing the CRP level (mg/L) by the serum albumin level (g/dl). [37]

The Statistical Analysis

All the statistical analysis was done using SPSS (Statistical Package for social sciences) software version 28.0 (IBM, Armonk, NY, The USA). Frequency and percentages were shown by categorical variable results. Descriptive statistics were shown by continuous variable results. Pearson Correlation Coefficient /Spearman correlation was used to test correlation between different continuous variables. 5% level of significance was used. All results were shown with 95% of confidence. ANOVA test was used to study the association amongst groups. P <0.05 was considered as statistically significant.

Observations and Results

In our study, we collected data for 75 clinically diagnosed cases of pancreatitis patients of both genders with age more than 18 years which included 29 females (38.7 %) and 46 males (61.3 %). The mean age of the patients was 43.42 ±16.15 years. A percent of males was found to be affected more (61.3%) as compared to females.

We found the mean value of CAR as 2.204 mg/g (0.22-171.31). The mean value of age in yrs was 43.42 yrs. Pain score was 0.96. Serum CRP was 64.55 mg/L. Serum albumin was 3.54 g/dl. Serum amylase was 292.468 U/L and serum lipase as 512.36 U/L.

We found that there was a negative correlation of serum albumin, serum amylase and serum lipase and a positive correlation with CRP(r=0.178) and CAR(r=0.182) with age in yrs. The p value of age in years was statistically significant for serum albumin with Pearson correlation coefficient(r=0.246).

Serum CRP was positively correlated with age in yrs and CAR while negatively correlated with serum lipase, serum amylase and serum albumin. Serum CRP was highly statistically significant with the p value <0.001 with CAR and significant with serum albumin with p value 0.012.

Serum albumin was positively correlated with serum amylase and serum lipase levels while negatively correlated with age, CAR, and serum CRP. Serum albumin was highly statistically significant with CAR with P value <0.001 and statistically significant with serum CRP. Serum albumin was found to be statistically significant with the p value of 0.035 with age in yrs.

As shown in Table no.2, CAR was found to be positively correlated with age in yrs, serum CRP and negatively correlated with serum albumin, serum amylase, serum lipase levels. The CAR was found to be highly statistically significant with serum CRP (r=0.938) and serum albumin (r=0.393) with the p value of <0.001.

Table 1: Correlation between various Parameters

Sr No		N=75	Serum CRP mg/L	Serum Albumin g/dl	CAR	Serum Amylase U/L	Serum Lipase U/L
1	**Age in yrs**	Pearson Correlation	0.178	-.246*	0.182	-0.078	-0.055
		p-value	0.128	**0.035**	0.12	0.509	0.640
2	**Serum CRP mg/L**		**Age in yrs**	**Serum Albumin g/dl**	**CAR**	**Serum Amylase U/L**	**Serum Lipase U/L**
		Pearson Correlation	0.178	-.289*	0.938**	-0.114	-0.094
		p-value	0.128	**0.012**	**<0.001**	0.329	0.422
3	**Serum Albumin g/dl**		**Age in yrs**	**Serum CRP mg/L**	**CAR**	**Serum Amylase U/L**	**Serum Lipase U/L**
		Pearson Correlation	-0.246*	-0.289*	-0.393**	0.089	0.06
		p-value	**0.035**	**0.012**	**<0.001**	0.447	0.609
4	**CAR**		**Age in yrs**	**Serum CRP mg/L**	**Serum Albumin g/dl**	**Serum Amylase U/L**	**Serum Lipase U/L**
		Pearson Correlation	0.182	0.938**	-0.393**	-0.108	-0.085
		p-value	0.120	**<0.001**	**<0.001**	0.357	0.466
5	**Serum Amylase U/L**		**Age in yrs**	**Serum CRP mg/L**	**Serum Albumin g/dl**	**CAR**	**Serum Lipase U/L**
		Pearson Correlation	-0.078	-0.114	0.089	-0.108	0.961**
		p-value	0.509	0.329	0.447	0.357	**<0.001**
6	**Serum Lipase U/L**		**Age in yrs**	**Serum CRP mg/L**	**Serum Albumin g/dl**	**CAR**	**Serum Amylase U/L**
		Pearson Correlation	-0.055	-0.094	0.06	-0.085	0.961**
		p-value	0.64	0.422	0.609	0.466	**<0.001**

