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Using Plasma C-Reactive Protein and ESR Levels to Predict the Severity of Acute Cholecystitis

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Abstract: ***Background:*** *Acute cholecystitis (AC) is a frequent surgical emergency, often resulting from gallstone obstruction and subsequent inflammation of the gallbladder. Timely and accurate assessment of disease severity is critical for guiding clinical decisions regarding the urgency and type of intervention. The Tokyo Guidelines 2018 (TG18) provide standardized criteria for grading the severity of AC; however, the predictive utility of commonly used inflammatory markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in this context has not been adequately established.*

Aim of the study: *This study aimed to investigate the diagnostic value of CRP and ESR as early predictors of disease severity in patients with acute cholecystitis, using TG18 as the reference standard for severity classification.*

Methods: *A prospective diagnostic cohort study was conducted involving 65 patients diagnosed with acute cholecystitis at a tertiary care center. All patients were graded into mild (Grade I), moderate (Grade II), or severe (Grade III) categories according to the TG18 criteria upon admission. Venous blood samples were collected to measure CRP and ESR levels. Statistical analyses were performed using SPSS to determine the association and correlation of CRP and ESR with the severity of AC. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of these biomarkers and to identify optimal cutoff values.*

Result*: The study population had a mean age of 46.75 ± 13.44 years, with a higher prevalence in females (61.5%). Moderate severity (Grade II) AC was the most common presentation (60.0%), followed by mild (26.2%) and severe (13.8%) forms. Both CRP and ESR levels were significantly elevated in patients with higher grades of severity ($p<0.001$). CRP showed a strong positive correlation with severity grade ($r=0.803$), while ESR showed a moderate correlation ($r=0.652$). CRP demonstrated excellent diagnostic accuracy for predicting severe AC, with an area under the curve (AUC) of 0.962 (95% CI: 0.919–1.000), while ESR yielded an AUC of 0.873 (95% CI: 0.775–0.971). A CRP cutoff value of ≥117 mg/L predicted severe AC with 100% sensitivity and 89.1% specificity.*

Conclusion: *This study highlights that CRP and ESR, two widely available and cost-effective inflammatory markers, are significantly associated with the severity of acute cholecystitis when classified using the Tokyo Guidelines 2018. Among the two, CRP exhibited superior diagnostic accuracy and strong correlation with disease progression. These findings support the incorporation of CRP—alongside clinical and imaging criteria—as a reliable tool for early risk stratification and guiding management strategies in patients with acute cholecystitis.*

Keywords: *Acute cholecystitis, C-reactive protein, Erythrocyte sedimentation, Severity prediction, Inflammatory markers*

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Original Research Article

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INTRODUCTION

Acute cholecystitis is defined as an acute inflammation of the gallbladder, most commonly caused by obstruction of the cystic duct due to gallstones (cholelithiasis), leading to distension, ischemia, and secondary infection [1]. Clinically, it

