

Assessment of the Role of Procalcitonin Level in Predicting the Severity of Acute Cholecystitis: A Prospective Observational Hospital-Based Study

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Abstract

Introduction: Acute cholecystitis (AC) is the inflammation of the gallbladder and one of the most common reasons for acute abdominal pain in surgical ward. Grading the severity of AC is very important for prognosis and also for planning the treatment. Previously, the levels of leukocytosis and C-reactive protein (CRP) were assessed for predicting its severity. And now, blood procalcitonin (PCT) levels can also be used as an effective laboratory method for assessing its severity.

Materials and Methods: Ethical clearance was obtained by the institute. The study was conducted in total of 104 patients, with complaint of the right upper quadrant (RUQ) pain, diagnosed based on Tokyo Guidelines. Thereafter, serum PCT level was measured. Then, the patients were divided into three grades according to the Tokyo classification based on their anamnesis, physical examination, and laboratory and imaging results. All $P < 0.05$ were considered to be statistically significant.

Results: AC was found more prevalent in the age group of 21–60 years. The RUQ pain is prevalent with $P = 0.028$, fever is seen to be common, 52.88% of patients showed positive ultrasonographic image findings. Raised total leukocyte count, CRP, and erythrocyte sedimentation rate seen with significant p value, which are proven factor in AC according to Tokyo Guidelines. Serum PCT level was raised in 13% of patients in Grade 1, 40% in Grade 2, and 78% in Grade 3. The prevalence of raised PCT is seen here with significant $P = 0.001$.

Conclusion: Within the given limitations of study, we can conclude that blood PCT levels can be used to determine the severity of AC effectively.

Key words: Acute cholecystitis, C-reactive protein, Erythrocyte sedimentation rate procalcitonin, Tokyo grading, Total leukocyte count

INTRODUCTION

Acute cholecystitis (AC) remains one of the major causes of abdominal morbidity and mortality throughout the world.^[1] The prevalence of the disease varies and has been reported as 2–29% in India and increasing in recent years.^[2]

Early diagnosis and treatment of AC has a positive effect on morbidity and mortality.^[2,3]

Previously, the levels of leukocytosis and C-reactive protein (CRP) were assessed for predicting the severity of AC, but neither have been found to be of value in predicting severity.^[3-6] Moreover, CRP is usually within normal range in the first 6–12 h of AC. On the other hand, procalcitonin (PCT) shown to increase in the 1st h after systemic inflammation and peaked earlier than CRP in plasma.^[4]

Sakalar *et al.* recently worked on the relation of PCT and AC,^[7] topic being “Plasma PCT is useful for Predicting the Severity of AC.” Here, patients were allocated into three severity grades according to the Tokyo Guidelines

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2013. Then, PCT level was measured after the clinical and radiological diagnosis of AC in the emergency department. So the result of the study finally concluded, that blood PCT levels can be used to determine the severity of AC effectively.

An ideal biomarker should possess high diagnostic accuracy, for an early and rapid diagnosis. PCT is a recently rediscovered biomarker that fulfills many of these requirements, especially in comparison to conventional and widely used other biomarkers that have demonstrated superior diagnostic accuracy for a variety of infections, including sepsis.

MATERIALS AND METHODS

Ethical clearance was obtained at the start of the study from the Institutional Review Board. This is an observational study. Sample size was calculated taking reference of the study of Alok *et al.*^[8] incidence to be 4%, $N(\text{sample size}) = Z\alpha^2p(1-p)/e^2$, where p is proportion and e is precision. Here, $\alpha = 5\%$ hence $Z\alpha = 1.96p$ (incidence of AC = 4%) $e = 5\%$. Thus, the calculated sample size was 60. Moreover, we conducted the study on 104 patients over a period of 1 year from September 2019 to 2020 admitted to general surgery department with complaint of the right upper quadrant (RUQ) pain.

Inclusion Criteria

The following criteria were included in the study:

1. All patients above the age of 18 years,
2. Both male and female,
3. Diagnosed as AC as per Tokyo Guidelines 2018.

Exclusion Criteria

The following criteria were excluded from the study:

1. Immunocompromised patients.
2. Patients with pancreatitis.
3. Patients with cholangitis and obstructive jaundice.
4. Patients with presence of sepsis from other than gallbladder disease.
5. Patients not willing to participate in the study.

