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Original Research Paper

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ROLE OF CRP IN ASSESSING SEVERITY OF ACUTE CHOLECYSTITIS.

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ABSTRACT

Background- Few studies have proposed C-reactive protein (CRP) as an indicator of the severity of acute cholecystitis. However, the evidence supporting the same is insufficient. Therefore, this study was undertaken to assess the diagnostic accuracy of CRP in determining the severity of Acute cholecystitis so that diagnosis of severity at hospital admission can help the surgeon decide on an appropriate therapy. **Materials & Methods-** This observational study included 33 patients with AC. Laboratory investigations included assessment of CRP levels and TLC count. In this study, the severity of AC was categorised as mild, moderate, and severe according to the TG 18 guidelines. Data were analysed using SPSS (Statistical Package for Social Sciences) 25.0 version, IBM, Chicago. **Results-** The grade I, II, and III AC was present in 63.6%, 24.2%, and 12.1% of patients respectively. The median (interquartile range) CRP levels 6.0 (1.71- 21.0). CRP levels significantly differed between grade I, II, and III AC patients (p-value= .003) [Table 1]. Post hoc analysis showed that the difference in CRP levels between grade I and grade II AC patients was non-significant (p-value= .250). The CRP levels were significantly greater among Grade III patients than Grade I (p-value= .001) and Grade II (p-value= = .029) patients. Thus, further analysis was done to assess the accuracy of CRP in diagnosing grade III AC. CRP showed an AUROC of 0.991 and an overall accuracy of 96.97% at a 134.0 mg/dL cut-off in differentiating Grade III AC from Grade I and II AC. **Conclusion-** CRP can accurately distinguish Grade II AC from Grade I and II AC.

KEYWORDS : Acute Cholecystitis, C Reactive Protein, Diagnostic Criteria, Severity Assessment.

INTRODUCTION

Acute cholecystitis (AC) is a disease that is frequently encountered by surgeons and it presents as a surgical emergency.[1] It is the acute inflammation of the gallbladder wall.[2] Cystic duct obstruction by gall bladder stones is responsible for 90% to 95% of the cases of acute cholecystitis, however, it may occur without the presence of stones (acalculous cholecystitis) in conditions of severe critical illness, autoimmune diseases, circulating toxins or vasoconstrictor substances, affecting chronically hospitalized patients, polytraumatized, septic, postoperative and elderly patients.[1,3]

It has been estimated that nearly 10–15% of the general population suffers from gallbladder stones and 10-15% 10–15% of the cases have acute calculus cholecystitis (ACC) is the first clinical presentation.[4] In AC, usually inflammation begins without infection, although infection may develop later. Inflammation causes thickening of the gallbladder wall and may cause the gallbladder to fill with fluid. Acute cholecystitis results in acute severe pain initially located in the right hypochondrium which may radiate to the epigastrium, and back and diffuse to the abdomen in the presence of complications. Patients may also develop fever, and nausea, which may be associated with eating.[1,3]

Management of AC includes cholecystectomy which can be performed laparoscopically or by open surgical method.[5] The treatment plan varies according to the severity of the AC. The 2013 update of the Tokyo Guidelines mentioned that grade I (mild) and grade II (moderate) AC patients should undergo early cholecystectomy i.e., within 72 hours of symptom emergence whereas Grade III (severe) AC patients which are characterized by end-organ failure and should be managed with urgent gallbladder drainage and delayed cholecystectomy, if endured by the patient.[6] Apart from the treatment plan, the severity of AC determines the outcome and prognosis of AC patients. Various guidelines including AAST (The American Association for the Surgery of Trauma) and TG 18 (Tokyo Guidelines 18) have been established to aid surgeons in characterizing the severity of AC.[7] These guidelines utilize the multifactorial characteristics of patients. Few studies have proposed C-reactive protein (CRP) as an indicator of the severity of acute cholecystitis. However, the evidence supporting the same is insufficient. Therefore, this study was undertaken to assess the diagnostic accuracy of CRP in determining the severity of Acute cholecystitis so that diagnosis of severity at hospital admission can help the surgeon decide on an appropriate therapy.

MATERIALS & METHODS

Study Design, Study Settings & Study Duration

This observational study was carried out in the Department of General Surgery in a tertiary care center in Indore City, M.P, India. It was conducted for a duration of 12 months (October 2023 to October 2024).