presents with right upper quadrant abdominal pain, fever, nausea, vomiting, and leukocytosis, and frequently necessitates hospitalization and surgical intervention [2]. If untreated, the condition can progress to severe complications such as gallbladder gangrene, perforation, empyema, peritonitis, or septic shock, significantly increasing patient morbidity and mortality [3]. Gallstone disease, the leading cause of acute cholecystitis, is highly prevalent worldwide. Global epidemiological data suggest that approximately 10–15% of adults harbor gallstones, and 1–3% of these individuals develop acute cholecystitis annually [4]. The incidence is increasing in low- and middle-income countries, including those in South Asia, due to dietary shifts, rising rates of obesity, and increasingly sedentary lifestyles [5]. In Bangladesh, a hospital-based study reported that approximately 11.1% of adults have gallstones, and acute cholecystitis remains a principal reason for gallbladder-related surgical admissions [6]. This rising burden underscores the importance of timely diagnosis and severity assessment to improve clinical outcomes and minimize postoperative complications, including the need for conversion from laparoscopic to open cholecystectomy [7]. Inflammatory biomarkers are indispensable tools in the early detection and severity grading of acute cholecystitis. Among these, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are widely used in routine clinical practice because they are readily available, inexpensive, and easily measurable [8]. CRP is a hepatic acute-phase protein produced in response to pro-inflammatory cytokines, especially interleukin-6. It begins to rise within 6–8 hours of an inflammatory stimulus and peaks between 36–50 hours [9]. CRP has been incorporated into the diagnostic framework of the Tokyo Guidelines for acute cholecystitis due to its high sensitivity in detecting inflammation [10]. Nevertheless, its role in determining disease severity and predicting surgical complexity such as inflammation-induced adhesions or gallbladder wall necrosis remains under investigation [11]. On the other hand, ESR is a non-specific inflammatory marker that reflects the aggregation of red blood cells influenced by fibrinogen and other acute-phase reactants. While ESR is often elevated in both acute and chronic inflammatory conditions, its use as a prognostic tool in acute cholecystitis remains limited, and clearly defined cut-off values for severity prediction have yet to be established [12]. The Tokyo Guidelines 2018 (TG18) provide a standardized, evidence-based approach for the diagnosis and severity grading of acute cholecystitis, incorporating clinical signs, laboratory findings, and radiological criteria [13]. However, enhancing this framework with additional laboratory parameters such as CRP and ESR may refine clinical judgment, improve preoperative risk stratification, and guide surgical planning more effectively [14]. Therefore, this study aims to evaluate the association between plasma CRP and ESR levels and the severity of acute cholecystitis, with the objective of guiding clinical decision-making, anticipating operative difficulty, and improving overall patient outcomes.

MATERIAL AND METHODS

This was a diagnostic, observational cohort study conducted at the Department of Surgery, Khulna Medical College Hospital, Khulna, Bangladesh from January 2023 to December 2024 involving patients diagnosed with acute cholecystitis. The study was prospective in design and utilized quantitative data collected from patient records and laboratory investigations. The primary variables of interest were plasma levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), correlated with the clinical severity of cholecystitis as per the Tokyo Guidelines 2018 (TG18).

Inclusion Criteria

- Patients aged 18 years or older.
- Presenting with clinical symptoms suggestive of acute cholecystitis.
- Diagnosis confirmed based on clinical, laboratory, and ultrasonographic findings, following the Tokyo Guidelines 2018.
- Underwent laparoscopic or open cholecystectomy during the study period.
- Evidence of gallbladder inflammation confirmed intraoperatively.

Exclusion Criteria

- Patients with concurrent infections (e.g., respiratory, urinary, or systemic infections).
- Known history of autoimmune disorders or chronic inflammatory conditions (e.g., rheumatoid arthritis, inflammatory bowel disease).
- Presence of malignancy (any cancer diagnosis).
- Use of corticosteroids, immunosuppressants, or antibiotics prior to hospital admission.
- Incomplete medical records or missing laboratory data (CRP or ESR values).

Ethical Considerations

Ethical approval for the study was obtained from the Institutional Ethics Committee of [Department Name], and all procedures were conducted in accordance with the [Hospital Name]. Written informed consent was obtained from each participant after a detailed explanation of the study's objectives, procedures, potential risks, and confidentiality protocols.

Data Collection Procedure

Clinical data were obtained from hospital records, including demographic characteristics, laboratory parameters (CRP and ESR), imaging findings, and intraoperative observations. CRP and ESR were measured at the time of admission using standardized hospital laboratory protocols. The severity of cholecystitis was graded according to the TG18 criteria (Grade

I: mild, Grade II: moderate, Grade III: severe). Surgical technique (laparoscopic or open cholecystectomy) and intraoperative findings were recorded by the attending surgeon.