AC was then diagnosed based on Tokyo Guidelines.

1. Presence of local inflammatory findings – Murphy's sign, palpable mass, tenderness, and/or pain in the right upper abdominal quadrant.
2. Systemic inflammatory findings – fever, raised CRP, and/or leukocytosis.
3. Specific finding for AC on ultrasonographic imaging – (like gallbladder wall thickening, and/or pericholecystic fluid collection).

Clinical suspicion and at least one of these signs are required for diagnosis of AC, and the diagnosis needs to be supported by Union of Students in Ireland (USI).

After making the diagnosis, serum PCT level was measured. Then, the patients was divided into three grades according to the Tokyo classification –

Grade 1 (Mild)

AC in healthy patients, with no organ dysfunction.

Grade 2 (Moderate)

Associated with any one of following conditions – white blood cell (WBC) >18,000 cells per cubic millimeter, palpable tender mass in RUQ, duration of complaints >72 h, or marked local inflammation (pericholecystic abscess, hepatic abscess, biliary peritonitis, and emphysematous cholecystitis).

Grade 3 (Severe)

Associated with any one – cardiovascular dysfunction, neurovascular dysfunction, respiratory dysfunction, renal dysfunction, or hepatic dysfunction.

Parameters that were recorded and compared are – WBC count, serum CRP level, erythrocyte sedimentation rate (ESR), and serum PCT level. Results of the patients were taken individually and then cumulatively the various biomarkers levels will be statistically analyzed.

RESULTS

In total, 112 patients were selected for study out of which 8 were excluded due to various reasons as mentioned in exclusion criteria. Hence, the study was conducted on 104 patients. Out of which, 58 (55.8%) was in Grade 1 (mild cholecystitis), 32 (30.8%) was in Grade 2 (moderate cholecystitis), and 14 (13.5%) was in Grade 3 (severe cholecystitis).

AC was more prevalent in the age group of 21–60 years with significant P value ($P = 0.009$). AC was more prevalent among female patients, comorbidities were seen in 36 (34.625%) patients with significant $P = 0.004$.

In Grade 1, 23 (39.66%) patients showed Murphy sign positive, in Grade 2, 12 (37.5%) patients, and in Grade 3, 10 (71.43%) patients. Thus, Murphy's sign is not significant ($P = 0.072$).

In Grade 1, RUQ pain was seen in 33 (56.9%) out of 58 patients, in Grade 2 seen in 17 (53.33%) out of 32 patients, and in Grade 3, seen in 13 (92.86) out of 14 patients, thus RUQ pain is prevalent with significant $P = 0.028$.

Fever was seen in 33.65% of patients of AC with significant $P < 0.001$. Fifty-five (52.88%) patients showed positive USI findings with significant $P = 0.002$.

Various systemic dysfunctions are mainly seen in Grade 3, more prevalent are respiratory, renal, and liver dysfunction with significant *P* value.

Mean value of thin-layer chromatography (TLC) in Grade 1 was 10,509, 12,693 in Grade 2, and 17,452 in Grade 3, the value of TLC was abnormal in 29.31% of patients in Grade 1, 50% in Grade 2, and almost in all patients in Grade 3. Raised TLC is proven factor in AC according to Tokyo Guidelines.

CRP was raised in 86.21% of patients of Grade 1, 40.63% of patients of Grade 2, and almost in all patients of Grade 3 with significant *P* value.

ESR was raised in 15.52% of patients of Grade 1, 34.38% of patients of Grade 2, and 71.43% of patients of Grade 3 with significant *P* value. Both CRP and ESR are proven significant parameters in Tokyo Guidelines.

Mean value of PCT in Grade 1 was 0.63, 2.45 in Grade 2, and 9.55 in Grade 3.

Statistical features of WBC count, ESR, CRP, and PCT Levels according to grades are shown in Table 1.

