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ROLE OF C-REACTIVE PROTEIN , PROCALCITONIN AND NEUTROPHIL LYMPHOCYTIC RATIO AS PREDICTOR OF SEVERITY AND PROGNOSIS OF GALLSTONE INDUCED PANCREATITIS

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ABSTRACT

Background: We aimed to explore the significance of procalcitonin (PCT), C-reactive protein (CRP) and neutrophil ratio (N%) in the early diagnosis, treatment, and prognosis of Gallstone Induced pancreatitis (GIP).**Methods:** A total of 40 patients with GIP were enrolled. The PCT and CRP in serum were detected by a full-automatic biochemical analyzer, and N% in peripheral blood was measured by a hemocyte analyzer. **Results:** The detection showed that the PCT, NLR ratio and CRP at Day 1 and CRP at Day 5 in the Severe group were significantly higher than those in the moderate severity . ($P < 0.001$). Taking baseline data and serological indicators as independent variables, and severe cases as a dependent variable, multivariate Logistic regression analysis showed that APACHE II score (P=0.001),, PCT at day 1 (P=0.012), CRP at day 1 (P=0.001), and NLR ratio at day 1 (P=0.001) were independent predictive factors for Severity **Conclusions:** Peripheral blood PCT, CRP, and N% contribute to the diagnosis and prognosis of GIP.

KEYWORDS

Gallstone induced pancreatitis, Procalcitonin, C-reactive protein, Neutrophil ratio, Diagnosis

INTRODUCTION

Gallstone induced pancreatitis" (GIP) is thought to be brought on by either the impaction of a gallstone in the ampulla of Vater, which can occur temporarily or over time, or by one or more gallstones passing through the intrapancreatic common bile duct and into the duodenum[1-2].

It is most common in women over 60, and the number of cases recorded each year is rising globally, potentially due to the obesity problem getting worse. Gallstone formation and GIP share many risk factors, including age, gender, obesity, pregnancy, genetics, family history, fasting and abrupt weight loss, and gallbladder stasis [3-8].

Up to 40% of instances of acute pancreatitis in the Western world are caused by gallstones [7].The annual risk of getting GIP is between 0.04% and 1.5% in cases of symptomatic gallstones, while the incidence of GIP is between 3% and 8% overall.[7- 8] Gallstones were linked to 47% of patients with acute pancreatitis in a recent Indian study. In addition, the GIP rate grew dramatically from 31% in 2015 to 52.4% in 2019.[9]After gallstones are linked to acute pancreatitis, 80% of people get a mild course of the illness, with 1% to 3% dying from it. Nonetheless, severe acute pancreatitis affects 20% of individuals, and fatality rates are close to 30%.[10]

Many severity rating systems have been developed to assist clinicians in triaging GIP patients and estimating their prognosis, due to the wide range of symptoms of GIP and its unclear pathogenesis.[10] Currently in widespread usage are the Glasgow- Imrie criteria [14], the Bedside Index for Severity in Acute Pancreatitis (BISAP) score [13], the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score [12], and the Ranson score [11]. These systems involve a lot of variables, which makes them time-consuming and challenging to apply to patients outside of intensive care units. Furthermore, they are not appropriate for evaluating patients at the time of admission or in the immediate aftermath. [15]

Anaerobic radioactive nucleic acids, proteolytic enzymes, and inflammatory cytokines are the first steps in the cascade of human inflammatory reactions that cause pancreatitis to damage tissue. Reducing the amount of incorrect pro-inflammatory mediators in the bloodstream is essential to the patient's recovery since, in extreme cases, local tissue damage is directly correlated with the balance of inflammatory factors.[16]

Tissue damage and acute inflammation are clearly associated with elevated levels of C-reactive protein (CRP), a type of inflammatory factor and a sensitive signal for the diagnosis of chronic inflammation. CRP is a marker reflecting inflammation.[17]