Study Population, Sample Size & Sampling Technique

This study included patients with Acute cholecystitis admitted to the Department of General Surgery. Adult patients were included in the study. Pregnant women and patients for whom insufficient medical information was available were excluded from the study.

The sample size was estimated using the G power 3.1.9.6 version. The sample size was estimated to achieve 99% power at 5% level of significance. The effect size was estimated to be 1.28 based on the values of CRP levels among Grade I, II & III AC given in the previous research by Kabul Gurbulak E et al.[8] The minimum required sample size was 18. However, 33 samples were included in the study. A convenience sampling technique was employed for the recruitment of the study subjects.

Methodology

Only those participants who were willing to participate were included in the study. Information related to age, gender, and presenting complaints were recorded. Laboratory investi-

gations included assessment of CRP levels and TLC count. In this study, the severity of AC was categorised as mild, moderate, and severe according to the TG 18 guidelines.[7]

Statistical Analysis Plan

Data were analysed using SPSS (Statistical Package for Social Sciences) 25.0 version, IBM, Chicago. Data were analysed for probability distribution using the Shapiro-Wilk test. Descriptive statistics were performed and data were described as numbers, percentages, mean ± standard deviation, and median (inter-quartile range). The inter-group comparison was done using Kruskal-Wallis test. The diagnostic accuracy of the CRP was assessed. P-value <.05 was considered statistically significant.

RESULTS

The mean ± standard deviation age of the patients was 49.24±14.656 years (range= 28 years to 77 years). The number of male and female patients was 19 (57.6%) and 14 (42.4%) respectively. There were 21 (63.6%), 8 (24.2%), and 4 (12.1%) patients with Grade I, II, and III AC respectively. All the patients had a complaint of pain. The median (interquartile range) duration of pain was 2.0 (2.0- 2.0) days [minimum duration- 1-day, maximum duration- 8 days]. Fever was the complaint among 8 (24.2%) subjects. The median (interquartile range) duration of pain was 3.0 (2.0- 4.0) days [minimum duration- 2 days, maximum duration- 4 days]. We found that 13 (39.4%) subjects had single calculus, 7 (21.2%) had multiple calculi, whereas 13 (39.4%) subjects had other etiology of AC. The mean ± standard deviation TLC count was 9025.81 ± 4439.00 cells/per cubic ml. The median (interquartile range) CRP levels 6.0 (1.71- 21.0). CRP levels significantly differed between grade I, II, and III AC patients (p-value= .003) [Table 1]. Post hoc analysis showed that the difference in CRP levels between grade I and grade II AC patients was non-significant (p-value= .250). The CRP levels were significantly greater among Grade III patients than Grade I (p-value= .001) and Grade II (p-value= = .029) patients. CRP showed an AUROC of 0.991 with a sensitivity of 100.0%. specificity of 96.55% and overall accuracy of 96.97% at a 134.0 mg/dL cut-off in differentiating grade III AC from Grade I and Grade II AC. CRP showed an AUROC of 0.655 with a sensitivity of 62.50%, specificity of 80.95%, and an overall accuracy of 75.86% at a 13.33 mg/dL cut-off in differentiating grade I AC from Grade II AC. CRP showed an AUROC of 0.969 with a sensitivity of 100.0%, specificity of 87.505% and overall accuracy of 91.67% at a 134.0 mg/dL cut-off in differentiating grade II AC from Grade III AC. [Table 2][Figure 1,2,3]

DISCUSSION

Acute cholecystitis if not treated promptly and efficiently can lead to serious complications.[9] The world's first guidelines for managing AC were introduced in 2007 as The Tokyo Guidelines for managing acute cholangitis and cholecystitis (TG07). These guidelines were later revised in 2013 [Tokyo Guidelines 2013 (TG13)] which are still adopted as TG18/TG13 diagnostic criteria and severity grading of acute cholecystitis without any modification.[7] These guidelines utilize the multifactorial characteristics of patients. Therefore, it was thought to identify such factors which can give quick insight into the severity of AC. Literature suggests that CRP levels can be a reliable predictor of severe conditions of inflammation in acute cholecystitis. However, there is a lack of evidence supporting this, therefore, the present study was undertaken.

