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Study to Evaluate the Utility of Inflammatory Markers TLC, CRP and Procalcitonin for Staging Acute Cholecystitis in Accordance with Tokyo Guidelines

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Abstract: ***Introduction: Acute cholecystitis (AC) is the inflammation of the gallbladder, which develops over hours, usually due to gallstones obstructing the cystic duct. The study aimed to evaluate the utility of inflammatory markers TLC, CRP and procalcitonin for staging acute cholecystitis in accordance with Tokyo guidelines. Methodology: In this prospective observational study, a total of 50patients with right upper quadrant pain were enrolled as per inclusion - exclusion criteria. As per their lipid profile, they were further divided into patients with dyslipidaemia and patients without dyslipidaemia. Along with clinic - demographical data, haemoglobin, platelet count, serum urea, creatinine, LFT, CRP, and PCT were measured. Results: The mean age of patients was 45.34 ± 14.6, with a female dominancy (60.00%). The mean value of Haemoglobin, total leucocyte count and platelet millionsof patientswere 11.73 ± 1.74, 10866.6 ± 5496.98 and 1.84 ± 0.57, respectively. In the present study, 56.00% of study subject's grade of acute cholecystitis was I, followed by II (32%). A significant (mild) positive correlation was seen between total leucocyte count with CRP and procalcitonin. A significant (mild) positive correlation was also seen between CRP with total leucocyte count and procalcitonin. A moderate positive correlation was observed between procalcitonin with total leucocyte count and CRP. Among all the parameters, total leucocyte count was the best predictor of grades I and II while procalcitonin was the best predictor of grade III. Conclusion: According to the results of the present study, TLC, CRP, and PCT can be a predictor in classifying mild/moderate grades of acute cholecystitis. Thus, it can be used as an effective laboratory method in the severity assessment of acute cholecystitis.***

Keywords: Gall bladder, Acute cholecystitis, Total Leukocyte Count, C - reactive protein, Procalcitonin.

1. Introduction

Acute cholecystitis (AC) is one of the important causes of abdominal pain, which presents to theemergency department. Acute cholecystitis is the inflammation of the gallbladder, which develops over hours, usually due to gallstones obstructing the cystic duct. The “4Fs” (forties, female, fat, fair) and “5Fs” (4Fs plus fecund or fertile) have been shown to be associated with gallstone formation. Even though the development of AC depends on hereditary and ethnic factors, its prevalence increases with age [1]. It was suggested that metabolic processes become catabolic and enzyme levels (cholesterol ester transporting protein (CETP), cholesterol 7 α - hydroxylase) decrease with age which leads to increased formation of gallbladder stones which may lead to AC. AC has been reported to develop in women three times more than in men up to the age of 50, but after this age, the difference decreases [1]. In most patients, gallbladder stones are the cause of acute cholecystitis. If no gallbladder stone is identified, it is called acute acalculous cholecystitis. Two main factors determine the progression to acute cholecystitis - the degree of obstruction and the duration of the obstruction. Acute cholecystitis is usually diagnosed based on the presence of characteristic local and/or systemic inflammatory findings and/or biochemical markers and/or the result of the radiographic examination. The classical features of acute cholecystitis are right hypochondria quadrant fever and tenderness in the right hypochondrium. The percentage of patients who presents with right hypochondrial pain and epigastric pain is around 72–93 % which is followed by patients presenting with nausea and vomiting. The percentage of patients with fever is not high; that of fever exceeding 38 (°C) is low (about 30 %). Guarding is also observed in the right hypochondrial region in around half of the cases. [2, 3] In order to prepare international guidelines based on the “Evidence - Based Practice Guidelines for the Management of Acute Cholangitis and Cholecystitis” an International Consensus Meeting was held in Tokyo, which framed Tokyo guidelines 2007. These were revised in 2013 and 2018. [3] The common biochemical test used for diagnosing acute cholecystitis include white blood cell (WBC) count, C reactive protein (CRP) and procalcitonin (PCT). CRP has been utilized as a marker of infection and cardiovascular events besides diagnosing acute cholecystitis according to Tokyo guidelines. CRP is synthesized primarily in liver hepatocytes but also by smooth muscle cells, macrophages, lymphocytes, and adipocytes. The plasma concentration of CRP and PCT increases during inflammatory disorders (4). Hence, we aimed to study the utility of inflammatory markers TLC, CRP and procalcitonin for staging acute cholecystitis per Tokyo guidelines.

