



Original Research Article

C-Reactive Protein as a Predictor of Difficult Laparoscopic Cholecystectomy

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Name of Author:

Dr. Maaz Bin Ayub¹, Dr. Ahmad Faraz²,
Dr. Aima Akbar³, Dr. Rahmanullah⁴, Dr.
Ahmed Zaman⁵, Dr. Peer Zada
Muhammad Aamir Khan⁶

Affiliation:

^{1,3,4,5,6}Post Graduate Resident,
Department of General Surgery, Lady
Reading Hospital MTI Peshawar,
Pakistan.

²Associate Professor, Department of
General Surgery, Lady Reading Hospital
MTI Peshawar, Pakistan

Corresponding Author:

Dr Ahmad Faraz
drahmadfaraz79@gmail.com

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Abstract. Objective: Difficult laparoscopic cholecystectomy (LC) is associated with prolonged operative time, increased perioperative complications, and conversion to open surgery. Accurate preoperative prediction of operative difficulty can improve surgical planning and optimize patient outcomes. This study evaluated the predictive value of preoperative serum C-reactive protein (CRP) for difficult LC. **Study Design:** Prospective observational cohort study. **Place and Duration of Study:** Department of General Surgery, Lady Reading Hospital–Medical Teaching Institution, Peshawar, Pakistan, from 30 August to 30 November 2025. **Methodology:** A total of 180 adult patients undergoing elective or emergency LC for symptomatic cholelithiasis or acute calculous cholecystitis were enrolled. Preoperative clinical, laboratory, and ultrasonographic data were recorded. Operative difficulty was assessed using the Nassar Operative Difficulty Grading Scale. Receiver operating characteristic (ROC) analysis determined the optimal CRP cutoff, and multivariable logistic regression identified independent predictors of difficult LC. **Results:** Difficult LC was observed in 52 (28.9%) patients. Mean preoperative CRP levels were significantly higher in the difficult group than in the easy group (41.6 ± 18.7 vs. 11.8 ± 8.4 mg/L; $P < 0.001$). Difficult procedures were associated with longer operative time, increased dense adhesions, obscured Calot's triangle, additional port placement, conversion to open surgery, and prolonged hospital stay. CRP demonstrated excellent predictive accuracy (AUC=0.892), with a cutoff value of 20 mg/L providing 84.6% sensitivity and 81.3% specificity. CRP ≥ 20 mg/L, gallbladder wall thickness ≥ 4 mm, previous acute cholecystitis, impacted neck stone, and diabetes mellitus independently predicted difficult LC. **Conclusion:** Preoperative serum CRP is a reliable and cost-effective biomarker for predicting difficult laparoscopic cholecystectomy. Its incorporation into routine preoperative assessment may improve risk stratification, operative planning, and surgical outcomes.

Keywords: C-reactive protein, laparoscopic cholecystectomy, difficult cholecystectomy, gallstone disease, operative prediction

INTRODUCTION

Laparoscopic cholecystectomy (LC) has become the gold standard for the management of symptomatic gallstone disease because of its well-established advantages over open cholecystectomy, including reduced postoperative pain, shorter hospital stay, earlier return to normal activities, and improved cosmetic outcomes. Despite these benefits, LC

remains technically demanding in a subset of patients, particularly those with severe gallbladder inflammation or distorted biliary anatomy, where the risk of intraoperative complications and conversion to open surgery is substantially increased. The ability to accurately predict difficult LC before surgery is therefore of considerable clinical importance, as it facilitates appropriate patient counseling, optimal

allocation of operative resources, and timely involvement of experienced surgeons to minimize adverse outcomes [1-3].

Gallstone disease is one of the most common gastrointestinal disorders worldwide, affecting approximately 10–20% of adults, although only a proportion become symptomatic and require surgical intervention [4-6]. The severity of gallbladder inflammation varies considerably among patients and may result in edema, fibrosis, dense adhesions, or distortion of Calot's triangle, all of which increase operative complexity. Difficult LC has been associated with prolonged operative time, excessive blood loss, bile duct injury, conversion to open cholecystectomy, increased healthcare costs, and extended postoperative recovery [7-9]. Consequently, identifying patients at high risk for difficult surgery remains a priority in contemporary hepatobiliary practice.