In healthy individuals , procalcitonin (PCT) is often undetectable, but it responds differently to infections and sepsis. Because it is rarely released into the blood, healthy individuals' serum concentration of it is relatively steady (<0.1 ng/mL). Pathogen-associated and damage-associated molecular patterns are seen in PCT pathologically. PCT is widely released into the blood from the cells of the thyroid, lung, liver, pancreas, colon, and other organs during the infection-induced systemic inflammatory response. [18]One helpful biological measure that helps distinguish between bacterial infectious diseases is PCT, which is particularly valuable in the diagnosis of sepsis. A small body of research supported PCT in the diagnosis of SAP, infected pancreatic necrosis (IPN), and mortality.[19]

Neutrophils make up the majority of leukocytes in the peripheral blood of healthy individuals, and their ratio is markedly elevated in bacterial infection and inflammation.The neutrophil-lymphocyte ratio (NLR) is a more complete biomarker that can be used to anticipate the severity of acute pancreatitis (AP) and respond quickly to the degree of inflammatory progression using neutrophil and lymphocyte counts. It is commonly known that AP is a pancreatic inflammation with a rapid start. Accurately predicting the severity of AP can help patients obtain appropriate treatment sooner, improving their prognosis. [20,21]

Considering the previously described background, the present investigation assessed the significance of c-reactive protein, procalcitonin, and neutrophil lymphocytic ratio as indicators of the severity and prognosis of pancreatitis caused by gallstones.

MATERIALS AND METHODS

The present Prospective observational study included 40 patients of gall stone induced pancreatitis admitted from OPD / Emergency/ transferred from other departments of CSSH Hospital attached to Netaji subhash Chandra bose Subharti Medical College, Meerut from February 2023 to August 2024

Patients >10 years of age Patients with clinical diagnosis of gall stone induced pancreatitis > 10 years of age , presenting within 5 days of onset of atleast 3 symptoms of gall stone induced pancreatitis including Fever Chills Jaundice Nausea/vomiting , Pain int upper abdomen and back that relived on bending forward ;Raised levels of Amylase/ lipase ;USG findings suggestive of gall stone induced pancreatitis ;CECT findings suggestive of gall stone induced pancreatitis.

Pregnancy ,Hemodynamically unstable patient (Systolic Blood pressure <90mm hg) ,Patient with history Chronic pancreatitis by other causes. ;Patient not giving consent for study. ,Patient presented after 5 days of onset of symptoms ,Patients who used anti-inflammatory and immunosuppressive drugs in the past month were excluded

Methodology

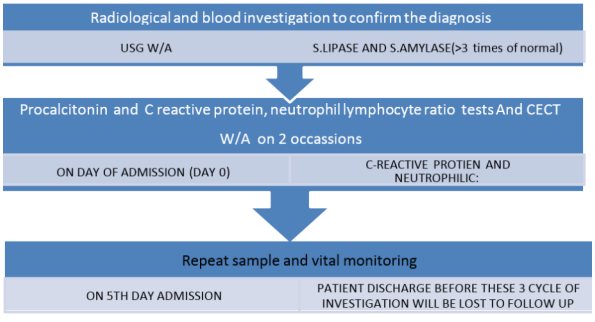
The study was approved by the Ethics Committee of our hospital. The subjects and their guardians were informed and signed fully informed consent forms.

Treatment Methods

After admission, all patients were given conventional symptomatic treatment , including gastrointestinal decompression, antacid, amylase inhibition, fasting, circulation improvement, maintenance of water and electrolyte and acid-base balance, and antibiotics when necessary. Important organ functions were strictly monitored and fluid resuscitation were carried out actively. Pancreatic imaging examination was performed on admission, and 3rd, 5th and 7th day of admission, and symptomatic treatment was performed on problems found.

Outcome Measures

Fasting peripheral blood (3mL) was drawn from the patients at the time of admission and placed in vacuum tubes without anticoagulant and anticoagulant tubes containing Ethylenediamine tetraacetic acid-K2 (EDTA-K2). Next, the blood was centrifuged for 10min with a radius of 10cm and a centrifugal force of 1450(×g) to separate the serum. The CRP and PCT in the serum were detected with Johnson Vitros5600 automatic biochemical-immune analyzer (Johnson & Johnson clinical diagnostics, Inc., NY, USA). The operations were carried out in strict accordance with the instruction manual of the instrument and kit. DxH 800 hematology analyzer (Beckman Coulter, Chaska, MN, USA) was used to measure N% in peripheral blood. These indexes of patients in the SAP group were repeatedly detected on the 5th day of admission. Normal CRP: 0–8 mg/L; normal PCT: 0–0.05 ng/ml ; Normal N%: 60–75% .Figure 1



Methodology was shown in figure 1.