2. Material and Methods

The present case - control study was conducted at the Department of Surgery, S. R. N. Hospital associated with M. L. N Medical College, Prayagraj, from September 2019 to September 2020. After ethical clearance and informed consent, patients (n=50) aged 18 - 65 years with right upper quadrant pain and ultrasonographic features suggestive of acute cholecystitis were included in this study. However, immunocompromised patients with diabetes, HIV, liver failure, autoimmune disorder, pregnancy, patients suffering from other acute biliary and pancreatic diseases like cholangitis, pancreatitis, and mirizzi syndrome, also patients who did not undergo cholecystectomy for the cholecystitis and patient in whom the definite diagnosis of acute cholecystitis could not be confirmed on histopathology were excluded. A sample of (6 ml) of blood was taken from every patient and was divided into 3 portions: A portion of (1.5) ml of blood was taken in an EDTA Tube, which was used to measure haemoglobin TLC DLC and platelet count measured at once. White blood cell count assays were performed. A portion of (2 ml) of blood was taken in a citrate tube which is used to measure the PT –INR of the patient. The remaining blood (2.5 ml) was allowed to clot in the plain tube, and the serum was separated after centrifugation at 3000 rpm for 3 minutes, which was then used for estimation of serum urea, creatinine, LFT, CRP, PCT. The radiological investigationwas done by USG usinga3.5 - 5 MHz probe to confirm the presence of acute cholecystitis according to Tokyo guidelines. Other radiological investigations were used if needed.

Statistical Analysis:
The presentation of the Categorical variables was done in the form of numbers and percentages (%). On the other hand, the presentation of the continuous variables was done as mean ± SD and median values. The data normality was checked by using the Kolmogorov - Smirnov test. In the cases in which the data was not normal, we used non - parametric tests. The following statistical tests were applied for the results: 1) The association of the variables, which were quantitative in nature, were analysed using the ANOVA test (for more than two groups) and the Kruskal Wallis test for not normally distributed data.2) Receiver operating characteristic curve was used to find out the cutoff point of total leucocyte count (cell/mm³), CRP (mg/L) and Procalcitonin (µg/L) for predicting grades I, II and III.3) Spearman rank correlation coefficient was used to correlate total leucocyte count (cell/mm³), CRP (mg/L) and Procalcitonin (µg/L). The data entry was done in the Microsoft EXCEL spreadsheet, and the final analysis was done using Statistical Package for Social Sciences (SPSS) software ver 21.0. For statistical significance, a p - value of less than 0.05 was considered significant.

3. Results

In the present study, the maximum number of patients, 26.00%, belonged to the age group 41 - 50 years. The mean age of patients was 45.34 ± 14.6. In the present study, 60.00% of patients were females. The general examination, systemic examination, comorbid conditions, and abdomen findings were normal in all the patients. **[TABLE - 1]** Mean value of Haemoglobin, total leucocyte countand platelet millions of patients were 11.73 ± 1.74, 10866.6 ± 5496.98 and 1.84 ± 0.57 with median (IQR) of 11.85 (10.75 - 13.075), 9000 (6850 - 13950) and 1.9 (1.6 - 2.1) respectively. **[Table - 2]** In the majority (68.00%) of patients, CRP was positive. The majority of the patients had elevated procalcitonin. **[Table - 3]** Mean values of urea and creatinine of study subjects were 40.88 ± 24.37 and 1.31 ± 0.79, respectively. Mean value of bilirubin, SGOT, SGPT, PT, INR and ALP of study subjects were 1.32 ± 1.48, 115.99 ± 134.56, 128.29 ± 143.72, 15.16 ± 2.31, 1.14 ± 0.24 and 391.62 ± 347.94, respectively. **[TABLE - 2]** In the present study, 56.00% of patients' grade of acute cholecystitis was I, followed by II (32%). [**FIGURE - 1]**Significant (mild) positive correlation was seen between total leucocyte countwith CRP, and procalcitoninwitha correlation coefficient of 0.31 and 0.532, respectively. A significant (mild) positive correlation was also seen between CRP with total leucocyte countandprocalcitonin (µg/L) with a correlation coefficient of 0.31 and 0.322, respectively. A moderate positive correlation was observed between procalcitonin with total leucocyte count, CRP with a correlation coefficient of 0.53 and 0.322, respectively. [**TABLE - 4]**Median total leucocyte countin grade 2 was significantly higher than grade 3 and grade (p value<.0001). [**FIGURE - 2]**Median of CRP in grade 3 was significantly higher as compared to grade 2 and grade 1 (p value=0.023). **[FIGURE - 3]**Mean procalcitoninin grade 3 was [10.9 ± 3.53], which was significantly higher as compared to grade 2 and grade 1 (p value<.0001). [**FIGURE - 4]**The area under the ROC curve showed that the performance of total leucocyte count (AUC 0.909; 95% CI: 0.793 to 0.972) and Procalcitonin (AUC 0.907; 95% CI: 0.790 to 0.971) was outstanding. Among all the parameters, total leucocyte count was the best predictor of grade I and II at cut off point of [≤9850 with 90.90%; >9850 with 88.90%], respectively. The area under the ROC curve showed that among all the parameters, procalcitonin was the best predictor of grade III at cut off point of >6.1 with 95.50% chances of correctly predicting grade III. [**TABLE - 5]**