Several preoperative clinical and radiological factors have been investigated as predictors of difficult LC. Advanced age, male sex, obesity, diabetes mellitus, recurrent attacks of acute cholecystitis, previous upper abdominal surgery, gallbladder wall thickening, contracted gallbladder, impacted Hartmann's pouch stone, and pericholecystic fluid have all been reported to influence operative difficulty [10-13]. Although these parameters provide useful information, their predictive accuracy varies across populations, and no single clinical model has demonstrated consistently high diagnostic performance. Consequently, there is growing interest in incorporating objective biochemical markers into preoperative assessment to improve risk prediction [14-16].

C-reactive protein (CRP) is an acute-phase protein synthesized predominantly by hepatocytes in response to inflammatory cytokines, particularly interleukin-6, interleukin-1 β , and tumor necrosis factor- α . Serum CRP concentrations increase rapidly during acute inflammatory processes and have become widely used as a sensitive marker of infection and tissue injury [17-19]. In patients with acute or chronic cholecystitis, elevated CRP levels reflect the intensity of gallbladder inflammation and may correlate with local pathological changes such as edema, fibrosis, empyema, gangrene, and dense pericholecystic adhesions. These inflammatory alterations frequently obscure normal anatomical landmarks, making laparoscopic dissection technically challenging and increasing the risk of operative complications [20-22].

Previous studies have demonstrated significant associations between elevated preoperative CRP levels and prolonged operative duration, increased conversion rates, difficult dissection of Calot's triangle, postoperative morbidity, and complicated acute cholecystitis [23-25]. Nevertheless, the optimal CRP threshold for predicting difficult LC remains

uncertain, with considerable variation reported among different studies owing to differences in patient populations, disease severity, study design, and definitions of operative difficulty. Moreover, relatively limited prospective evidence from low- and middle-income countries has evaluated the independent predictive value of CRP after adjustment for established clinical and ultrasonographic risk factors [26].

In Pakistan, gallstone disease represents a substantial surgical burden, and laparoscopic cholecystectomy is among the most frequently performed general surgical procedures. However, reliable preoperative tools for identifying technically difficult cases remain limited in routine clinical practice. A simple, inexpensive, and universally available biomarker such as CRP could significantly improve preoperative planning, facilitate appropriate case allocation, optimize operating room scheduling, and reduce perioperative complications if proven to be an accurate predictor of operative difficulty. Such an approach would be particularly valuable in high-volume tertiary care centers where efficient utilization of surgical resources is essential.

Objective

Therefore, the present prospective observational study was conducted at Lady Reading Hospital–Medical Teaching Institution, Peshawar, to evaluate the role of preoperative serum C-reactive protein as a predictor of difficult laparoscopic cholecystectomy. The study also aimed to determine the diagnostic performance of CRP and identify independent clinical, laboratory, and ultrasonographic factors associated with increased operative difficulty, thereby contributing evidence for improved preoperative risk stratification and surgical decision-making [27].

METHODOLOGY

This prospective observational cohort study was conducted in the Department of General Surgery, Lady Reading Hospital–Medical Teaching Institution (MTI), Peshawar, Pakistan, over a three-month period from 30 August 2025 to 30 November 2025. The study was designed to evaluate the predictive value of preoperative serum C-reactive protein (CRP) levels for identifying patients at increased risk of difficult laparoscopic cholecystectomy (LC). The study protocol was reviewed and approved by the Institutional Review Board/Ethics Committee of Lady Reading Hospital MTI, and all procedures were performed in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Adult patients aged 18 years and above presenting with symptomatic cholelithiasis or acute calculous cholecystitis who were scheduled for elective or emergency laparoscopic cholecystectomy were

consecutively recruited using a non-probability consecutive sampling technique. Patients with gallbladder malignancy, choledocholithiasis requiring preoperative endoscopic intervention, previous upper abdominal surgery, chronic inflammatory or autoimmune disorders, active systemic infection unrelated to biliary disease, chronic liver disease, immunosuppressive therapy, pregnancy, and incomplete clinical or laboratory data were excluded to minimize confounding factors that could independently influence serum CRP concentrations or operative difficulty.