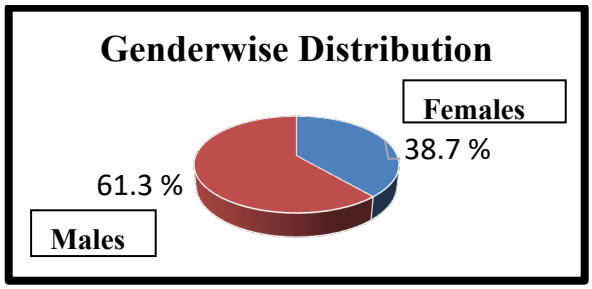

Figure 1: Gender-wise Distribution

Table 2: Relationship between CRP /Alb ratio and other parameters

S. N.		CRP/Albumin Ratio	
		r	P value
1	**Age in yrs**	0.182	0.120
2	**Serum CRP mg/L**	0.938	**<0.001**
3	**Serum Albumin g/dl**	-0.393**	**<0.001**
4	**Serum Amylase U/L**	-0.108	0.357
5	**Serum Lipase U/L**	-0.085	0.466

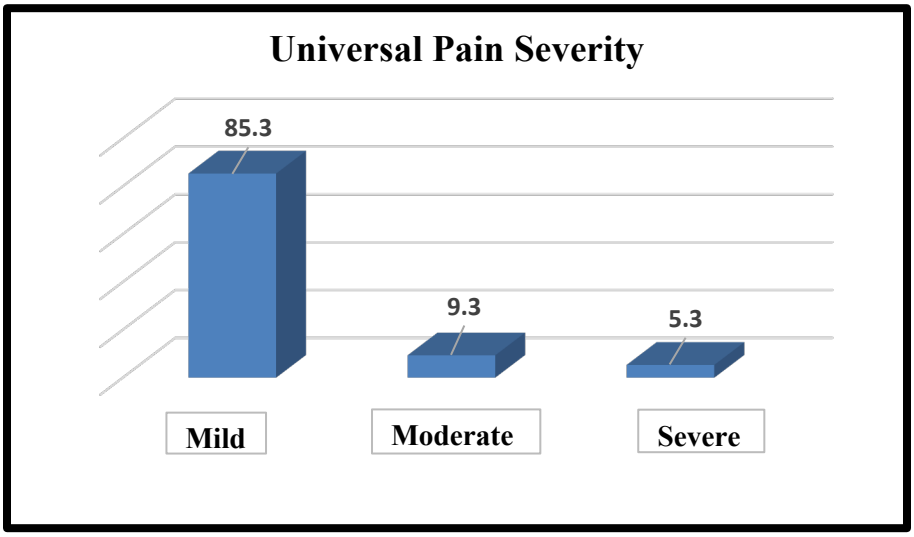

Figure 2:Universal Pain Severity

Serum amylase was found to be negatively correlated with age in yrs, serum CRP, CAR and positively with serum albumin, serum lipase. Serum amylase was highly statistically significant with p value<0.001 with serum lipase.

Serum lipase was positively correlated with serum albumin, serum amylase levels and negatively correlated with age in yrs, serum CRP and CAR. We found the highly statistical significance of serum lipase with amylase with p value <0.001.

The universal pain score was found to be negatively correlated with age is yrs, serum CRP, serum albumin, CAR and positively correlated with serum lipase and serum amylase with statistical significance. As shown in graph no II., mild pain severity was found to be highest (85.3 %) in patients with pancreatitis. The pain score was not

statistically significant with the other study parameters.

Discussion

We collected the data for 75 clinically diagnosed patients of pancreatitis. In our study, we found that the mean value of CAR as 2.204 mg/g (0.22-171.31). The mean age in yrs was 43.42, pain score 0.96, CRP 64.55 mg/L, albumin 3.54 g/dl, serum amylase 292.468 U/L, serum lipase 512.36 U/L. The CAR was positively correlated with age in yrs, CRP and negatively correlated with serum albumin, serum amylase, serum lipase levels. The CAR was found to be highly statistically significant with CRP (r=0.938) and albumin (r=0.393) with the p value less than 0.001.CRP was significantly negatively correlated with albumin. The median value of the CAR was 1.64 and the cut off was found to be 1.89 in Uhl *et al*.[38] study and authors suggested that based on the CAR and Glasgow Prognostic Score, other prognostic scores can be explored.