4. Discussion

The present study included patients of age 18 - 65 years with a mean age of 44.78±13.65 years. There were more females and fewer males (M: F=3: 2). Similar to the present study; the age distribution has been varied among the studies with female predominance. **Umefune et al. (2016)** [5] included 213 patients who were >20 years of age. The median age of the patients was 74 years. Male: female ratio was 1.6: 1. There were more males than females in the study. Ina study by **Kabul Gurbulak et al. (2015)** [6], 682 patients (in the age range of 18 to 93 years) were enrolled; the mean age was 51.61 ± 16.65 years. Females were more than males as the Female: male ratio was 1.55: 1. In a study by **Yuzbasioglu Y et al. (2016) [**7], including 200 patients >17 years diagnosed with acute cholecystitis; the mean age was 59.97±18.6 years.67% of the patients were females. In the studies by **Pinto et al.** [8] and **Cameron et al.** [9] mean age of patients with acute cholecystitis was 54 years. It has been seen that the development of acute cholecystitis is dependent on hereditary as well as ethnic factors; however, its prevalence increases with age. This may be due to the fact

that metabolic processes become catabolic and enzyme levels decrease with age, and the formation of gallstones may lead to AC. It has been reported to develop in women three times more than in men up to the age of 50, after which the difference decreases. [7, 8] In our study, assessment of the grades of acute cholecystitis showed that there were 56.00% cases of grade I, 32.00% cases of grade II and 12.00% cases of grade III acute cholecystitis. Grade I is defined as acute cholecystitis in a patient with no organ dysfunction and limited disease in the gallbladder, making cholecystectomy a low - risk procedure. Grade II is associated with no organ dysfunction, but there is an extensive disease in the gallbladder, resulting in difficulty in safely performing a cholecystectomy. Grade III is defined as acute cholecystitis with organ dysfunction. [10] In other studies, **Yuzbasioglu et al. (2016)** [7] reported that 55% of the cases belonged to grade I, 30.5% of grade II, and 14.5% of grade III acute cholecystitis. In another study by **Yuzbasioglu et al. (2017)** [11], it was reported that grade I, grade II and grade III acute cholecystitis were present in 57.6%, 28.8%, and 13.6% of patients, respectively. In the study by **Kabul Gurbulak et al. (2015) [**6], grade I was present in 64.36% of patients, grade II in 32.25%, and grade III in 3.39% of patients with acute cholecystitis. **Cheng et al. (2014) [**12] reported that out of 103 patients, grade I, grade II and grade III acute cholecystitis were present in 48, 31, and 24 patients, respectively. In the study by **Sakalar et al. (2020)** [13], 42.1% were allocated to grade I, 20% to grade II, and 37.9% to grade III. So, it was pretty much observed that all three grades' patients were seen in the study population, which warrants the need for a novel marker to predict and diagnose the third stage early for the appropriate management. We investigated the patients for various baseline tests where we tried to determine the correlation and cut offs of the inflammatory markers with the grades of acute cholecystitis. The inflammatory process encompasses the increase in TLC count of the blood along with an increase in inflammatory markers such as CRP and Procalcitonin. TLC is a routine investigation where we assessed the total cell count, and further DLC was done to know the individual proportion of cells. CRP holds importance in various inflammatory conditions as it increases in cases of inflammation. Procalcitonin is another marker found useful in that could be useful in the diagnosis of infection. [11]In cases with systemic bacterial infection, procalcitonin is readily produced by various organs throughout the body, and serum procalcitonin level increases dramatically. Accumulating evidence suggests that procalcitonin level well predicts the presence and severity of acute systemic infectious diseases with superior sensitivity and specificity compared with conventional inflammation markers such as white blood cell (WBC) count and C - reactive protein (CRP) level, particularly in respiratory tract infection or severe sepsis in intensive care units. [14, 15] In our study, their values showed a significant correlation among themselves ($p<0.05$), indicating that all the inflammatory markers increased in conjunction. Individually, we found that TLC values showed an interesting trend of median values from grade II>III>I (17300 vs 11100 vs 7100; $p<0.0001$). The values were highest in grade II followed by grade III, and least by grade I. The values were such that the cut offs derived for predicting the grades of acute cholecystitis were significant only for grade I and II and not for grade III. The cut off values of TLC for grade I was ≤9850 cells/cumm with a diagnostic accuracy of 86% ($p<0.0001$); for grade II was >9850 cells/cumm with a diagnostic accuracy of 78.00% ($P<0.0001$) and for grade III was >9850 cells/cumm with a diagnostic accuracy of 62.00% ($P=0.0742$). In comparison to the present study, **Yuzbasioglu et al. (2017)** [11]observed the WBC count was low in Grade 1 patients and high in Grades 2 - 3 patients (9500 vs 12200 vs 12100). The WBC values of the patients were determined to rise in parallel with increasing grade ($p<0.05$). It was suggested that the WBC count could be considered not to respond sufficiently depending on the increase in age in parallel with the grade. It must also be remembered that leukopenia could have developed in the patient group with bad clinical symptoms due to the additional system pathologies or immune suppression. **Yuzbasioglu et al. (2016)** [7]found that as the disease severity increased, the WBC count was found to be statistically significantly elevated. Literature shows that the acute cholecystitis or severe disease, white blood cell count (WBC) may be elevated. [16, 17]In one of the studies, this was reconfirmed when **Yazici et al. (2015) [**18] stated that the WBC count of 43% of the patients in their study wasnormal. Leukocytosis may not be seen in elderly, diabetic and immunosuppressive patients, although such patients may have leucopenia. The WBC count has been stated to be over 18, 000 in Grade 2 of the Tokyo classification. [10] As for CRP, we found that its values showed a decreasing trend of median values from grade III>II>I (17.95 vs 11.8 vs 9.05; $P =0.023$). The values were such that the cut offs derived for predicting the grades of acute cholecystitis were significant only for grade I and III and not for grade II. The cut off values of CRP for grade I was ≤14.1 mg/L with a diagnostic accuracy of 76% ($p=0.0065$); for grade II was >25.6 mg/L with a diagnostic accuracy of 80% ($p=0.1861$) and for grade III was >12.9 mg/L with a diagnostic accuracy of 78% ($p=0.046$). Similar to the present study, **Yuzbasioglu et al. (2017)** [11]reported the CRP values of the patients were determined to rise in parallel with increasing grade ($p<0.05$). **Yuzbasioglu et al. (2016)** [7] also found that as the disease severity increased, the CRP levels (mg/dL) were found to be statistically significantly elevated (grade I vs grade II vs Grade III: 1.5 vs 1.80 vs 5.6) ($p<0.05$). **Mok et al. (2014) [**19] investigated the diagnostic value of CRP in acute gangrenous cholecystitis. It was found that CRP cutoff value of 200 mg/L has 100% (95% CI: 78.2% - 100%) sensitivity and 88% (95% CI: 80.9% - 93.1%) specificity in predicting acute gangrenous cholecystitis. In the study by **Kabul Gurbulak et al. (2015) [**6] CRP values were found to be highly correlated with the disease grade, and these correlations are statistically significant and moderately positive ($P < 0.001$, $r = 0.743$), as was seen in the present study. In a study by **Nikfarjam et al. (2011)** [20], CRP value > 94 mg/L was found to be a significant risk factor for gangrenous cholecystitis. Similarly, **Asai et al. (2012)** [21] reported a significant correlation between a high risk of bactobilia and advanced age, high levels of CRP, and the evidence of significant gallbladder infection. In their study, the cutoff CRP value was found to be 134 mg/L for bactobilia. According to Tokyo guidelines, CRP, a well - known acute phase reactant that increases rapidly in inflammatory processes, is included in the laboratory