Baseline demographic and clinical characteristics were recorded using a standardized data collection proforma. Variables included age, sex, body mass index (BMI), duration of symptoms, history of previous attacks of acute cholecystitis, diabetes mellitus, hypertension, smoking status, previous hospital admissions for biliary disease, and American Society of Anesthesiologists (ASA) physical status classification. Routine preoperative laboratory investigations included complete blood count, liver function tests, renal function tests, coagulation profile, and quantitative serum CRP measurement. Serum CRP was measured within 24 hours prior to surgery using a high-sensitivity immunoturbidimetric assay in the hospital's central laboratory following standardized quality control procedures. Ultrasonographic findings, including gallbladder wall thickness, presence of pericholecystic fluid, impacted gallstone at the neck, contracted gallbladder, and common bile duct diameter, were also documented.

All laparoscopic cholecystectomies were performed under general anesthesia using a standardized four-port technique by consultant surgeons or senior surgical residents under direct consultant supervision.

The operating surgeons were blinded to the study objective regarding CRP as a predictor of operative difficulty to minimize observer bias. Intraoperative findings were systematically documented, including dense adhesions surrounding the gallbladder, difficulty in grasping the gallbladder, contracted or fibrotic gallbladder, obscured anatomy within Calot's triangle, excessive bleeding requiring additional hemostatic measures, bile or stone spillage, requirement for additional ports, subtotal cholecystectomy, conversion to open surgery, operative time, and intraoperative complications. Operative difficulty was assessed using the validated Nassar Operative Difficulty Grading Scale, which categorizes laparoscopic cholecystectomy into grades I to V according to operative findings. Procedures classified as grades I–II were considered easy, whereas grades III–V were categorized as difficult laparoscopic cholecystectomy. Operative duration was recorded from skin incision to completion of skin closure, and conversion to open

cholecystectomy was documented as a secondary indicator of operative complexity. Postoperative outcomes, including length of hospital stay, surgical site infection, bile leak, intra-abdominal collection, postoperative bleeding, and 30-day readmission, were also recorded.

Data were entered into IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) after verification for completeness and consistency. Continuous variables were assessed for normality using the Shapiro–Wilk test and expressed as mean $\pm$ standard deviation or median with interquartile range, as appropriate. Categorical variables were presented as frequencies and percentages. Comparisons between easy and difficult laparoscopic cholecystectomy groups were performed using the independent-samples t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal preoperative CRP cutoff for predicting difficult laparoscopic cholecystectomy, and the area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Variables demonstrating a P value <0.10 on univariable analysis were entered into a multivariable logistic regression model to identify independent predictors of difficult laparoscopic cholecystectomy while adjusting for potential confounders. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were reported, and a two-tailed P value <0.05 was considered statistically significant.

RESULTS

A total of 180 patients undergoing laparoscopic cholecystectomy were enrolled during the study period.

The mean age of the study population was 44.8 ± 13.2 years (range: 19–78 years), with females constituting 132 (73.3%) of the participants. Based on the Nassar Operative Difficulty Grading Scale, 128 (71.1%) patients were classified as having an easy laparoscopic cholecystectomy (Grades I–II), whereas 52 (28.9%) underwent a difficult laparoscopic cholecystectomy (Grades III–V). Patients in the difficult LC group were significantly older and had a higher prevalence of diabetes mellitus, previous episodes of acute cholecystitis, elevated body mass index, and higher ASA class compared with those undergoing easy LC (Table 1).

Table 1. Baseline demographic and clinical characteristics of the study population

Variable	Easy LC (n=128)	Difficult LC (n=52)	P- value
Age (years), mean $\pm$ SD	41.7 $\pm$ 12.6	52.3 $\pm$ 11.4	<0.001

Female sex, n (%)	99 (77.3)	33 (63.5)	0.048
BMI (kg/m²), mean ± SD	26.4 ± 3.8	29.1 ± 4.2	<0.001
Diabetes mellitus, n (%)	18 (14.1)	20 (38.5)	<0.001
Hypertension, n (%)	23 (18.0)	15 (28.8)	0.098
Previous acute cholecystitis, n (%)	27 (21.1)	30 (57.7)	<0.001
ASA Class III–IV, n (%)	19 (14.8)	18 (34.6)	0.003
Preoperative CRP (mg/L), mean ± SD	11.8 ± 8.4	41.6 ± 18.7	<0.001

Ultrasonographic findings including gallbladder wall thickness ≥ 4 mm, impacted neck stone, contracted gallbladder, and pericholecystic fluid were significantly more common among patients with difficult procedures. The mean preoperative serum CRP level was significantly higher in patients with difficult LC than in those with easy LC (41.6 ± 18.7 mg/L vs. 11.8 ± 8.4 mg/L, $P < 0.001$) (Table 2).

