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RESEARCH ARTICLE

EVALUATION OF PROGNOSTIC SIGNIFICANCE OF HYPOCALCAEMIA AND HYPOALBUMINEMIA IN PATIENTS WITH ACUTE PANCREATITIS: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background: Acute pancreatitis is the leading cause of gastrointestinal-related hospitalizations worldwide and its frequency is continuing to rise. While diagnosis of acute presentation is relatively simple, the major challenge is the progression of the disease course and outcome. Hypocalcemia and hypoalbuminemia are frequently associated with severe pancreatitis. Therefore, in our study, we aimed to evaluate the prognostic significance of hypocalcemia and hypoalbuminemia in acute pancreatitis.

Aims: To assess the prognostic significance of hypocalcemia and hypoalbuminemia associated with acute pancreatitis in predicting the severity of the disease

Methodology: A prospective observational study was conducted with a total of 25 patients diagnosed with acute pancreatitis at J.J.M. Medical college, Davangere, Karnataka for a period of 6 months from April to September 2024. The ethical committee approval was obtained prior to conduct of study and written consent was taken from all the participants.

Results: The mean values of serum calcium, serum albumin and albumin corrected calcium was found to be 7.80 mg/dl, 3.52 g/dl, and 7.78 mg/dl respectively. The mean Ranson's score was found to be 1.84. Serum calcium showed sensitivity, specificity, PPV, and NPV values of 85%,72%,88%, and 100% respectively for predicting the severity of acute pancreatitis. Albumin corrected calcium showed sensitivity, specificity, PPV, NPV of 86%,83%,93% and 100% respectively. Ranson's score also showed sensitivity, specificity, PPV, and NPV values of 73%,78%,85% and 100% respectively for severity of acute pancreatitis.

Conclusion: Serum calcium and serum albumin obtained within the first 24 hours of admission were found to be useful predictors of severity of acute pancreatitis. They are easily available and comparable

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to the conventional prognostic scales in predicting the severity of acute pancreatitis. Therefore, they can be used as early predictors of severity of acute pancreatitis thus enabling the initiation of early intensive care and treatment.

Introduction:-

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with varying involvement of other regional tissues or remote organ systems,[1] and it is defined as an acute condition presenting with abdominal pain and is usually associated with raised pancreatic enzyme levels in the blood or urine as a result of pancreatic inflammation.[2] There are many causes of acute pancreatitis, but the mechanisms by which these conditions trigger pancreatic inflammation have not been identified.[3] The estimated incidences of acute pancreatitis in industrialized countries is 10-20/100,000 per year.[4] However, its incidence generally varies in the range of 20 to 40 per 100,000 population. The overall mortality rate from acute pancreatitis has substantially dropped from >10% several years ago to less than 2% in recent years.[5]

Alcohol is a common cause of acute pancreatitis.[6] Alcoholic pancreatitis is more common in men and usually occurs in individuals with long standing alcohol abuse. Hypertriglyceridemia is the cause of acute pancreatitis in 1.3 to 3.8% of cases.[7] Approximately 2 to 5% of cases of acute pancreatitis are drug induced. Drugs cause pancreatitis either by a hypersensitivity reaction or by the generation of toxic metabolites.[8]

The diagnosis of acute pancreatitis is usually based on a combination of clinical findings, laboratory investigations, and imaging techniques. There is no gold standard test available for diagnosis at present.[9,10]Calcium plays a central role in the pathogenesis of pancreatitis. Calcium is required for normal secretory function of the pancreatic acinar cells, but these signals are transient and mainly confined to apical pole. It has been shown that sustained global increase in cytosolic Ca^{++} is responsible for premature trypsinogen activation, vacuolization, and acinar cell death.[11]

Albumin can bind to an extremely wide range of endogenous and exogenous ligands to transport them to specific tissues and organs to increase their solubility in plasma or to dispose off when they are toxic. The chemical structure of albumin can be altered by some specific processes (oxidation, glycation) leading to rapid clearance and catabolism.Various diseases, including cancer, infections or other inflammatory conditions have been found to be frequently associated with low serum albumin levels. According toliterature reports, the phenomenon of hypoalbuminemia in these diseases is due to abnormal metabolism of albumin which is led by inflammatory response, as well as a low intake of proteins, thus indicating the severity of the disease.[12]