findings for diagnosing acute cholecystitis. In various studies, CRP has been found to be a strong predictive factor in determining the severity of gallbladder inflammation. [20, 22 - 25]According to Tokyo guidelines, grade 1 patients were cases with uncomplicated acute cholecystitis. These patients constitute the group without bacteremia or sepsis. Therefore, very high CRP levels are not usually encountered in patients with grade 1 acute cholecystitis. Unlike the cases with grade 1, gallbladder inflammation in grade 2 patients gets complicated and may be accompanied by bacteremia, systemic inflammatory response syndrome (SIRS) or sepsis, but not organ dysfunction. Thus, CRP is expected to be at higher levels in this group. [6]Procalcitonin (PCT), a diagnostic parameter, selectively increases in bacterial infections, sepsis, and multiple organ dysfunction syndromes. [13] In the present study, Procalcitonin was the only specific marker which was found significant for predicting all three grades of acute cholecystitis. We found that PCT values showed a decreasing trend of median values from grade III>II>I (11.1 vs 6.2 vs 2.5, $p<0.0001$). The values were such that the cut offs derived for predicting the grades of acute cholecystitis were significant for all grades. The cut off values of PCT for grade I was ≤5.2 µg/L with a diagnostic accuracy of 94% ($p<0.0001$); for grade II was >5.2 with a diagnostic accuracy of 82% ($p=0.0028$), and for grade III, was >6.1 with a diagnostic accuracy of 82% ($p<0.0001$). Similar to the present study, **Yuzbasioglu et al. (2016)** [7]found that as the disease severity increased, the PCT levels were found to be statistically significantly elevated ($p<0.05$). The cut off values of PCT for grade I was ≤0.52; for grade II, was >0.14; and for grade III was >0.8. In their study, the rate of increases in PCT level in patients with AC was 27%; this increase was correlated with the clinical status and increases in WBC count, CRP level, and ESR. Even**Sakalaret al. (2020)** [13]reported that Blood procalcitonin levels can be used to determine the severity of acute cholecystitis effectively. A relationship was found between PCT values and acute cholecystitis severity levels. There is a scarcity of previous studies that evaluated the effect of PCT level in determining the severity of AC. However, PCT level increase in proportion to the severity of systemic inflammation. A continual increase in PCT level indicates that infection has not been controlled and that treatment is insufficient.3 **Al - Bahrani et al. (2005)** [26] and **Reinhart (2006)** [27]and **Meisner et al. (2001)** [28]reported that PCT level was highly effective for showing the severity of inflammation in acute pancreatitis. As suggested by **Qu J et al. (2014)** [29], PCT level is more sensitive and specific than other acute - phase response indicators such as CRP, interleukin - 6, and tumor necrosis factor - α in defining bacterial infections. It was also demonstrated that in cases of bacterial invasion, PCT level increases and then returns to normal levels faster than CRP level. Considering that CRP level, ESR, and WBC count may increase for several reasons, PCT level may be more meaningful in supporting the diagnosis of AC and in defining the clinical severity of the disease and adequacy of the treatment.3 Our results corroborate with these aspects as we found that PCT was able to predict all the three grades of acute cholecystitis, respectively. Among other studies, **Yuzbasioglu et al. (2016)** [7]reported that PCT was the best predictor of grade I at cut off point of ≤0.52. PCT, TLC and CRP had sensitivity of 95.45%, 81.82%, and 70%, respectively, and specificity of 46.67%, 51.11%, and 64%, respectively. In the study by **Beliaevet al. (2015)** [4], among all the parameters, Total leucocyte count (cell/mm³) was the best predictor at cut off point of >9850 with 88.90% chances of correctly predicting grade II. Our findings were in line with the study by **Yuzbasioglu et al. (2016)** [7], who reported that only TLC had significant discriminatory power to predict grade II. PCT, TLC and CRP had sensitivity of 62.3%, 67.21%, and 29.51%, respectively, and specificity of 56.83%, 61.87%, and 85.61%, respectively. In the study by **Beliaev et al. (2015)** [4] cutoff point value of WCC for diagnosing moderate/severe, AC was 11.05 (95% CI: 10.2 – 11.9). Sensitivity at the cutoff point was 84%, specificity 90%, AUC 87%. The cutoff point of CRP in diagnosing moderate/severe AC was 67 (95% CI: 61.9 –72.1). Sensitivity at the cutoff point was 96%, specificity 100%, AUC 97%. Among other studies, **Yuzbasioglu et al. (2016)** [7] reported that TLC, CRP and PCT had significant discriminatory power to predict grade III whilst comparing AUC of PCT (AUC 0.813, $P<0.001$), CRP (AUC, 0.782, $P<0.001$), and WBC (AUC, 0.564, $P=0.399$), it was observed that PCT was the best predictor of grade III at cut off point of >0.8. PCT, TLC and CRP had sensitivity of 72.4%, 37.93%, and 86.2%, respectively, and specificity of 90.06%, 94.15%, and 61.4%, respectively. In the study by **Beliaevet al. (2015)** [4] (which did not compare PCT), CRP had better discriminative power than WBC for the diagnosis of AC. Overall, it can be seen that all three inflammatory markers hold importance in predicting the grades of acute cholecystitis. Procalcitonin is the most corroborative with all grades at an individual level, but the usefulness of others cannot be ignored either. The results show that they can be used in conjunction for increasing the accuracy of prediction since they all showed significant correlations among themselves.