Statistical Methods

SPSS 20.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis, and GraphPad Prism 6 was used to plot the figures. The counting data were expressed by the number of cases/percentage [N(%)] and the chi-square test was used for comparison between groups. Measurement data accorded with normal distribution were expressed by mean±standard deviation ($\bar{x}$±SD) and independent samples t-test was used for the comparison between groups. Measurement data not accorded with normal distribution were expressed by M (P25, P75) and Mann-Whitney U test was used for the comparison between groups. The data between different time points were compared by repeated measures analysis of variance (ANOVA), and Bonferroni method was used for pairwise comparison between different time points in the group. The receiver operating characteristic (ROC) curve was plotted and the optimal Youden index-based cutoff point was selected to evaluate the diagnostic value of CRP, PCT, and N% in SAP, and to determine their area under curve (AUC), sensitivity, and specificity. The difference was statistically significant with $P < 0.05$.

RESULTS

Demographic Profile

The mean age of the patients was 46.9 ± 14.5 years (Median: 47.5 [Min: 21 - Max: 71]). Majority of the patient were in the age group of 41-50 (27.50%) followed by 61- 71 years (20.00%) Majority of the patients were female (60%)

The mean severity score of the patients based on modified Mortele CTSI score was

8.1 ± 1.4. (Median: 8 [Min: 6 - Max: 10]).Majority of the patient were categorized as severe (62.5%) .

Laboratory Parameters

The Mean value of S.AMYLASE was 789.2 ± 957.6 u/l (Median: 338.5 [Min: 122 - Max: 3762]).It was observed that there had been a 5-6 fold increase in the baseline s.amylase value from the normal range (40 to 140 u/l).

The Mean value of S.LIPASE was 1352.1 ± 1834.3 u/l. (Median: 468 [Min: 119 - Max: 7955]). It was observed that there had been a 13 fold increase in the baseline s.lipase value from the normal range (20 to 150 u/l).

C-reactive Protein

The Mean value of C-REACTIVE PROTEIN at DAY 1 was 232.3 ± 101.4. (mg/l) (Median: 219.5 [Min: 2.8 - Max: 425]) and at DAY 5 ,it was 109 ± 65.1. (mg/l) (Median: 112 [Min: 4 - Max: 247]).we observed significant reduction in CRP level at day 5 than day 1 (p=0.024)

Procalcitonin

The Mean value of PROCALCITONIN at DAY 1 was 3.4 ± 2.9. (ng/dl) (Median: 3 [Min: 0.4 - Max: 13.4]) and at day 5 it was 0.9 ± 0.7. (ng/dl) (Median: 0.7 [Min: 0.1 - Max: 4.2]). we observed significant reduction in Procalcitonin level at day 5 than day 1 (p=0.018)

N/l Ratio

The Mean value of **N/L RATIO** at DAY 1 was 11 ± 4.5. (Median: 9.4 [Min: 3.7 - Max: 21]) and at day 5 it was 8.6 ± 6.3. (Median: 7.1 [Min: 3.3 - Max: 41]). we observed significant reduction in N/L ratio at day 5 than day 1 (p=0.036)

Prognosis based on APACHE II score

We observed fair prognosis in 37 patients with a mean APACHE II score of 6.5±3.2 and poor prognosis in 3 patients (7.5%) with a mean APACHE II score of 12.4±3.8

Mortality

The observed mortality was in one patient (2.5%).