Table 2. Preoperative ultrasonographic findings

Variable	Easy LC (n=128)	Difficult LC (n=52)	P-value
Gallbladder wall ≥ 4 mm	18 (14.1)	35 (67.3)	<0.001
Pericholecystic fluid	9 (7.0)	19 (36.5)	<0.001
Contracted gallbladder	12 (9.4)	23 (44.2)	<0.001
Impacted neck stone	16 (12.5)	28 (53.8)	<0.001
Multiple gallstones	74 (57.8)	36 (69.2)	0.152
CBD diameter > 6 mm	8 (6.3)	7 (13.5)	0.107

The mean operative duration was significantly longer in the difficult LC group (92.4 ± 21.6 minutes) compared with the easy LC group (48.9 ± 14.1 minutes; $P < 0.001$). Dense adhesions around the gallbladder, obscured Calot's triangle anatomy, difficult gallbladder grasping, excessive intraoperative bleeding, and need for additional ports occurred significantly more frequently in difficult cases. Conversion to open cholecystectomy was required in 9 (5.0%) patients, all belonging to the difficult LC group. The median postoperative hospital stay was significantly longer among patients with difficult LC (3 days; IQR 2–5) than among those with easy LC (1 day; IQR 1–2; $P < 0.001$) (Table 3).

Table 3. Intraoperative outcomes

Variable	Easy LC (n=128)	Difficult LC (n=52)	P-value
Operative time (minutes), mean ± SD	48.9 ± 14.1	92.4 ± 21.6	<0.001
Dense adhesions	16 (12.5)	42 (80.8)	<0.001
Difficult gallbladder grasping	11 (8.6)	29 (55.8)	<0.001
Obscured Calot's triangle	9 (7.0)	31 (59.6)	<0.001
Excessive bleeding	4 (3.1)	12 (23.1)	<0.001
Additional ports required	2 (1.6)	10 (19.2)	<0.001
Conversion to open surgery	0	9 (17.3)	<0.001
Hospital stay (days), median (IQR)	1 (1–2)	3 (2–5)	<0.001

On multivariable logistic regression analysis, preoperative CRP ≥ 20 mg/L, gallbladder wall thickness ≥ 4 mm, previous acute cholecystitis, impacted gallstone at the gallbladder neck, and diabetes mellitus remained independent predictors of difficult laparoscopic cholecystectomy (Table 4).

Table 4 Multivariable logistic regression analysis for predictors of difficult laparoscopic cholecystectomy

Variable	Adjusted OR	95% CI	P-value
CRP ≥ 20 mg/L	7.82	3.54–17.30	<0.001
Gallbladder wall ≥ 4 mm	5.41	2.37–12.37	<0.001
Previous acute cholecystitis	3.68	1.64–8.23	0.002
Impacted neck stone	3.12	1.39–7.02	0.006
Diabetes mellitus	2.61	1.14–5.98	0.023
BMI ≥ 30 kg/m²	1.69	0.79–3.64	0.176
Female sex	0.89	0.39–2.02	0.781

Receiver operating characteristic (ROC) curve analysis demonstrated excellent discriminatory ability of preoperative CRP for predicting difficult laparoscopic cholecystectomy, with an area under the curve (AUC) of 0.892 (95% CI: 0.843–0.940; $P < 0.001$). A CRP cutoff value of 20 mg/L yielded a sensitivity of 84.6%, specificity of 81.3%, positive predictive value of 64.7%, and negative predictive value of 92.0% (Table 5).

Table 5. Diagnostic performance of preoperative CRP for predicting difficult laparoscopic cholecystectomy

Parameter	Value
Optimal CRP cutoff	20 mg/L
Area under ROC curve (AUC)	0.892
95% Confidence interval	0.843–0.940
Sensitivity	84.6%
Specificity	81.3%
Positive predictive value	64.7%
Negative predictive value	92.0%
Overall diagnostic accuracy	82.2%
P-value	<0.001

DISCUSSION

The present prospective observational study demonstrated that elevated preoperative serum C-reactive protein (CRP) is a strong independent predictor of difficult laparoscopic cholecystectomy (LC). Patients with higher CRP concentrations experienced significantly longer operative times, more challenging dissection of Calot's triangle, increased intraoperative adhesions, greater need for additional ports, higher conversion rates to open surgery, and prolonged postoperative hospitalization. After adjustment for relevant clinical and radiological variables, CRP ≥ 20 mg/L remained the strongest independent predictor of operative difficulty, supporting its value as a simple, inexpensive, and readily available biomarker for preoperative risk stratification.