CRP is the widely utilized biomarker in clinical practice for acute pancreatitis. CRP rises steadily with severity. It is commonly used because it is inexpensive and readily available [39-41] CRP is an acute-phase protein produced by hepatocytes. It is recognized as a prognostic factor for malignancy [42]. The first study on the role of CRP in prediction of the outcome of acute pancreatitis was conducted by Mayer *et al*. [43] with conclusion that the increased levels of CRP may predict the severity of acute pancreatitis. Yu *et al*., retrospectively studied 159 hypertriglyceridemia induced pancreatitis Chinese patients and found that CRP has a predictive value and high CRP and BMI are risk factors for severe hypertriglyceridemia induced pancreatitis [44]. CRP levels of > 150 mg/L 48 h after the onset of symptoms have a high sensitivity for predicting the severity of acute pancreatitis. A rise of > 90 mg/dl from admission or an absolute value of > 190 mg/dl at 48 h predicted severe disease [45].

Vasudevan *et al*. [46] evaluated the early risk assessment of acute pancreatitis and Miko *et al*. [47] evaluated the severity and mortality related with the acute pancreatitis by comparing various scores and biochemical markers. They verified that CRP presented an AUC of 0.73, with a sensitivity and specificity of 71% and 87%, respectively. Farkas *et al*.[48] developed a multicenter study to assess the role of CRP as a tool to include patients in clinical trials. CRP is the most promising biochemical marker, with many studies showing a correlation of higher levels with pancreatic necrosis development and a severe acute pancreatitis course [41]. In obesity and/or alcoholism induced liver disease CRP levels are influenced [49]. Though non-specificity, late peak (48 to 72 h), not associated with the infection [50] are the major disadvantages of CRP, it is widely used in clinical practice.

Cardoso *et al.* [51] study concluded that within 48 h of admission, the combined detection of CRP and procalcitonin can be more valuable for predicting moderate and severe acute pancreatitis.

Increased CRP levels was associated with decreased survival but the survival was always lower in the context of lower albumin levels. The combination of CRP with albumin, as in the Glasgow Prognostic Index was found to be significantly associated with survival. [52] According to Banks *et al*. [53] during the early phase of acute pancreatitis, systemic disturbances are provoked by local pancreatic injury. In this phase, SIRS is the clinically manifestation by local inflammation induced cytokine cascade activation. There is an increased risk of developing multiorgan dysfunction, if SIRS (_>2) persists for more than 48 hr after admission.

Albumin is a stable and very flexible heart-shape-molecule with 585 residues and three domains of similar size, each one containing two sub-domains [54]. It has a median half-life around 18 to 19 days and synthesized only by liver at a rate of 9 to 14 g per day in healthy individuals [55]. Albumin is catabolized in most organs of the body at a similar rate by endocytic vesicles uptake on the endothelial surface and finally turn into amino acids as breakdown products [56-58].

Albumin levels in the blood decreases during inflammation. Due to its relationship between inflammation and malnutrition, albumin is associated with inflammation severity, the disease prognosis and mortality [59]. Hypoalbuminemia due to capillary leak resulting from inflammatory processes is very common in acute pancreatitis and represents as an independent risk factor for severity and mortality. Hypoalbuminemia signals clinical worsening and guide in identifying high-risk acute pancreatitis patients. The missed opportunity to frequently measure serum albumin delays timely intervention. Thus, it is recommended that routine monitoring of serum albumin should be done as hypoalbuminemia during hospitalization is associated with severity and mortality. This suggests that there is need for albumin administration as a therapeutic intervention in acute pancreatitis. Based on these, suggestions given are (1) Albumin levels should be measured for all acute pancreatitis patients, (2) albumin levels should be controlled at least in those patients whose condition is worsening and (3) albumin administration should at least be considered in patients with severe hypoalbuminemia (< 25 g/L). A few studies have evaluated hypoalbuminemia as a predictor of severe acute pancreatitis [60]. Hong *et al*. [61] concluded that hypoalbuminemia within 24 hr of hospital admission is independently associated with increased risk of the development of persistent organ failure and death in acute pancreatitis. Shoukang Li *et al*. (2017) [62] studied that albumin is a valuable tool for a rapid assessment of persistent organ failure in patients with acute pancreatitis.