Distribution of sensitivity and specificity of different blood parameters in different grades are shown in Table 2.

The value of PCT was raised in 13.79% of patients in Grade 1, 40.63% in Grade 2, and 78.57% in Grade 3. PCT level could discriminate Grade 2 from Grade 1 to 3 with 71.4% sensitivity and 88.9% specificity. However, PCT level could not discriminate Grade 1 from Grade 2 to 3 with 91.7% sensitivity and 20.6% specificity. Furthermore, PCT level could not discriminate Grade 3 from Grade 1 to 2 with 100% sensitivity and 61.5% specificity. Raised PCT not yet proven factor in AC. The prevalence of raised PCT is seen here with significant *P* < 0.001.

DISCUSSION

AC is a common complication of cholelithiasis. Delay in diagnosis increases the risk of morbidity and mortality; therefore, early diagnosis and determining the severity of AC are crucial.

AC might develop at any age, but its incidence is the highest at the 2nd and the 8th decade.^[9] The mean age of the patients in our study was in line with the literature.

Its prevalence increases with age, Pinto *et al.*^[10] and Cameron *et al.*^[11] found that the mean age of AC patients was 54 years. In our study, the mean age of patients with AC was 40 years,

which is almost in consistent with that reported in the literature. Therefore, we suggest that metabolic processes become catabolic and enzyme levels decrease with age and the formation of gallstones may lead to AC.

AC has been reported to develop in women 3 times more than in men up to the age of 50, after which the difference decreases. Gurer *et al.*^[12] found that the incidence was 4 times higher in women than in men who underwent laparoscopic cholecystectomy. In our study, the ratio of female patients was higher, female patient was 66.35% as compared to male patients, which is consistent with that reported in the literature.

In the literature, the specificity of Murphy's sign was stated as 35–98% and its sensitivity as 63–96% for AC

Table 1: Statistical features of WBC count, ESR, CRP, and PCT Levels according to grades

Grade	Area under the curve	Std. error	<i>P</i> value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Grade 1					
TLC	0.588	0.079	0.259	0.433	0.742
CRP	0.733	0.076	0.003	0.584	0.882
ESR	0.483	0.076	0.825	0.334	0.632
PCT	0.439	0.077	0.430	0.289	0.589
Grade 2					
TLC	0.929	0.060	<0.001	0.810	1.000
CRP	0.437	0.106	0.543	0.228	0.645
ESR	0.442	0.105	0.582	0.237	0.648
PCT	0.804	0.089	0.004	0.629	0.978
Grade 3					
TLC	0.808	0.111	0.321	0.589	1.000
CRP	0.231	0.124	0.385	<0.001	0.475
ESR	0.038	0.057	0.137	<0.001	0.151
PCT	0.692	0.135	0.535	0.428	0.957

TLC: Thin-layer chromatography, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PCT: Procalcitonin

Table 2: Distribution of sensitivity and specificity of different blood parameters in different grades

Grade	Blood parameters	Cutoff	Sensitivity	Specificity
Grade 1	TLC	10,450.000	0.529	0.750
	CRP	0.900	0.882	0.708
	ESR	5.000	1.000	0.235
	PCT	0.150	0.917	0.206
Grade 2	TLC	11,500.000	0.857	0.944
	CRP	4.500	0.357	0.778
	ESR	7.500	0.833	0.357
	PCT	1.650	0.714	0.889
Grade 3	TLC	18,650.000	1.000	0.769
	CRP	6.000	1.000	0.154
	ESR	6.000	0.923	1.000
	PCT	11.500	1.000	0.615

TLC: Thin-layer chromatography, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PCT: Procalcitonin

in the physical examination.^[13,14] Murphy's sign identified in 45 (43.27%) patients in our study not appeared as the most frequently seen physical examination finding, but in Grade 3, it was present in 10 (71.43%) patients.

Gallstone disease is one of the most common causes of RUQ pain. Gallstones are present in \square 10% of the population. In our study, RUQ pain was present in 63 (60.58%) of patients which is almost in consistent with that reported in the literature.