Surgical Techniques

Laparoscopic cholecystectomy was performed under general anesthesia. After insufflation and trocar placement (two 5 mm ports and two 10 mm ports), the Rouvière's sulcus was identified, and Calot's triangle was dissected to achieve the critical view of safety. Hemostasis was achieved by applying clips to the cystic duct and artery, and the gallbladder was detached from the liver bed. For open procedures, a right subcostal incision provided access to the gallbladder. The triangle of Calot was carefully dissected, and electrocautery or harmonic scalpel was used for gallbladder removal. Common bile duct exploration was performed in selected cases based on intraoperative findings such as elevated bilirubin or bile duct dilation.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 26. Descriptive statistics were used to summarize baseline characteristics. Continuous variables (e.g., CRP, ESR) were expressed as mean ± standard deviation or median with interquartile range, depending on normality. Categorical variables were presented as frequencies and percentages. The association between CRP and ESR levels and the severity grade of acute cholecystitis was assessed using the Chi-square test for categorical variables and ANOVA or Kruskal-Wallis test for continuous variables, as appropriate.

RESULTS

The study included sixty-five patients diagnosed with acute cholecystitis. The mean age was 43.95±12.75 years, with the highest number of patients belonging to the 41–50 years group, followed by those aged 31–40 and 51–60 years, as described in Table 1. Ultrasonographic findings demonstrated that most patients had a gall bladder wall thickness less than 4 mm and a common bile duct diameter under 6 mm. A majority had single stones, with the dominant size being greater than 1 cm. Impacted stones and bile spillage were absent in most individuals (Table 2). Inflammatory markers revealed that most patients had CRP levels below 1 mg/l, with a mean value of 4.123±4.99. The serum ESR was primarily within the 14–18 mm/hour range, and the mean ESR was 26.24±12.45 (Table 3). The distribution of patients by grade of cholecystitis showed that the majority had mild disease, followed by moderate and severe cases, as illustrated in Figure 1. Table 4 represented a significant association between age and the grade of cholecystitis. Mild disease was more common among patients under 30 years, whereas severe disease appeared more frequently among those aged 51–60 years. Moderate grades were observed across the middle age groups. Table 5 described the association between ultrasonographic parameters and severity. Mild cases were consistently associated with gall bladder wall thickness below 4 mm, common bile duct diameter under 6 mm, single stones, and absence of impacted stones or bile spillage. In contrast, moderate and severe cases demonstrated greater wall thickness, ductal dilation, multiple and larger stones, impacted stones, and bile spillage. Stone size showed near-significant correlation with disease grade. Table 6 demonstrated a strong relationship between CRP and cholecystitis severity. All mild cases had CRP levels below 1 mg/l. Moderate cases were associated with intermediate levels, while all severe cases showed values above 6 mg/l. The mean CRP was 0.782±0.248 in mild, 6.400±1.35 in moderate, and 14.60±3.37 in severe grades. Table 7 represented a similar trend with ESR levels, where mild cases fell within the lowest ESR range, moderate cases had intermediate elevations, and severe cases had the highest values. The mean ESR was 16.89±1.65 in mild, 35.60±3.28 in moderate, and 49.60±0.843 in severe cases.

Table 1: Distribution of cases according to age (n=65).

Variable	Frequency (N)	Percentage (%)
Age (years)		
≤30	10	15.38
31-40	17	26.15
41-50	20	30.77
51-60	12	18.46
>60	6	9.23
Mean±SD	43.95±12.75	

Table 2: Distribution of cases according to findings of ultrasonography (n=65).

USG parameters	Frequency (N)	Percentage (%)
Gall bladder wall thickness		
<4 mm	59	90.77
>4 mm	6	9.23
CBD diameter		
<6 mm	55	84.62
>6 mm	10	15.38

Number of stone		
Single	53	81.54
Multiple	12	18.46
Size of stone		
<1 cm	9	13.85
>1 cm	56	86.15
Impacted stone		
Absent	58	89.23
Present	7	10.77
Bile spillage		
Absent	52	80.00
Present	13	20.00

Table 3: CRP levels & Serum ESR in patients with acute cholecystitis (n=65).