Albumin has been suggested as a predictive factor for the severity of acute pancreatitis [59]. Hypoalbuminemia predominantly reflects malnutrition as well as inflammatory condition and was found to be associated with the impaired survival outcome of cancer patients [63]. Albumin was found as an independent predictor of severe acute pancreatitis and in-hospital mortality in acute pancreatitis patients. [64]

As an acute phase reaction due to the inflammatory response of hypertriglyceridemia, a decrease of albumin due to increased vasopermeability allowing more albumin to permeate into the extravascular tissue space may result in accumulation of free fatty acids contributing to the inflammatory progression [65].

A novel combination model based on inflammation and nutrition, CRP and albumin—CRP/Alb ratio (CAR) is considered as a predictor of a clinical outcome in patients with serious infectious diseases, cancers, [66,67] and sepsis [68]. The CAR indicates dynamic changes of systemic inflammation. [41]

He *et al*. [69] investigated the role of CAR in nonmetastatic NPC and found that CAR has a prognostic value in nonmetastatic NPC.

Wang *et al* [70] showed that low albumin and high CRP were markers of the poor outcome and this supported the idea that CRP and albumin could be used for predicting the mortality risk in acute pancreatitis patients.

Fairclough *et al*. [71] proposed the concept of use of CAR for acute medical admissions. Kim *et al* [65] showed that the CRP/albumin ratio was superior to the CRP level in predicting mortality in patients with septic

shock and asserted that a CAR > 5.09 yielded the highest sensitivity and specificity in predicting the 180-day mortality of patients with sepsis. Ranzani *et al*. [72] observed lower survival in septic patients with a CAR > 2.

Consistent with Ferreira's study, CAR, Atlanta and Ranson scores, presence of necrosis was found to be an independent risk factors of mortality. [73] Atlanta classification, another global standard tool for assessment of acute pancreatitis severity were found to be complex for interpretation due to confusing terms related to disease severity. The Ranson score has been used in the acute pancreatitis prognosis for more than three decades with its biggest disadvantage that it requires 48 hours for assessment. So based on study data, authors found that the CAR was directly related and may be useful for prognostic purposes in acute pancreatitis.[74] Disadvantages of the time-tested scores such as Ranson score, Atlanta classification guidelines which are used in pancreatitis are :1. These need at least 48 hrs for interpretation, 2. Need to get the data like which is not routinely done.3. Many parameters are included like glucose, platelet count, etc.

CAR ratio usage would offer a variable capable of combining the information of inflammation and nutrition provided by CRP and albumin, i.e., a higher ratio indicates a higher inflammation status. [75]

The universal pain score was found to be negatively correlated with age is yrs, serum CRP, serum albumin, CAR and positively correlated with serum lipase and serum amylase with statistical significance. The mild pain severity was found to be highest (85.3 %) in patients with pancreatitis. The pain score was not statistically significant with the other study parameters.

We did not find any study with respect to study the correlation between CAR and enzymatic markers i.e. Serum amylase and serum lipase. In our study, we found that there is a negative correlation of CAR with the enzymatic markers i.e. Serum amylase and serum lipase. This correlation needs to be explored further with larger sample size.

Limitations: Study duration was less so we could not explore the CAR association with pancreatitis outcome, other etiological factors, other routinely used scores like Ranson score etc. and could not calculate the cut off value, sensitivity, specificities, etc.

In conclusion, 1. The CAR can be used as the good prognostic marker of severity of pancreatitis.2. CAR is an easy, repeatable, cost effective mathematical inflammatory ratio which can be used along with other scores as a predictive marker of pancreatitis severity and outcome.3.It can be considered as a candidate biomarker for screening the worst pancreatitis cases before going for invasive and costly radiological investigations for predicting the prognosis as it is derived from routinely done laboratory parameters.4.CAR can be used along with time tested scores like Ranson score, Atlanta score over their disadvantages as a screening tool or for predicting the pancreatitis symptom severity due to its advantages of being calculated from routinely done parameters, easy and cost effective and can be considered as candidate biomarker.

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