In AC, WBC count increases, but it is not specific to this condition and leukocytosis is not reliable for diagnosis, especially in patients admitted to the ED.^[15] The mean WBC value of our patients was 12115/mm³. When we examine the relationship between the clinical grade and WBC count, the mean was measured 10,400/mm³ in Grade 1, 12,693/mm³ in Grade 2, and 17,452/mm³ in Grade 3. In addition to severe AC^[16] and gangrenous cholecystitis,^[17] leukocyte counts were also found higher in the elderly than young patients.^[18] Like stated in the literature, the mean WBC count of the patients included in our study was found raised. Furthermore, we can see a statistical difference between the WBC count and severity grade. We also did not have patients with severe complications.

The delay in diagnosis can cause complications such as gangrene and perforation, which increase mortality and morbidity. Furthermore, the method of treatment and surgery choice might change in relation to the admission time to the ED after the beginning of the symptoms. We observed a higher grade of severity in our patients when their admission time was prolonged. However, the admission time did not affect the method of surgery.

CRP, which increases in 12–18 h as a result of tissue damage due to bacterial and viral infections, is a low specificity marker. It can be used to support the diagnosis of AC. Beliaev *et al.*^[19] showed that CRP level has better discriminative power than WBC count in most forms of AC and is a useful diagnostic marker of AC. CRP level increased in direct proportion with the severity of AC in literature which is consistent in our study.

In the literature, we found no studies that show a relationship between ESR and the clinical severity of cholecystitis. However, ESR is a marker with low sensitivity and specificity, which increases in several clinical conditions such as infections, autoimmune events, neoplasia, and pregnancy.^[19]

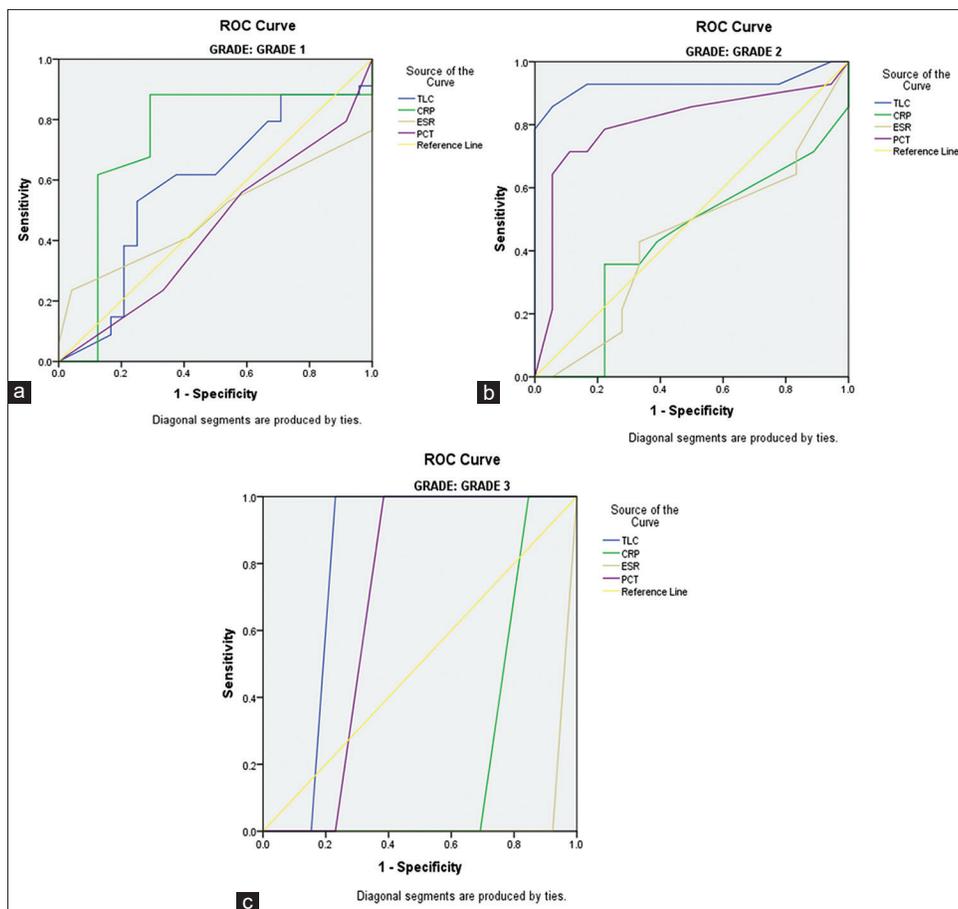
Ultrasonographic imaging examination determines the diagnosis of cholelithiasis with almost 98% sensitivity. Its diagnostic value for AC patients was reported as 54–90%