5. Conclusion

All three inflammatory markers (TLC, CRP, PCT) showed significant association with the grades of acute cholecystitis as per the TOKYO guidelines. Also, the values of these markers showed a significant correlation among themselves ($p<0.05$), indicating that all the inflammatory markers increased in conjunction. According to the results of the present study, TLC, CRP, and PCT can be a predictor in classifying mild/moderate grades of acute cholecystitis. Procalcitonin was the only specific marker which was found significant for predicting all three grades of acute cholecystitis, and overall, it was the best predictor for diagnosing grade III at cut off point of >6.1 with 95.50% chances of correctly predicting it. Thus, it can be used as an effective laboratory method in the severity assessment of acute cholecystitis.

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Tables and Figures

Table 1: Age, gender and general examination of study subjects (n=50).

		Frequency	Percentage
Age (years)	<=30	10	20.00%
	31 - 40	9	18.00%
	41 - 50	13	26.00%
	51 - 60	12	24.00%
	>60	6	12.00%
	Mean ± SD	45.34 ± 14.6	
	Median (IQR)	45 (32.75 - 56)	
	Range	18 - 78	
Gender	Female	30	60.00%
	Male	20	40.00%
General examination	Normal	50	100.00%
Systemic examination	Normal	50	100.00%
Respiratory system	Normal	50	100.00%
Co morbid conditions	Normal	50	100.00%
Abdomen	Normal	50	100.00%
	Total	**50**	**100.00%**

Table 2: Descriptive statistics of complete blood count, RFT and KFT of study subjects

		Mean ± SD	Median (IQR)	Range
Complete blood count	Hemoglobin (g/dL)	11.73 ± 1.74	11.85 (10.75 - 13.075)	7.3 - 15.2
	Total leucocyte count (cell/mm³)	10866.6 ± 5496.98	9000 (6850 - 13950)	3800 - 23100
	Platelet million (cells/mm³)	1.84 ± 0.57	1.9 (1.6 - 2.1)	0.6 - 3.1
Renal function test parameters	Urea (mg/dL)	40.88 ± 24.37	31.85 (23.275 - 46.75)	15.2 - 114
	creatinine (mg/dL)	1.31 ± 0.79	1.06 (0.852 - 1.368)	0.53 - 3.9
Liver function test parameters	Bilirubin (mg/dL)	1.32 ± 1.48	0.82 (0.53 - 1.515)	0.24 - 8.9
	SGOT (IU/L)	115.99 ± 134.56	57.5 (32.9 - 118.625)	17.95 - 605.2
	SGPT (IU/L)	128.29 ± 143.72	76.25 (38.275 - 150.025)	15.8 - 584.2
	PT (secs)	15.16 ± 2.31	14.7 (13.2 - 16.9)	12 - 20.5
	INR	1.14 ± 0.24	1.1 (0.96 - 1.28)	0.88 - 1.93
	ALP (IU/L)	391.62 ± 347.94	254.45 (195.125 - 482.125)	93 - 1615

Table 3: Distribution of CRP (mg/L) and Procalcitonin (µg/L) of study subjects

		Frequency	Percentage
CRP (mg/L)	Negative	16	32.00%
	Positive	34	68.00%
	Mean ± SD	14.71 ± 14.6	
	Median (IQR)	10.65 (6.3 - 13.575)	
	Range	1.6 - 68.15	
Procalcitonin (µg/L)	Elevated	49	98.00%
	Normal	1	2.00%
	Mean ± SD	4.78 ± 3.63	
	Median (IQR)	4.65 (1.825 - 6.2)	
	Range	4.78 ± 3.63	

Table 4: Correlation of total leucocyte count (cell/mm³), CRP (mg/L) and Procalcitonin (µg/L)

Variables	Total leucocyte count (cell/mm³)	CRP (mg/L)	Procalcitonin (µg/L)
Total leucocyte count (cell/mm³)			
Correlation coefficient	-	**0.310**	**0.532**
P value	-	**0.029**	**0.0001**
CRP (mg/L)			
Correlation coefficient	**0.310**	-	**0.322**
P value	**0.029**	-	**0.023**
Procalcitonin (µg/L)			
Correlation coefficient	**0.532**	**0.322**	-
P value	**0.0001**	**0.023**	-