Changes in CRP level according to Severity

It was observed that CRP levels were significantly higher in severe patients day 1 (291.84±65.40 mg/ml) than moderate patients (128.49 ±35.40 mg/ml) (p =0.002)

At day 5 , CRP levels were significantly higher in severe patients (138.63±32.45 mg/ml) than moderate patients (58.98 ±15.40 mg/ml) (p =0.001)

Changes in CRP level according to Prognosis

It was observed that CRP levels were significantly higher in patients with poor prognosis at day 1 (243.66±67.42 mg/ml) than patients with fair prognosis(223.21±65.35mg/ml) (p =0.001)

At day 5 , CRP levels were significantly higher in with poor prognosis (207.66±72.45 mg/ml) than patients with poor prognosis(109.05 ±36.30 mg/ml) (p =0.001)

Changes in Procalcitonin level according to Severity

It was observed that procalcitonin levels were significantly higher in severe patients day 1 (4.01±1.40 mg/ml) than moderate patients (2.11±0.56 ng/dl) (p =0.034*)

At day 5 ,no statistically significant difference was found between procalcitonin levels of severe patients (1.02±0.10 ng/dl) and moderate

patients (0.69 ±0.15 mg/ml) (p =0.185)

Changes in Procalcitonin level according to Prognosis
It was observed that procalcitonin levels were significantly higher in patients with poor prognosis at day 1 (3.93±67.42 mg/ml) than patients with fair prognosis(2.13
±65.35mg/ml) (p =0.001)

At day 5 , No significant difference in the procalcitonin values was observed between patients wirh poor prognosis (0.96±0.08 mg/ml) than patients with poor prognosis(0.54 ±0.03mg/ml) (p =0.197)

Changes in N/L ratio according to Severity
It was observed that mean N/L were significantly higher in severe patients day 1 (11.76±5.20) than moderate patients (9.46±3.62) (p =0.0264*)

At day 5 ,no statistically significant difference was found between mean N/L levels of severe patients (8.45±2.28 ng/dl) and moderate patients (8.05 ±2.10) (p =0.194)

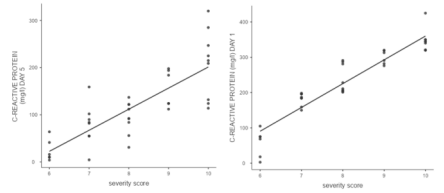
Changes in Procalcitonin level according to Prognosis
It was observed that N/L ratio was significantly higher in patients with poor prognosis at day 1 (11.92±4.12) than patients with fair prognosis(9.8 ±3.02) (p =0.0354)

At day 5 , No significant difference in the mean N/L ratio was observed between patients with poor prognosis (8.71±2.84) than patients with poor prognosis(7.75 ±2.10) (p =0.182)

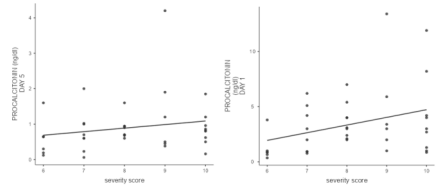
Association of Laboratory parameters with Disease severity
We observed highly significant strong correlation of CRP level at day 1 (r=0.937, p<0.001) , and CRP level at day 5 (r=0.827 , p<0.001) and significant mild correlation of procalcitonin level at Day 1 (r=0.334 , p=0.040) with disease severity. Table 1. Graph 1

Table 14. Association of Laboratory parameters with Disease severity

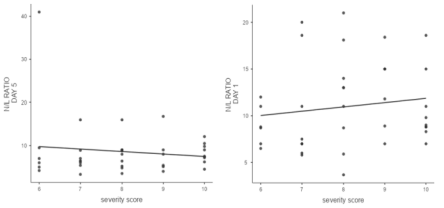
Parameters	Pearson coefficient	df	P value
CRP at Day 1	0.937	36	<0.001*
CRP at Day 5	0.827	33	<0.001*
Procalcitonin at Day 1	0.334	36	0.040*
Procalcitonin at Day 5	0.210	26	0.205
N/L ratio at Day 1	0.185	36	0.266
N/L ratio at Day 5	-0.219	36	0.186



Graph 12. Corelation of CRP at day 1 and day 5 with severity score



Graph 13. Corelation of Procalcitonin value at day 1 and day 5 with severity score



Predictive Factors for Gall stone Induced Pancreatitis
The detection showed that the PCT, NLR ratio and CRP at Day 1 and CRP at Day 5 in the Severe group were significantly higher than those in the moderate severity . (P < 0.001). Taking baseline data and serological indicators as independent variables, and severe cases as a dependent variable, multivariate Logistic regression analysis showed that APACHE II score (P=0.001),, PCT at day 1 (P=0.012), CRP at day 1 (P=0.001), and NLR ratio at day 1 (P=0.001) were independent predictive factors for Severity. Table 2