in the literature.^[20,21] Moreover, no correlation has been reported between USI findings and histopathological results for AC. We observed that only 55 (52.88%) of the AC patients had positive USI findings that confirmed the diagnosis. In the present study, we did not limit the criteria of positivity for AC to the presence of a gallbladder stone, also included an increase in the wall diameter of the gallbladder and pericholecystic fluid in the criteria.

We have found only two studies that investigated the effect of PCT level in determining the severity of AC. However, PCT level increases in proportion to the severity of systemic inflammation. However, the literature is scarce for PCT and cholecystitis. Yuzbasioglu *et al.* showed that PCT could be used as a laboratory parameter to define AC severity.^[22] They also described a positive relationship between PCT and CRP, leukocyte, and sedimentation levels. In another study, Sakalar *et al.*^[7] worked in the same topic and concluded that blood PCT levels can be used to determine the severity of AC effectively. A continual increase in PCT level indicates that infection has not been controlled and that treatment is insufficient. Al-Bahrami *et al.*^[23] and Reinhart and Meisner reported that PCT level is highly effective for showing the severity of inflammation in acute pancreatitis.^[13]

In our study, the rate of increases in PCT level in patients with AC was 32 (30.77%); this increase was correlated with the clinical status and increases in WBC count, CRP level, and ESR. ROC curves of different blood parameters are shown according to different grades in Graph 1. It is suggested that 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.^[24,25] It has been shown that in cases of bacterial invasion, PCT level increases and then returns to normal levels faster than CRP level.^[13] Considering that CRP level, ESR, and WBC count may increase for several reasons, PCT level may be more accurate in supporting the diagnosis of AC and in defining the clinical severity of the disease and therefore increasing the adequacy of the treatment. The data obtained from our patients demonstrated that PCT levels could be used as a diagnostic parameter in AC patients, it also could be used as an efficient parameter in the severity assessment.

Our study also revealed that the comorbidities were seen in 34% of patients which were statistically significant. We encounter a study which shows the relation of disease with comorbidities, Sol Lee *et al.*^[26] in his study concluded that male gender and old age are risk factors for AC, patients with diabetes or hypertension are apt to develop AC.



Graph 1: (a-c) Receiver operating characteristic curves for erythrocyte sedimentation rate, C-reactive protein, thin-layer chromatography, and procalcitonin levels according to stages

The treatment options vary according to severity, such as mild cholecystitis patients can be a candidate for laparoscopic cholecystectomy, moderate cholecystitis patients can be treated with laparoscopically or percutaneous cholecystostomy, and severe cases require percutaneous cholecystostomy. According to the Tokyo Guidelines 2018, laparoscopic cholecystectomy is recommended for mild and moderate AC patients.^[27] However, it is reported that laparoscopic cholecystectomy can be difficult in severe patients because of edema and adhesions. Therefore, it may be foreseen that PCT levels can be valuable in helping the decision of the surgical approach.

PCT level also affects the cost of the patient, increase in PCT level results in a prolonged hospital stay and consequently the cost increases.

CONCLUSION

AC is more prevalent in female gender and old age. The presence of fever or leukocytosis is significantly correlated with AC. Patients with comorbidities are more prone to develop AC, though further studies needed to validate this.

Moreover, the higher the severity level of the patients, the higher the PCT levels in patients. We found a difference between the patients PCT values and their severity grades of AC. PCT level alone is not effective for the assessment of the severity of AC, but may be considered to be a parameter that could be added to the assessment of the severity of AC in the Tokyo Guidelines, though more studies are needed to confirm the findings of this study.

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