Table 5: Receiver operating characteristic curve of total leucocyte count (cell/mm³), CRP (mg/L) and Procalcitonin (µg/L) for predicting grade I, II and III

		Total leucocyte count (cell/mm³)	CRP (mg/L)	Procalcitonin (µg/L)
Grade I vs II+III	Area under the ROC curve (AUC)	0.909	0.714	0.907
	Standard Error	0.0394	0.0788	0.0529
	95% Confidence interval	0.793 to 0.972	0.569 to 0.833	0.790 to 0.971
	P value	<0.0001	0.0065	<0.0001
	Cut off	≤9850	≤14.1	≤5.2
	Sensitivity (95% CI)	85.71% (67.3 - 96.0%)	100% (87.7 - 100.0%)	100% (87.7 - 100.0%)
	Specificity (95% CI)	86.36% (65.1 - 97.1%)	45.45% (24.4 - 67.8%)	86.36% (65.1 - 97.1%)
	PPV (95% CI)	88.9% (70.8 - 97.6%)	70% (53.5 - 83.4%)	90.3% (74.2 - 98.0%)
	NPV (95% CI)	82.6% (61.2 - 95.0%)	100% (69.2 - 100.0%)	100% (82.4 - 100.0%)
	Diagnostic accuracy	86.00%	76.00%	94.00%
Grade II vs I+III	Area under the ROC curve (AUC)	0.889	0.625	0.74
	Standard Error	0.0484	0.0945	0.0803
	95% Confidence interval	0.768 to 0.960	0.477 to 0.758	0.596 to 0.854
	P value	<0.0001	0.1861	0.0028
	Cut off	>9850	>25.6	>5.2
	Sensitivity (95% CI)	87.5% (61.7 - 98.4%)	43.75% (19.8 - 70.1%)	81.25% (54.4 - 96.0%)
	Specificity (95% CI)	73.53% (55.6 - 87.1%)	97.06% (84.7 - 99.9%)	82.35% (65.5 - 93.2%)
	PPV (95% CI)	60.9% (38.5 - 80.3%)	87.5% (47.3 - 99.7%)	68.4% (43.4 - 87.4%)
	NPV (95% CI)	92.6% (75.7 - 99.1%)	78.6% (63.2 - 89.7%)	90.3% (74.2 - 98.0%)
	Diagnostic accuracy	78.00%	80.00%	82.00%
Grade III vs I+II	Area under the ROC curve (AUC)	0.653	0.742	0.955
	Standard Error	0.0859	0.121	0.0336
	95% Confidence interval	0.506 to 0.782	0.599 to 0.856	0.855 to 0.993
	P value	0.0742	0.046	<0.0001
	Cut off	>9850	>12.9	>6.1
	Sensitivity (95% CI)	83.33% (35.9 - 99.6%)	83.33% (35.9 - 99.6%)	100% (54.1 - 100.0%)
	Specificity (95% CI)	59.09% (43.2 - 73.7%)	77.27% (62.2 - 88.5%)	79.55% (64.7 - 90.2%)
	PPV (95% CI)	21.7% (7.5 - 43.7%)	33.3% (11.8 - 61.6%)	40% (16.3 - 67.7%)
	NPV (95% CI)	96.3% (81 - 99.9%)	97.1% (85.1 - 99.9%)	100% (90.0 - 100.0%)
	Diagnostic accuracy	62.00%	78.00%	82.00%

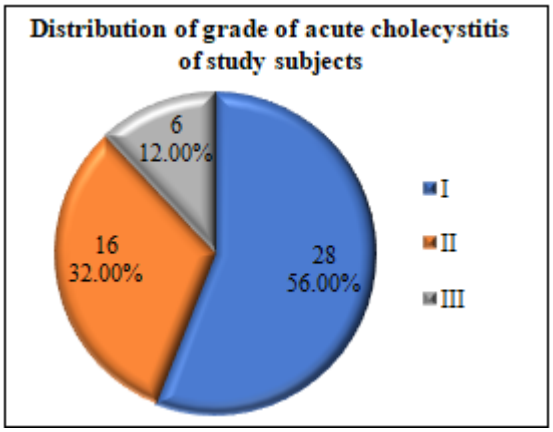

Figure 1: Distribution of grade of acute cholecystitis of study subjects.