Furthermore, calcium binds to albumin and only the unbound (free or ionized) calcium is biologically active, therefore, the serum level must be adjusted for abnormal albumin levels. For every 1 g/dl drop in serum albumin below 4 g/dl, measured serum calcium decreases by 0.8 mg/dl. Literature reports evidenced that hypocalcemia is associated with hypoalbuminemia in severe pancreatitis; when correction of serum calcium is made for hypoalbuminemia, most patients are found to be normocalcaemic or eucalcemic in mild to moderate pancreatitis. The occasional hypocalcaemia as shown by the 'corrected' serum calcium or by serum ionized calcium measurement in mild or moderate pancreatitis is usually mild and transient, indicating that the normal homoeostatic mechanisms of the body can efficiently maintain the physiologically active fraction of the serum calcium within, or close to, the normal range when it is associated with mild pancreatitis.[13]

Several studies have been conducted to find the significance of serum calcium and corrected calcium levels in predicting the severity of acute pancreatitis.[14] Independently, hypocalcaemia has been evaluated as a mortality prognostic factor and it has also been evaluated as a predictor of severe pancreatitis with infection.[15] Hence the present study was designed with the main objective to assess the prognostic significances of hypocalcaemia and hypoalbuminemia in patients with acute pancreatitis.

Methodology:-

Study design and patients

This is a prospective observational study conducted with total of 25 patients diagnosed with acute pancreatitis at J. J. M. Medical College, Davangere, Karnataka, over a period of 6 months, from April 2024 to September 2024. A written informed consent was taken from all the subjects participating in the study. The ethical committee approval was obtained before the conduct of study.

Inclusion criteria

1. Age: ≥ 18 years
2. Diagnosed with acute pancreatitis based on the Revised Atlanta classification 2012
3. Who gave consent for participating in the study.

Exclusion criteria

1. Diagnosed with any acute or chronic illness
2. Previously treated for acute pancreatitis
3. Hypocalcemia due to other causes such as CKD, hypoparathyroidism, drug induced hypocalcemia
4. Other causes of hypoalbuminemia such as CLD, chronic inflammation, protein losing enteropathies or malignancy

Data collection and Assessment parameters

After obtaining informed consent, a detailed history was collected from qualifying patients using a pre-designed, structured proforma. Furthermore, general examination and a detailed systematic examination, followed by relevant investigations were conducted and the results were noted within 24 hours of admission, serum calcium, serum albumin, albumin corrected calcium were determined. Albumin corrected calcium (mg/dL) was calculated using the following formula: Albumin corrected calcium (mg/dL) = total calcium (mg/dL) + 0.8 × [normal albumin-serum albumin (g/dL)].[14]

Diagnosis of acute pancreatitis, its severity, and local and systemic complications were defined as per the Revised Atlanta Classification 2012. Scoring system like Ranson's score was also used in predicting the severity of acute pancreatitis. Ranson's score of "0–2", "3–4", "5–6" and "7–11" indicates low risk of mortality (0–3%), increased risk of severe pancreatitis and mortality (15%), high risk of mortality (40%), and nearly 100% risk of mortality respectively.[16]

Statistical analysis

Data were entered in Microsoft Excel 2021 and statistical analysis was done using IBM Statistical Package for Social Sciences (SPSS) version 22. Categorical variables were represented in the form of percentages and frequencies. Continuous variables were presented as descriptive statistics (Mean and Standard deviation). The one-way ANOVA, paired t-test and the chi-square test were employed to establish the statistical significance of the differences between groups. $p \leq 0.05$ was considered statistically significant. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was calculated for hypocalcemia and hypoalbuminemia.

Results:-

Majority of study subjects i.e., 36% each, belonged to age group of 21 to 30 years and 31 to 40 years with mean age of 35.56. The minimum and maximum age of study subjects enrolled in the study was found to be 24 years and 49 years respectively. All the study subjects enrolled were male (Table 1).

Table 1:-Distribution of study subjects based on demographic characteristics.

