Original Article

Predictive Role Of C-Reactive Protein (CRP) In Determining The Severity Of Acute Cholecystitis Presenting In The Emergency Department Of A Tertiary Care Hospital

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Abstract

Objective: This research aims to explore the predictive role of CRP in determining the severity and grading of acute cholecystitis, particularly in our local population presenting to the emergency department.

Methods: A Cross-sectional (validation) study was conducted at the Department of Surgery, Holy Family Hospital, Rawalpindi, on 288 patients aged 18 to 70 years who had clinical symptoms suggestive of acute cholecystitis. Baseline CRP levels from blood samples taken at the time of admission were determined. Additional CRP measurements were taken at predefined intervals, such as 24 hours and 48 hours after admission. All patients were subjected to follow-up imaging findings via Histopathology as a gold standard technique. The hospital lab was used for the results of the investigation, i.e CRP.

Results: CRP levels sensitivity was (93.30%), specificity (85.32%), PPV (91.26%), NPV (88.57%), and diagnostic accuracy (90.28%) in predicting the severity of the acute cholecystitis, taking histopathology as the gold standard.

Conclusion: According to the study's findings, CRP has a good predictive value for assessing the severity and grading of acute cholecystitis and can be used as a diagnostic criterion for the condition.

Keywords: acute cholecystitis, severity, CRP, predictive value, sensitivity.

Contributions:
HW, BIK, AN, AK - Conception, Design
HW, BIK, AA, QA - Acquisition, Analysis, Interpretation
HW, BIK, AN, QA - Drafting
HW, BIK, AA, AK - Critical Review

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Introduction

Acute cholecystitis (AC) is one of the most common gastrointestinal emergency conditions, characterised by inflammation of the gallbladder.[1] AC is usually caused by the obstruction of the cystic duct, mainly due to gallstones, which can block the flow of bile and lead to inflammation. Early assessment of its severity is crucial for timely and appropriate management due to its complications.[2,3] The Tokyo guidelines state that the physical examination, test results, and radiologic evaluation are all part of the diagnostic criteria.[3,4]

The liver produces the nonspecific acute-phase reactant protein CRP, which is correlated with the degree of inflammation and infection.[4] Therefore, it can act as a potential biomarker for predicting the severity of inflammatory diseases,[4,5,] but whether or not the CRP is linked with disease severity and grading in patients with acute cholecystitis needs to be explored. For acute inflammatory reactions, CRP levels up to 10 mg/L are typically regarded as clinically unimportant.[6] Several studies reported a correlation between CRP level and cholecystitis.[7,8]

A study noted the occurrence of acute cholecystitis as the first clinical presentation in 12.3% of gallstone cases.[9] Mehmood et al. reported that considering the cut-off CRP level at 55 mg/L, the sensitivity and specificity of CRP in predicting Complicated Acute Cholecystitis were 73.9% and 73.1% respectively.[10] According to a different study, ROC curve analysis predicted surgical difficulties of grade IV or V at laparoscopic cholecystectomy with a cut-off CRP value of 90 mg/l, 71.5% sensitivity, and 70.5% specificity.[11]

Acute cholecystitis can be diagnosed using CRP level, although there is currently no recommended critical or cut-off level of CRP to categorise the disease's grades. This research aims to explore the predictive role of CRP in determining the severity and grading of acute cholecystitis, particularly in our local population presenting to the emergency department. This study contributes to the existing knowledge by providing evidence on the clinical utility of CRP as a predictive marker and helps in improving the early identification and management of patients with acute cholecystitis in the emergency setting.

Materials And Methods

This cross-sectional validation study was conducted on 288 patients aged 18 to 70 years presenting to the Department of Surgery, Holy Family Hospital, Rawalpindi, and who had clinical symptoms suggestive of acute cholecystitis (e.g., right upper quadrant pain, fever, leukocytosis) and ultrasound finding (Pericholecystic fluid, Gall bladder wall thickness, Edema of GB). The sample size of 288 was calculated by using the sensitivity specificity calculator (using the following data: Confidence level = 95%, Sensitivity 73.9%[10], Specificity = 73.1%[10], Prevalence = 26.1%[10], Precision = 10%). Using a non-random consecutive sampling strategy, patients were chosen. Patients with a history of cholecystectomy, known history of chronic inflammatory conditions, pregnant patients, recently undergone any surgical procedure and accompanying pancreatitis or cholangitis were excluded.