In our study, there were 21 (63.6%), 8 (24.2%), and 4 (12.1%) patients with Grade I, II, and III AC respectively. Yuzbasioglu YU et al. also observed an almost similar proportion of Grade I, II, and III AC in their study. They found the severity of AC to be mild in 57.6%, moderate in 28.8%, and severe in 13.6% of patients.[10]

CRP is an acute-phase reactant protein that is produced during the acute phase of an inflammatory/infectious process.[11] The levels of CRP increase within 6–10 hours of any tissue-damaging event. The increase in CRP levels correlates with the level of tissue damage and associated inflammation.[12] This is reflected in the findings of our study also, CRP levels were highest to lowest in Grade III AC patients, followed by Grade II AC patients, followed by Grade I AC patients. The difference in CRP levels between grade I and grade II AC patients was non-significant (p-value= .250). The CRP levels were significantly greater among Grade III patients than Grade I (p-value= .001) and Grade II (p-value= = .029) patients. Similar to the findings of the present study, Kabul Gurbulak E et al. reported CRP levels of 18.96 mg/L in Grade I, 133.51 mg/L in Grade II, and 237.23 mg/L in Grade III AC patients (P < 0.001).[8] We found CRP to have an AUROC of 0.991 with a sensitivity of 100.0%. specificity of 96.55% and overall accuracy of 96.97% at a 134.0 mg/dL cut-off in differentiating grade III AC from Grade I and Grade II AC. CRP showed an AUROC of 0.655 with a sensitivity of 62.50%, specificity of 80.95%, and an overall accuracy of 75.86% at a 13.33 mg/dL cut-off in differentiating grade I AC from Grade II AC. CRP showed an AUROC of 0.969 with a sensitivity of 100.0%, specificity of 87.505% and overall accuracy of 91.67% at a 134.0 mg/dL cut-off in differentiating grade II AC from Grade III AC. Similar findings were reported by Kabul Gurbulak E et al.[8] Sato N et al. also found that inflammation-based prognostic scores including C-reactive protein/albumin (CRP/Alb) ratio and neutrophil-to-lymphocyte ratio (NLR) could predict the severity grade independently in patients with AC.[13] Yuzbasioglu YU et al. found a rise in CRP levels with the increase in the severity of AC.[10]

According to Schäfer M et al. laboratory markers such as CRP can be used to predict the severity of inflammation.[14] Few researchers have studied the role of CRP in differentiating between complicated and uncomplicated AC. They found that CRP showed an AUC (area under the curve) of 0.773 (95% CI: 0.698- 0.849) in differentiating between complicated and uncomplicated AC.[15]

Our study and previous studies suggest that CRP can be used for accurately distinguishing Grade I, II, and Grade III AC patients. Thus, CRP levels may play a complementary role in predicting disease severity in patients with AC in conjunction with the Tokyo guidelines severity grade.

Limitations of the Study

The study included small sample size with disproportionate distribution of patients with Grade I, II, and III AC.

Table 1. Comparison of CRP Levels Among Subjects with Different Severity of Acute Cholecystitis.

Severity	Median (interquartile range)	Mean rank	Kruskal-wallis H value	p-value
Grade 1 (n= 21)	4.12 (0.75-9.0) mg/dL	13.76	11.255	.004*
Grade II (n=8)	17.66 (1.7525-101.0) mg/dL	18.38		
Grade III (n=4)	231.5 (160.0-264.75) mg/dL	31.25		

Kruskal-Wallis test. *p-value<.05 was considered statistically significant.

Table 2. Diagnostic Accuracy of CRP in Differentiating Grade I, II, and III.