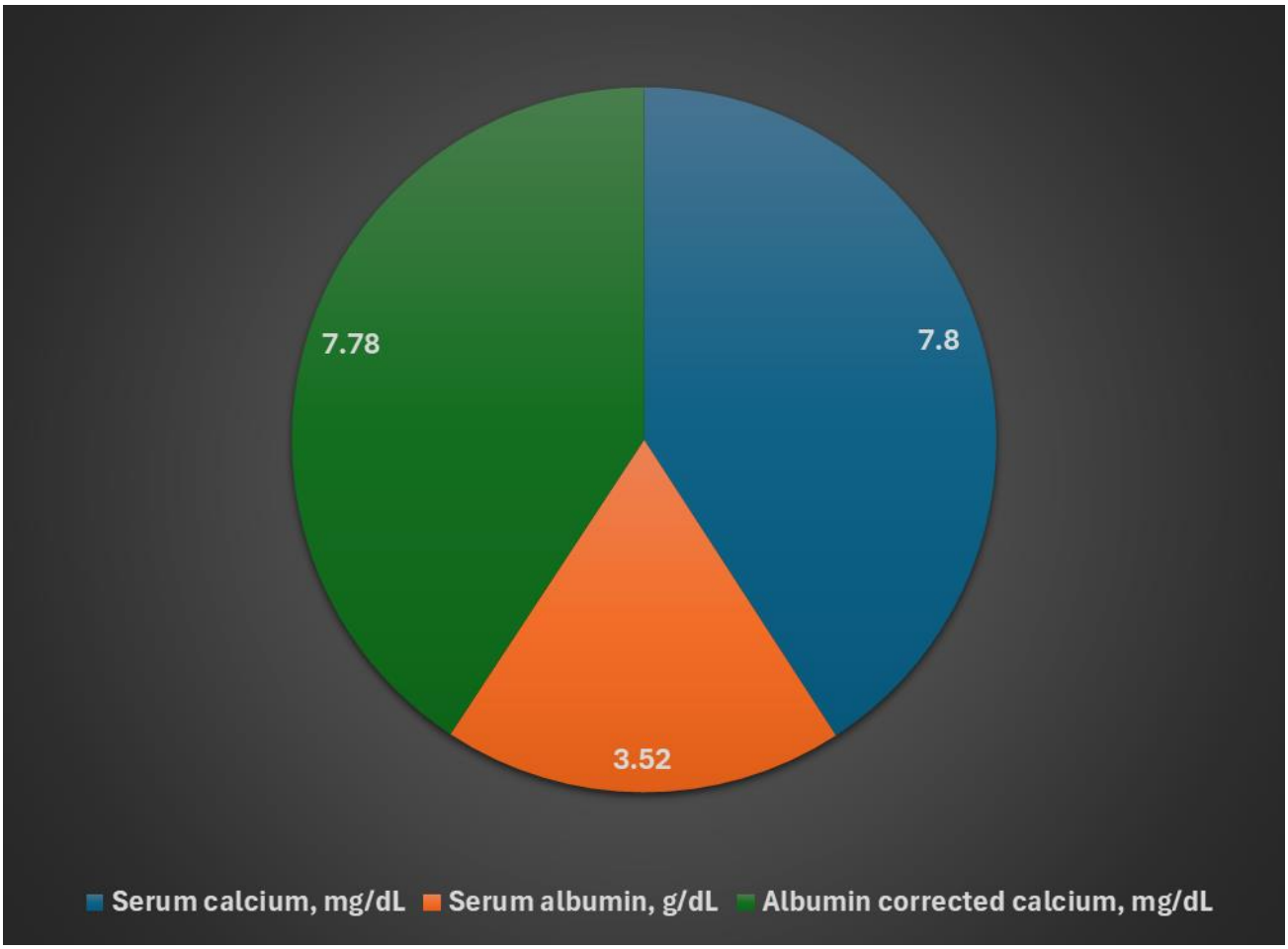
Variables	Frequency	Percentage
Age (Years)		
21 to 30	9	36.00
31 to 40	9	36.00
41 to 50	7	28.00
Mean ± SD	35.56 ± 7.12	
Minimum	24	
Maximum	49	
Gender		
Male	25	100.00

Female	0	0.00

The mean values for serum calcium, albumin, and albumin corrected calcium were found to be 7.80 mg/dL, 3.52 g/dL, and 7.78 mg/dL respectively (Table 2 and Figure 1).