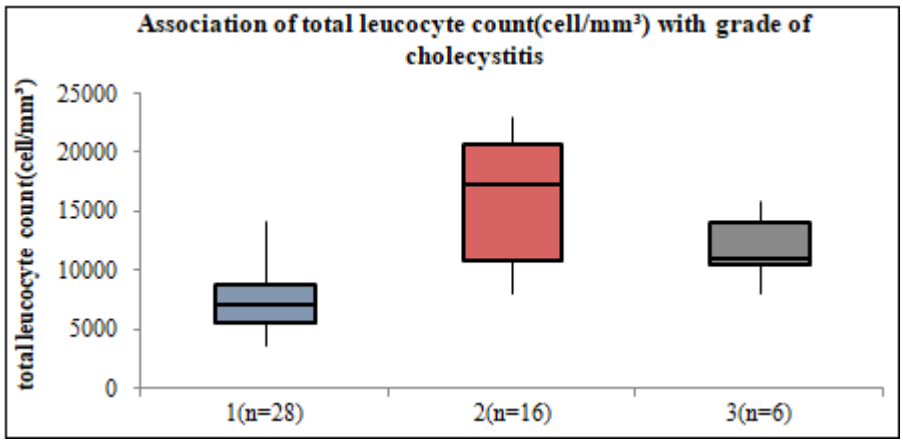

Figure 2: Association of total leucocyte count (cell/mm³) with grade of cholecystitis

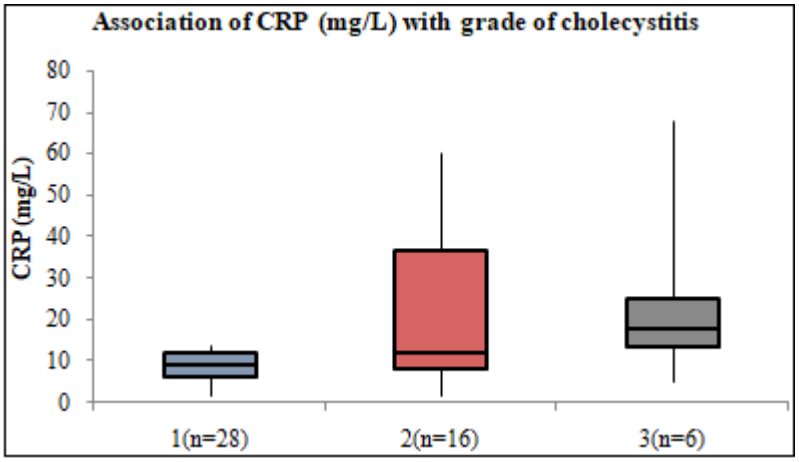

Figure 3: Association of CRP (mg/L) with grade of cholecystitis

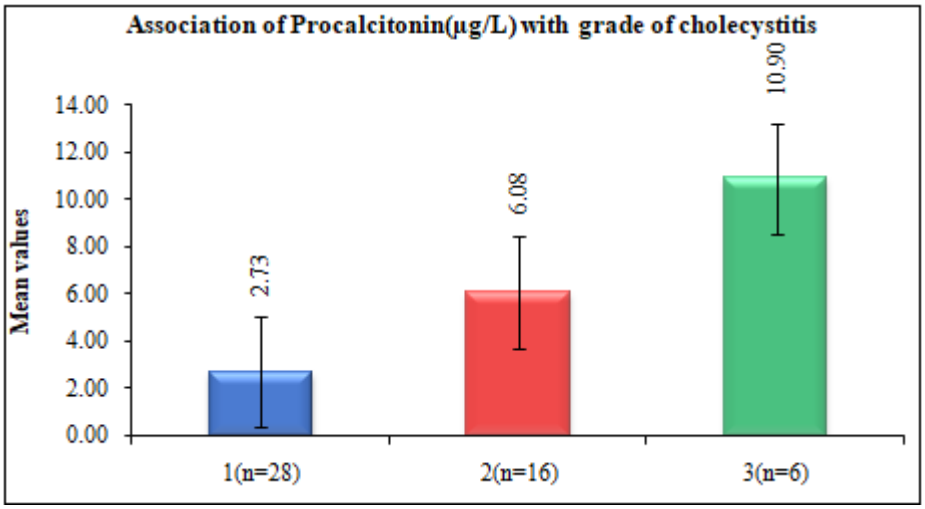

Figure 4: Association of Procalcitonin (µg/L) with grade of cholecystitis.