This study was conducted after the approval of the institutional ethical review board. Informed consent was taken from all the patients before assigning them to the study. Medical history, presenting symptoms and demographic data (age, weight, height, and BMI) of all patients were recorded in a predesigned Performa (Annexe I).

Age, gender, comorbidities, obesity, time of presentation (Patients presenting at different stages of the disease) and antibiotic use before admission are the confounding variables of the study that must be controlled to ensure the internal validity and reliability of the results and to isolate the effect of CRP on the outcomes.

There was no bias, as all eligible patients were included and the selection process was not influenced by certain characteristics. Furthermore, a validated method of measurements and blinding of the assessor interpreting the imaging studies to the patient details mitigated this. Baseline CRP levels from blood samples taken at the time of admission were determined. Additional CRP measurements were taken at predefined intervals, such as 24 hours and 48 hours after admission, which provided a CRP trend during the early phase of acute cholecystitis. All patients were subjected to follow-up imaging findings via Histopathology as a gold standard technique. The hospital lab was used for the results of the investigation, i.e CRP.

Data was analysed using SPSS version 23.0. Qualitative variables like gender, HTN, DM, and obesity were expressed in the form of frequency and percentages and quantitative variables like age, duration of symptoms, and CRP levels were expressed as mean (Standard deviation) and median (range). Sensitivity, specificity, Positive predictive value, negative predictive value and accuracy were calculated by a 2x2 table as follows. Data was stratified for gender, age and duration of symptoms, HTN, DM and obesity. Post-stratification, diagnostic accuracy was calculated.

		Histopathology	
		+	-
CRP	+	TP	FP
	-	FN	TN

Results

The study's age range was 18–70 years old, with a mean age of 48.94 ± 9.74 years. According to Table I, the majority of the patients—184, or 63.89%—were in the 45–70 age range. Out of these 288 patients, 131 (45.49%) were males and 157 (54.51%) were females, with a male-to-female ratio of 1:1.2. The symptoms lasted 4.99 ± 2.15 days on average. Table I displays the distribution of patients with different variables. Mean CRP levels were 98.23 ± 9.43 mg/L

Of the patients who tested positive for acute cholecystitis on CRP levels, 167 (True Positive) had acute cholecystitis, while 16 (False Positive) had no acute cholecystitis on histopathology. Of the 105 patients who tested negative for CRP levels, 12 (False Negative) had acute cholecystitis on histopathology, but 93 (True Negative) did not (p=0.0001), as Table 2 demonstrates. CRP levels sensitivity was (93.30%), specificity (85.32%), PPV (91.26%), NPV (88.57%), and diagnostic accuracy (90.28%) in predicting the severity of the acute cholecystitis, taking histopathology as the gold standard. Table 3 displays the diagnosis accuracy stratification by gender, age and duration of symptoms, HTN, DM and obesity.

Table 1: Distribution of patients with other confounding variables (n=288)

Confounding variables		Frequency	%age
Age (years)	18-45	104	36.11
	46-70	184	63.89
Gender	Male	131	45.49
	Female	157	54.51
Duration of disease (days)	≤5	165	57.29
	>5	123	42.71
BMI (kg/m2)	≤30	171	59.38
	>30	117	40.62
HTN	Yes	125	43.40
	No	163	56.60
DM	Yes	132	45.83
	No	156	54.17