Table 2:-Descriptive statistics of biochemical parameters.

Biochemical parameters	Mean ± SD	Range
Serum calcium, mg/dL	7.80 ± 0.44	7.12 – 8.52
Serum albumin, g/dL	3.52 ± 0.69	1.80 – 4.70
Albumin corrected calcium, mg/dL	7.78 ± 0.40	6.94–8.98



Values were expressed as mean

Figure 1:-Descriptive statistics of biochemical parameters.

The mean Ranson's score of study subject was found to be 1.84 and Ranson's score was distributed in the range of 0 to 5 (Table 3).

Table 3:-Descriptive statistics of Ranson's score.

Parameters	Mean ± SD	Range
Ranson's Score	1.84 ± 1.54	0.00 – 5.00

There was a non-significant (p=0.0.421) association found between Ranson's score and serum calcium values of study subjects (Table 4). These findings implied that there was an association found between serum calcium values with severity of acute pancreatitis and risk of mortality.

Table 4:-Association between serum calcium and Ranson's score.

		Serum calcium levels (mg/dL)			Total	p-value
		7-7.5	7.5-8.0	>8		
Ranson's Score	**0**	0	0	6	6	0.421
	1	0	3	3	6	
	2	1	4	0	5	
	3	2	1	1	4	
	4	1	1	0	2	
	5	2	0	0	2	
Total		6	9	10	25	

There was a non-significant (p=0.164) association found between Ranson's score and albumin corrected calcium values of study subjects (Table 5). These findings depicted thatthere was an association found between albumin corrected calcium values with severity of acute pancreatitis and risk of mortality.

Table 5:-Association between albumin corrected calcium and Ranson's score.

		Albumin corrected calcium levels (mg/dL)			Total	p-value
		7-7.5	7.5-8.0	>8		
Ranson's Score	**0**		4	2	6	0.164
	1	1	5	0	6	
	2	1	3	1	5	
	3	1	2	1	4	
	4	1	1	0	2	
	5	2	0	0	2	
Total		6	15	4	25	

The results of sensitivity, specificity, PPV, and NPV values assessed for predicting progression to severe pancreatitis was represented in Table 6. Results depicted that serum calcium showed sensitivity, specificity, PPV, and NPV valuesof 85%, 72%, 88%, and 100% respectively for severity of acute pancreatitis. Similarly, albumin corrected calcium showed sensitivity, specificity, PPV, and NPV values of 86%, 83%, 93%, and 100% respectively for the same. Ranson's score also showed sensitivity, specificity, PPV, and NPV values of 73%, 78%, 85%, and 100% respectively for severity of acute pancreatitis.

Table 6:-Sensitivity, specificity, PPV, and NPV values assessed for predicting progression of Acute pancreatitis.

Parameters	Sensitivity	Specificity	PPV	NPV
Serum calcium, mg/dL	85	72	88	100
Albumin corrected calcium, mg/dL	86	83	93	100
Ranson score	73	78	85	100

PPV, Positive predictive value; NPV, Negative predictive value

Majority of study subjects i.e., 56% stayed in the hospital for 4-7 days followed by 1-3 days (32%), and 8-10 days (8%). The mean hospital stay of study subjects was found to be 5 days. 84% of the study subjects condition improved on the day of discharge. However, 8% of the study subjects died due to complications of acute pancreatitis (Table 7).

Table 7:-Distribution of study subjects based on length of hospital stay and discharge status.

Variables	Frequency	Percentage
Length of Hospital Stay		
1 to 3 days	9	36.00
4 to 7 days	14	56.00
8 to 10 days	2	8.00
Mean ± SD	4.68 ± 1.93	

Minimum	2	
Maximum	10	
Status of Discharge		
Improved	21	84.00
Death	2	8.00
DAMA	2	8.00

DAMA, Discharge against medical advice

There was a non-significant (p=0.161) association found between Ranson's score and length of hospital stay of study subjects (Table 8). These findings depicted that there was an association found between severity of acute pancreatitis and duration of hospital stay of patients.