Variable	Frequency (N)	Percentage (%)
CRP (mg/l)		
<1	39	60.00
1-6	10	15.38
>6	16	24.62
Mean±SD	4.123±4.99	
Serum ESR (mm/hour)		
14-18	34	52.31
19-38	20	30.77
39-50	11	16.92
Mean±SD	26.24±12.45	

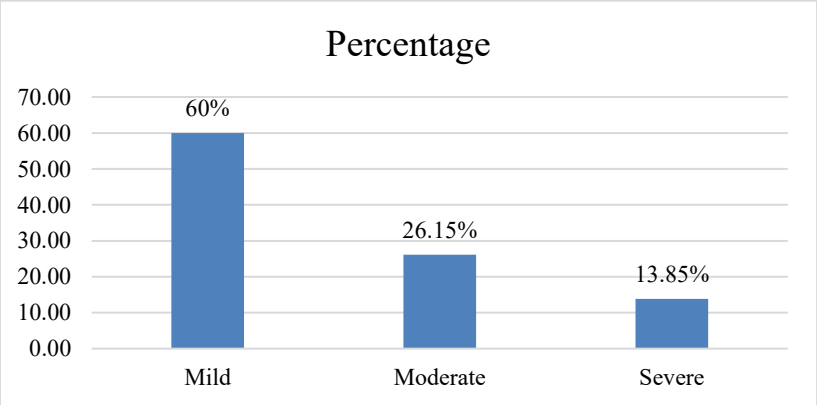

Figure 1: Distribution of patients according to grade of cholecystitis.

Table 4: Association of grade of acute cholecystitis with age (n=65).

Age (years)	Mild (n=35)		Moderate (n=15)		Severe (n=15)		χ^2	P value
	N	%	N	%	N	%		
<30	7	10.77	1	1.54	3	4.62	17.35	0.027
31-40	13	20.00	2	3.08	2	3.08		
41-50	10	15.38	6	9.23	3	4.62		
51-60	3	4.62	3	4.62	6	9.23		
>60	2	3.08	3	4.62	1	1.54		

Table 5: Association of grade of acute cholecystitis with USG findings (n=65).

Variables	Mild (n=35)		Moderate (n=20)		Severe (n=10)		χ^2	P value
	N	%	N	%	N	%		
Gall bladder wall thickness								
<4 mm	35	53.85	12	18.46	10	15.38	12.37	0.02
>4 mm	0	0.00	3	4.62	5	7.69		
CBD diameter								

<6 mm	33	50.77	11	16.92	9	13.85	10.59	0.005
>6 mm	2	3.08	4	6.15	6	9.23		
Number of stone								
Single	31	47.69	13	20.00	8	12.31	8.73	0.014
Multiple	4	6.15	2	3.08	7	10.77		
Size of stone								
<1 cm	4	6.15	2	3.08	6	9.23	5.93	0.052
>1 cm	31	47.69	13	20.00	9	13.85		
Impacted stone at neck of GB								
Absent	35	53.85	12	18.46	8	12.31	22.002	0.001
Present	0	0.00	3	4.62	7	10.77		
Bile spillage								
Absent	35	53.85	10	15.38	1	1.54	43.13	0.001
Present	0	0.00	5	7.69	14	21.54		

Table 6: Association of grade of acute cholecystitis with CRP (n=65).

CRP (mg/l)	Mild (n=35)		Moderate (n=15)		Severe (n=15)		χ^2	P value
	N	%	N	%	N	%		
<1	35	53.85	0	0.00	0	0.00	100	0.001
1-6	0	0.00	9	13.85	0	0.00		
>6	0	0.00	6	9.23	15	23.08		
Mean±SD	0.782±0.248		6.400±1.35		14.60±3.37			

Table 7: Association of grade of acute cholecystitis with ESR (n=65).

Serum ESR (mm/hour)	Mild (n=35)		Moderate (n=15)		Severe (n=15)		χ^2	P value
	N	%	N	%	N	%		
14-18	30	46.15	0	0.00	0	0.00	106.88	0.001
19-38	5	7.69	13	20.00	0	0.00		
39-50	0	0.00	2	3.08	15	23.08		
Mean±SD	16.89±1.65		35.60±3.28		49.60±0.843			