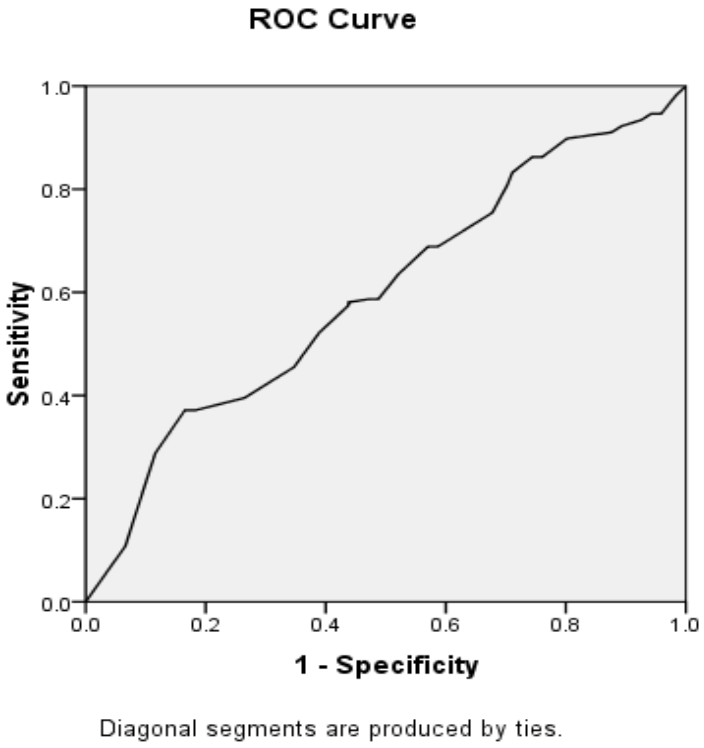

Figure 1: Receiver Operating Characteristic (ROC) curve of CRP levels in predicting the severity of acute cholecystitis

Table 2: Diagnostic accuracy of CRP levels in predicting the severity of acute cholecystitis, taking histopathology as the gold standard

	Histopathology (+ive)	Histopathology (-ive)	P-value
CRP (+ive)	167 (True positive)	16 (False Positive)	
CRP (-ive)	12 (False negative)	93 (True Negative)	0.0001

Sensitivity: 93.30%
Specificity: 85.32%
Positive Predictive Value (PPV): 91.26%
Negative Predictive Value (NPV): 88.57%
Likelihood ratio for positive test result: 6.36
Likelihood ratio for negative test result: 0.078
Diagnostic Accuracy: 90.28%

Table 3: Stratification of diagnostic accuracy concerning gender, age and duration of symptoms, HTN, DM and obesity

		Sensitivity	Specificity	PPV	NPV	DA	
Age (years)	18-45	88.14%	88.89%	91.23%	85.11%	88.46%	0.001
	46-70	97.25%	80.43%	92.17%	92.50%	92.26%	0.001
Gender	Male	91.84%	87.50%	91.84%	87.50%	90.12%	0.001
	Female	97.14%	83.78%	91.89%	93.94%	92.52%	0.001
Duration (days)	≤5	92.91%	88.10%	92.19%	89.16%	90.99%	0.001
	>5	97.56%	76.47%	90.91%	92.86%	91.38%	0.001
BMI (kg/m2)	≤30	92.78%	90.48%	93.75%	89.06%	91.88%	0.001
	>30	95.77%	78.95%	89.47%	90.91%	89.91%	0.001
DM	Yes	93.20%	88.68%	94.12%	87.04%	91.67%	0.001
	No	95.38%	83.33%	88.57%	93.02%	90.27%	0.001
HTN	Yes	97.14%	83.78%	91.89%	93.94%	92.52%	0.001
	No	92.91%	88.10%	92.19%	89.16%	90.99%	0.001

Discussion

Significant inflammatory alterations are linked to acute cholecystitis, a disorder typified by gallbladder inflammation, and the severity of cholecystitis may be predicted using inflammation markers. The Tokyo recommendations criteria state that radiologic evaluation, laboratory data (such as WBC, CRP, etc.), and physical examination results should be used to diagnose acute cholecystitis. The factors to determine the severity of the condition are also suggested by these guidelines.[12] However, according to Tokyo recommendations, CRP has been utilised as a marker for diagnosis but not for determining the severity of acute cholecystitis.[13] In addition to CRP, another acute phase reactant that is a non-specific indicator of inflammation is ESR, which begins to increase 6 to 8 hours after inflammation starts. According to Tokyo guidelines, CRP should be used instead of ESR.[13] There were 288 people with acute cholecystitis in all, with an average age of 48.94 ± 9.74 years. According to research, women are around 1.5 times more likely than men to develop acute calculous cholecystitis after the age of 50, and three times more likely to do so before that.[14] The bulk of the cases in our study were from those between the ages of 46 and 70, with cases from those between the ages of 18 and 45 coming in second. Consequently, the majority of our research participants were middle-aged. In our study, we found a slight female preponderance for acute cholecystitis, with a female: male ratio of 1.2:1. Nearly half of the incidents involved females. Patients between the ages of 51 and 60 had more severe cholecystitis than patients under the age of 50, even though we could not identify a significant association between gender and cholecystitis grade. Our study's findings were supported by Gurbulak et al., who discovered that the mean age of patients with acute cholecystitis was 51.61±16.65 years, and that women made up 60.8% of the total. The mean ages of patients with mild, moderate, and severe cholecystitis were 48.97, 55.06, and 68.78 years, respectively, suggesting that cholecystitis severity rose with age. However, the majority of patients were female across all severity groups.[14]