Table 18. Multvariate Logistic regression analysis of severe gall stone induced

pancreatitis						
Variable	B	S.E	Wals	P	OR	95% CI
APACH E-II score	0.291	0.071	16.799	0.001	1.338	1.164–1.538
PCT (at day1)	1.929	0.764	6.383	0.012	6.883	1.541–30.743
CRP (at day1)	0.128	0.024	28.520	0.001	1.136	1.084–1.191
NLR ratio (at day1)	2.290	0.474	23.375	0.001	9.873	3.902–24.978
PCT (at day 5)	0.651	0.259	6.315	0.012	1.917	1.154–3.184
CRP (at day 5)	0.132	0.029	26.412	0.001	1.132	1.094–1.196
NLR ratio (day 5)	0.564	0.385	7.824	0.078	1.917	1.254–6.272

DISCUSSION

In the present study ,the mean age of the patients was 46.9 ± 14.5 Majority of the patient were in the age group of 41-50 (27.50%) followed by 61-71 years (20.00%) and majority of the patients were female (60%).Similar findings were reported by Manadhar S et al ,2013 [22] in their study the mean age of the patients was 45 ± 10 years and the most frequent age group was 40–50 years which comprised 46.7 % of the cases .Female predominance was observed in their study with 40 % male patients and a male-to-female ratio of 1:1.5.. Similarly ,Marwah S et al (2020)[23] in north India ,reported 33% males and 67% females in their study and the mean age of the patients was 44.2 years.

Contrary to our findings , Kamal AK et al 2024[24] in their descriptive study conducted in Ranchi ,India including 72 patients diagnosed with acute gallstone- induced pancreatitis, 64%were males, and 36% were females (male-to-female ratio: 1.7:1).However their participants' ages ranged from 19 to 75 years with a mean age of 42.5 years, which is consistent with our findings, although the age is lower than the mean age reported for Western countries.

In the present study modified Mortele CTSI scoring was used to assess the severity of the patients as it is easier to calculate and correlate more closely with patient outcome measures like the length of the hospital stay, the need for surgery/intervention, and the occurrences of infection, organ failure and death than the Balthazar CT severity index, with similar inter observer variability [25]The mean severity score of the patients observed was 8.1 ± 1.4. and majority of the patient were categorized as severe (62.5%) .Similarly ,Kamal AK et al[24] observed 62.5% severe patients and Manadhar S et al[22] reported 60% severe patients . The high incidence of severe cases might be because of late presentation at our tertiary center.

In the present study highly elevated levels of S.AMYLASE (789.2 ± 957.6 u/l)and S.LIPASE (1352.1 ± 1834.3 u/l.) than its normal range was observed. This is consistent with the findings of Kamal AK et al [24]who found , threefold elevated values of serum amylase, lipase, ALT levels in 55.5%, 81.9%, and 73.6% cases, respectively, which is consistent with the findings by Manandhar et al [22]who also reported threefold raised serum amylase (51 %), lipase (73 %), and ALT (80 %) . In the study by Marwah S et al, [23]the mean serum amylase was 387 IU/L and was raised in 70.3% patients .Amylase and lipase pancreatic enzymes were synthesized by acinar cells of pancreas. . In acute pancreatitis, the increased permeability of cells producing serum lipases allows the release of enzymes to circulate at a high level. Hence, the elevation of serum lipase arises within three to six hours of onset symptoms, peaks within 24 h, and has a persistent elevation of up to two weeks.[26]

We observed highly significant strong correlation of CRP level at day 1 and day 5.

Similar findings were reported by Liang Yi et al 2019[27] ,who reported significantly higher CRP levels in patients with severe pancreatitis. The authors also observed the changes in CRP within 7 days, and their findings showed that CRP values in the deaths were

significantly higher than those in survivors at different time points. Cardoso FS et al 2013[28] reported that CRP level of severe patients reached a peak at 48h after admission, then gradually decreased with time . Fisic E etal 2013 [29]and Khanna AK et al[25] also suggested that inflammatory cytokines like CRP measured on the 3rd day of admission could predict systemic complications in patients and aids in early prediction and severity assessment of acute pancreatitis.