Statistics	Grade I vs. Grade II		Grade II vs. Grade III		Grade I & II vs. Grade III	
	Value	95% CI	Value	95% CI	Value	95% CI
AUROC	0.655	0.402-0.908	0.969	0.876-1.000	0.991	0.965-1.000
Cut off	13.33	-	134.0	-	134.0	-

Sensitivity	62.50 %	24.49% to 91.48%	100.00 %	39.76% to 100.00%	100.00%	39.76% to 100.00%
Specificity	80.95 %	58.09% to 94.55%	87.50 %	47.35% to 99.68%	96.55 %	82.24% to 99.91%
Positive Likelihood Ratio	3.28	1.17 to 9.21	8.00	1.28 to 50.04	29.00	4.23 to 198.98
Negative Likelihood Ratio	0.46	0.18 to 1.16	0.00	-	0.00	-
Positive Predictive Value	55.56 %	30.81% to 77.82%	80.00 %	39.00% to 96.16%	80.00 %	36.83% to 96.48%
Negative Predictive Value	85.00 %	69.34% to 93.42%	100.00 %	59.04% to 100.00%	100.00%	87.66% to 100.00%
Accuracy	75.86 %	56.46% to 89.70%	91.67 %	61.52% to 99.79%	96.97 %	84.24% to 99.92%

CI- Confidence interval

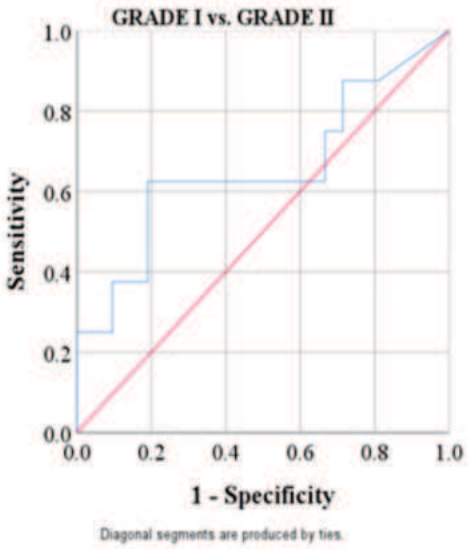

Figure 1. ROC Curve Showing AUROC of CRP in Differentiating Between Grade I from Grade II AC.

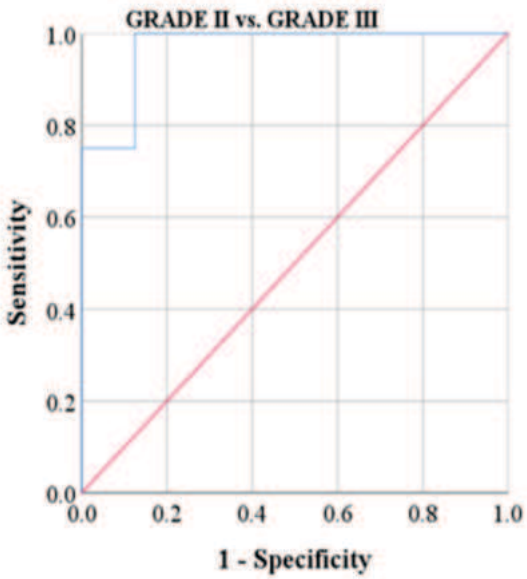

Figure 2. ROC Curve Showing AUROC of CRP in Differentiating Between Grade II from Grade III AC.

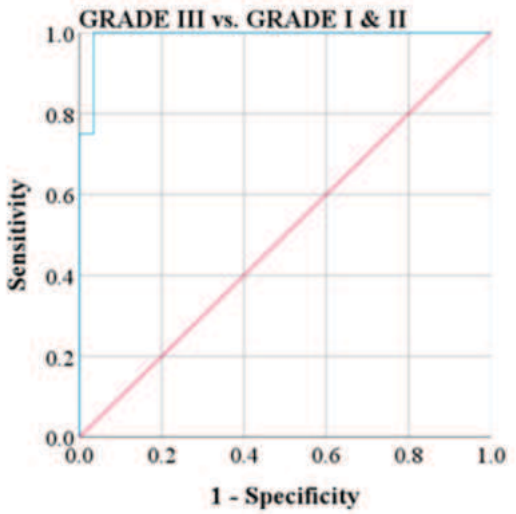

Figure 3. ROC Curve Showing AUROC of CRP in Differentiating Between Grade I & II from Grade III AC.

CONCLUSION

CRP can be used for accurately differentiate between Grade I, II and III grade III AC patients.

Ethical Consideration

The study was conducted after obtaining approval from the Institutional Ethics Committee [Registration number-SAIMS/IEC/282/2021]. Written informed consent was obtained from the participants or their legal representatives. Confidentiality of data was maintained.

Conflict of Interest: None

Financial Inputs and Fundings: None

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