The average age of the patients in a study by Muhammad et al. was 40.32±5.3 years. The authors discovered that 75% of instances of acute cholecystitis were in women, and that about half of the patients were over 40.[15] Sakalar et al. found a significant correlation between the severity of acute cholecystitis and advancing age ($p<0.05$), but not with gender ($p>0.05$), which supported our study's findings, even though the study's mean patient age was higher than ours (59.87±1.96 years) and that there was a reported male predominance (50.5%).[16] Our findings were also supported by Park et al.'s findings. In comparison to patients with grade II (64.3±15.4 years) and grade I (56.9±13.9 years), they found that patients with grade III AC (69.9±9.9 years) were significantly older ($p<0.05$).[17]

The acute phase of an inflammatory or infectious condition occurs when CRP, an acute-phase reactant protein, is generated.[18] Within six to ten hours of every tissue-damaging incident, CRP levels rise. The degree of tissue injury and related inflammation is correlated with elevated CRP levels.[12] This is also supported by the results of our investigation, which showed that Grade III AC patients had the highest CRP levels, followed by Grade II AC patients and Grade I AC patients.

Using histopathology as the gold standard, the current study found that CRP levels had a sensitivity of 93.30%, specificity of 85.32%, PPV of 91.26%, NPV of 88.57%, and diagnostic accuracy of 90.28 in predicting the severity of acute cholecystitis. Similar results were published by Kabul.[10] Sato N et al.,[20] and Gurbulak E et al.,[19] also discovered that prognostic factors based on inflammation, such as C-reactive protein, may predict the severity grade in patients with AC on their own. Laboratory indicators like CRP can be used to predict the degree of inflammation, claim Schäfer M et al.[21.] The function of CRP in distinguishing between complex and uncomplicated AC has not been well investigated. They discovered that when it came to distinguishing between difficult and simple AC, CRP displayed an AUC of 0.773.[21]

According to Mohammad et al., patients with acute cholecystitis had significantly higher CRP levels than the control group (75% versus 33.3%; $p<0.05$).[22] The results of Gurbulak et al.,[20,] who found that the mean CRP levels in patients with acute cholecystitis increased with the severity of disease. The authors discovered a correlation between mean CRP levels and disease severity, meaning that CRP levels rose as disease severity increased ($p<0.05$).[20]

Additionally, Rai K et al.,[23] found that CRP was a strong predictor of acute cholecystitis severity ($p<0.05$), with higher CRP values corresponding to higher infection grades. The results of our investigation also aligned with those of Utsumi et al.[24] In comparison to the group responding to treatment, the group not responding to medical treatment had the highest mean CRP levels, indicating a greater grade of Ac (19.3±13.9 versus 9.6±5.2; $p=0.0003$). Additionally, Yilmaz S et al.,[25] demonstrated that CRP

was a significant criterion for differentiating between individuals with acute cholecystitis and those with moderate cholecystitis ($p<0.05$).

There were certain restrictions on the current investigation. The results could not be generalised because the investigation was only carried out at one location. Second, only the severity of acute cholecystitis with CRP was evaluated; the patients' long-term results were not.

Conclusions

According to the study's findings, a patient's CRP level can be utilised as a diagnostic criterion for acute cholecystitis, and it has a significant predictive effect in assessing the severity and grading of acute cholecystitis in patients who arrive at the emergency room. By demonstrating the clinical usefulness of CRP as a predictive marker, this study advances our understanding of the condition and facilitates the early detection and treatment of individuals with acute cholecystitis in an emergency situation.

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