DISCUSSION

Plasma C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are widely used inflammatory markers that play an important role in predicting the severity of acute cholecystitis [15]. This study presents a comprehensive evaluation of acute cholecystitis, focusing on demographic patterns, ultrasonographic characteristics, levels of inflammatory markers, and severity grading according to standardized clinical guidelines. The mean age of patients in this study was 43.95±12.75 years, with the highest prevalence observed in the 41–50 years age group. This pattern is consistent with prior findings in Lasa et al, (2020), which reported a mean age of 50.3 years, suggesting a higher prevalence among middle-aged individuals [16]. However, contrasting data from Sun et al, (2019), reported a much younger cohort with a mean age of 25.84±3.3 years, reflecting possible regional, environmental, or genetic differences in disease onset [17]. Such variability highlights the importance of localized epidemiological data in understanding disease patterns. Ultrasonographic findings were essential in evaluating disease presentation. Most patients had gallbladder wall thicknesses less than 4 mm and common bile duct diameters below 6 mm. The presence of single gallstones larger than 1 cm was the most common finding, while impacted stones and bile spillage were relatively uncommon. These findings align with the study by [18], which emphasized gallbladder wall thickening and the presence of gallstones as significant ultrasonographic indicators of acute cholecystitis. The imaging results in this study further supported the role of ultrasonography in not only diagnosing but also assessing the extent and complications of the disease. In terms of inflammatory markers, the mean CRP level was 4.123±4.99 mg/L. Most mild cases had CRP levels below 1 mg/L, whereas severe cases had significantly elevated levels. The ESR levels had a mean value of 26.24 ± 12.45 mm/hour, with the majority of patients in the 14–18 mm/hour range. These values are comparable to previous studies [19], and are consistent with the observations made by [20], which identified a strong association between elevated CRP levels and severe cholecystitis. These findings underscore the utility of CRP and ESR in assessing disease severity. The severity grading of cholecystitis in this study revealed that mild cases were the most common, followed by moderate and then severe cases. This contrasts with findings from Matcuk et al, (2014), where grade 2 cholecystitis was more frequent [21]. Such differences may result from variations in patient populations, diagnostic criteria, or adherence to different clinical guidelines. The Tokyo Guidelines, provide a widely accepted framework for standardizing the diagnosis and severity classification of acute cholecystitis and likely contribute to improved consistency in reporting [22]. A significant association was also observed between patient age and disease severity. Younger patients, particularly those under 30, were more likely to have mild cholecystitis, while those aged 51–60 exhibited higher rates of moderate to severe disease. This trend mirrors findings from Riegler et al, (2000), which

reported increased severity with advancing age possibly due to age-related physiological decline or the presence of comorbidities [23]. Additionally, ultrasonographic abnormalities increased gallbladder wall thickness, dilated bile ducts, multiple or large gallstones, impacted stones, and bile leakage were more commonly seen in moderate to severe cases [24]. These features were less evident in mild cases, supporting the use of sonography for evaluating disease progression. These results are consistent with prior studies [25] that emphasized the role of ultrasonography in determining the extent of gallbladder inflammation. CRP and ESR levels also demonstrated a consistent correlation with disease severity. Mild cases showed low inflammatory marker levels, while higher levels were predominantly found in moderate and severe cases. These trends align with [25], further confirming the relevance of these markers as non-invasive tools for severity assessment in acute cholecystitis.

Limitations of the study:

- Single-center study, limiting the generalizability of findings.
- Small sample size (n=65), reducing statistical power.
- No long-term follow-up to assess prognostic outcomes.
- Absence of a control group for comparative analysis.
- Possible selection bias due to strict inclusion criteria.
- Sole reliance on Tokyo Guidelines 2018 without cross-validation.
- No histopathological correlation to confirm severity grading.

CONCLUSION AND RECOMMENDATIONS

This study highlights that serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are significantly associated with the severity of acute cholecystitis as per Tokyo Guidelines 2018. Both biomarkers demonstrated clear stepwise increases across mild, moderate, and severe cases, with CRP >6 mg/l and ESR >35 mm/h reliably identifying more severe disease. These findings suggest that CRP and ESR can serve as accessible, cost-effective early indicators of disease severity, aiding in timely triage and management decisions. However, larger multicenter studies with broader demographic representation are warranted to validate these biomarkers as standard predictors in clinical practice.

DECLARATIONS

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Ethical approval: *The study was approved by the Institutional Ethics Committee*

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