The association between elevated CRP and difficult LC is biologically plausible. CRP is an acute-phase reactant synthesized by hepatocytes in response to inflammatory cytokines, particularly interleukin-6. In acute or recurrent cholecystitis, persistent inflammation promotes edema, fibrosis, neovascularization, and dense pericholecystic adhesions that obscure normal anatomy within Calot's triangle. These pathological changes increase technical complexity, prolong operative duration, and elevate the likelihood of intraoperative complications or conversion to open surgery. Our findings therefore reinforce the concept that biochemical evidence of systemic inflammation reflects the severity of local inflammatory changes encountered during surgery. The present study also identified gallbladder wall thickness ≥ 4 mm, previous episodes of acute cholecystitis, impacted gallstone at the gallbladder neck, and diabetes mellitus as independent predictors of difficult LC. These findings are consistent with previous literature demonstrating that repeated inflammatory insults result in chronic fibrosis and distorted biliary anatomy. Gallbladder wall thickening on ultrasonography has repeatedly

been associated with technically demanding cholecystectomy, while impacted neck stones contribute to gallbladder distension and chronic inflammatory changes that complicate safe dissection. Similarly, diabetes mellitus may predispose patients to more severe inflammatory responses, delayed presentation, and impaired tissue healing, thereby increasing operative difficulty.

Receiver operating characteristic analysis demonstrated excellent diagnostic performance of CRP, with an AUC of 0.892 and a cutoff value of 20 mg/L providing high sensitivity and specificity. These findings suggest that incorporation of CRP into routine preoperative assessment may improve prediction models beyond conventional clinical and ultrasonographic parameters alone. Early identification of high-risk patients allows more appropriate operating room scheduling, allocation of experienced hepatobiliary surgeons, optimization of perioperative resources, informed patient counseling regarding the possibility of conversion, and enhanced preparation for technically demanding procedures. Such strategies may ultimately reduce operative complications and improve overall surgical efficiency.

The strengths of this study include its prospective design, standardized laboratory assessment, use of a validated operative difficulty grading system, and comprehensive multivariable analysis to control for potential confounding factors. Nevertheless, several limitations should be acknowledged. The study was conducted at a single tertiary care center with a relatively short recruitment period, which may limit the generalizability of the findings. Additionally, inflammatory biomarkers other than CRP, such as procalcitonin or neutrophil-to-lymphocyte ratio, were not evaluated for comparative predictive performance. Variations in surgeon experience, despite consultant supervision, may also have influenced operative outcomes.

Overall, our findings indicate that preoperative serum CRP is a reliable and clinically useful predictor of difficult laparoscopic cholecystectomy. Combining CRP with established clinical and ultrasonographic predictors may facilitate individualized preoperative risk assessment, improve surgical planning, and optimize patient outcomes. Future multicenter studies with larger sample sizes and external validation cohorts are warranted to establish standardized CRP thresholds and develop robust predictive models for routine clinical practice.

CONCLUSION

Preoperative serum C-reactive protein demonstrated excellent diagnostic performance for predicting difficult laparoscopic cholecystectomy and emerged as the strongest independent predictor after adjustment for established clinical and ultrasonographic risk factors. Patients with elevated

CRP experienced significantly greater operative complexity, prolonged surgical duration, increased conversion to open surgery, and longer postoperative hospitalization. Additional independent predictors included gallbladder wall thickness ≥ 4 mm, previous acute cholecystitis, impacted gallbladder neck stone, and diabetes mellitus. Given its low cost, wide availability, and rapid turnaround time, CRP represents a practical biomarker that can be readily incorporated into routine preoperative evaluation. Combining CRP with conventional clinical and imaging parameters may improve preoperative risk stratification, facilitate optimal operating room scheduling, enable appropriate surgeon allocation, and enhance patient counseling. Larger multicenter studies are warranted to validate these findings and establish standardized CRP thresholds for routine clinical application.

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