The Mean value of PROCALCITONIN in the study by Khanna AK [25]at DAY 1 was 3.4 ± 2.9. (ng/dl) at day 5 it was 0.9 ± 0.7. (ng/dl).We observed significant reduction in Procalcitonin (PCT)level at day 5 than day 1 . It was observed that procalcitonin levels were significantly higher in severe patients day 1 than moderate patients .At day 5 ,no statistically significant difference was found between procalcitonin levels of severe patients and moderate patients . We observed a significant mild correlation of procalcitonin level at Day 1 (r=0.334 , p=0.040) with disease severity.Also , It was observed that procalcitonin levels were significantly higher in patients with poor prognosis at day 1 than patients with fair prognosis.At day 5 , No significant difference in the procalcitonin values was observed between patients with poor prognosis than patients with poor prognosis.Similar findings were reported by Liang Yi et al 2019[27] ,who reported significantly higher procalcitonin levels in patients with severe pancreatitis. Mofidi R et al 2009[30] in a systematic review of 24 studies the sensitivity and specificity of PCT for severity were 0.72 and 0.86, respectively (area under the curve [AUC] = 0.87]Paliwal A et al 2023[31] , found area under curve of 0.9 with cut-off value 1.15. The sensitivity and specificity of 92.3% and 100% to predict outcome. Madhu C P et al(2017) [32] found that Serum Procalcitonin to be raised in all patients . Ammori BJ et al [33]studied the role of procalcitonin in gut barrier dysfunction in patients with acute pancreatitis and concluded that plasma concentrations of procalcitonin appear to reflect more closely the derangement in gut barrier function rather than the extent of systemic inflammation.

It was observed that mean N/L were significantly higher in severe patients day 1 than moderate patients .At day 5 ,no statistically significant difference was found between mean N/L levels of severe patients and moderate patients.It was observed that N/L ratio was significantly higher in patients with poor prognosis at day than patients with fair prognosis.At day 5 , No significant difference in the mean N/L ratio was observed between patients with poor prognosis than patients with good prognosis.

Similar findings of higher N/Lratio at admission were noted by Keshav Pathak et al. in 2023[34]. The mean NLR for patients with mild pancreatitis was 5.29, whereas it was 8.04 for patients with severe pancreatitis. Similarly , when the NLR was determined 48 hours after admission and contrasted with the pancreatitis severity. Patients with moderate pancreatitis had a mean NLR of 3.88, but those with severe pancreatitis had a mean NLR of 11.51.

One of the key cells involved in the active inflammatory response is the neutrophil, which is the primary cause of tissue death brought on by inflammatory cytokines like interleukin 1 and interleukin 6. Consequently, the acute and severe pancreatic tissue injury and inflammation in SAP produce neutrophilia, which raises the NLR. Conversely, in patients with acute pancreatitis, less peripheral total and lymphocyte subsets were observed within 48 hours of admission. [35,36]

Previous studies have shown that individuals with severe pancreatitis had far less lymphocytes than those with the milder form of the illness, which further raised the NLR. It most likely results from patients with acute pancreatitis having a compromised lymphocyte proliferative response to mitogens. [36-38] According to the literature evaluation, in the early phase of severe acute pancreatitis, increase of the NLR was thought to reflect an abnormality in cellular immunity brought on by early lymphocyte apoptosis and delayed neutrophil apoptosis.[38]

Three patients (7.5%) had a poor prognosis, while 37 patients (92.5%) had a satisfactory prognosis.One subject experienced the observed mortality (2.5%). 10.7% mortality rate was reported by Pathak K et al.[34] 10.7% was the death rate reported by Paliwal A et al.[31]

CONCLUSION

It can be concluded that day 1 c-reactive protein, procalcitonin and neutrophil lymphocytic ratio values were significantly increased in severe pancreatitis patients as compared to moderate pancreatitis patients. Hence it can be suggested that the aforementioned markers could be a predictor of severity and prognosis of gallstone induced pancreatitis .However the diagnostic value of our multiparameter scoring system could not be generalized owing to limited sample size and single centre study setting .

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