Table 8:-Association between Ranson's score and length of hospital stay.

		Length of hospital stay								**Total**	**p-value**
		2	**3**	**4**	**5**	**6**	**7**	**9**	**10**		
Ranson's Score	**0**	1	4	0	1	0	0	0	0	6	0.161
	1	1	2	1	2	0	0	0	1	6	
	2	0	0	1	3	1	0	0	0	5	
	3	0	0	0	2	1	0	1	0	4	
	4	0	0	0	0	1	1	0	0	2	
	5	0	1	0	0	0	0	1	0	2	
Total		2	7	2	8	3	1	1	1	25	

Discussion:-

Acute pancreatitis remains a common disease with mortality of severe attacks reaching as high as 30% to 50%.[17]This vulnerable group of patients need immediate diagnosis and grading of severity to be treated aggressively to prevent morbidity and mortality. Also, early identification of mild disease avoids unnecessary overtreatment, thus reducing cost of treatment. Therefore, in the current prospective observational study, we aimed to assess the prognostic significance of hypocalcaemia, and hypoalbuminemia associated with acute pancreatitis.

Results of our study revealed that majority of study subjects i.e., 36% each, belonged to age group of 21 to 30 and 31 to 40 years with the mean age being 35.56, and all the study subjects enrolled were male. The mean values for serum calcium, was found to be 7.80 mg/dL. The serum calcium showed sensitivity, specificity, PPV, and NPV values of 85%, 72%, 88%, and 100% respectively for severity of acute pancreatitis. Similarly, in a study conducted by Edakkepuram et al., on patients of acute pancreatitis showed that patients with mean calcium value of 6.9 developed significant complications whereas those with mean calcium value of 7.84 did not develop any complications.[18]

In our study, mean albumin corrected calcium was found to be 7.78 mg/dL and showed sensitivity, specificity, PPV, and NPV values of 86%, 83%, 93%, and 100% respectively for severity of acute pancreatitis. These high prediction levels and the ease in calculating them when the serum albumin level is known, make obtaining the albumin corrected calcium concentration worthwhile, since it considerably increases diagnostic accuracy.

The mean Ranson's score of our study subjects was found to be 1.84 and Ranson's score was distributed in the range of 0 to 5. Ranson's score also showed sensitivity, specificity, PPV, and NPV values of 73%, 78%, 85%, and 100% respectively for severity of acute pancreatitis. Furthermore, results on Ranson's score of study subjects in our study implied that subjects with Ranson's score of greater than 3 died due to complications of acute pancreatitis. Papachristou et al., showed that the sensitivity of Ranson's score in predicting the mortality is 100% which is similar to our study observations.[19]Moreover, Simoes et al., in their study demonstrated that Ranson's score has a sensitivity of 91.2% and specificity of 71.4% in predicting severity of pancreatitis.[20]

Hypocalcemia is one of the components of Ranson's scoring system done to assess the severity of pancreatitis. Ammori et al., reported that hypocalcaemia was more frequent during severe attacks as compared to mild attacks of pancreatitis (86% versus 39%).[21] Proposed mechanisms for hypocalcaemia in early phase are autodigestion of mesenteric fat by pancreatic enzymes and release of free fatty acids, which form calcium salts, transient

hypoparathyroidism, and hypomagnesemia.[22-24] Later stages of pancreatitis are frequently complicated by sepsis. Whitted et al., proposed that increased circulating catecholamines in sepsis cause a shift of circulating calcium into the intracellular compartment, leading to relative hypocalcemia. This causes increased parathyroid hormone secretion by negative feedback loop, leading to further increase in intracellular calcium overload, oxidative stress, and cell death.[25]

Conclusion:-

In conclusion, serum calcium and albumin-corrected calcium obtained within the first 24 hours of hospital admission are useful predictors of severity of acute pancreatitis. Hence, hypocalcemia and hypoalbuminemia could be used as prognostic markers of acute pancreatitis. Since, they are easily available and comparable to conventional prognostic scales in predicting the severity of acute pancreatitis, they can be used as early predictors of severity of acute pancreatitis, thus facilitating the initiation of early aggressive intensive care and treatment, leading to better patient outcomes.

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