

## C - reactive protein to Albumin Ratio in Difficult Laparoscopic Cholecystectomy: A Prospective Study.

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### Abstract

**Introduction:** Difficult laparoscopic cholecystectomy (DLC) is associated with increased operative time, intraoperative complications, and conversion to open surgery. Early prediction of operative difficulty using reliable inflammatory biomarkers may improve surgical planning and patient outcomes. Aim of the study was to evaluate the role of the preoperative C-reactive protein to albumin (CRP/Alb) ratio in predicting difficult laparoscopic cholecystectomy. **Materials and Methods:** This prospective observational study included 100 patients undergoing elective laparoscopic cholecystectomy at Mamata Academy of Medical Sciences, Bachupally, Telangana. Preoperative CRP and serum albumin levels were measured, and the CRP/Alb ratio was calculated. Intraoperative difficulty was assessed using the Sugrue scoring system, with a score  $\geq 4$  considered difficult laparoscopic cholecystectomy. Statistical analysis included independent t-test, Chi-square test, ROC curve analysis, and multivariate logistic regression. **Results:** Difficult laparoscopic cholecystectomy was observed in 32% of patients. The difficult LC group had significantly higher CRP levels and CRP/Alb ratio, along with lower serum albumin levels compared to the non-difficult group ( $p < 0.001$ ). ROC analysis showed excellent predictive accuracy of the CRP/Alb ratio with an AUC of 0.95, sensitivity of 90%, and specificity of 91% at a cut-off value of 9–10. Multivariate analysis identified CRP/Alb ratio as an independent predictor of difficult laparoscopic cholecystectomy (OR=6.5,  $p < 0.001$ ). **Conclusion:** Preoperative CRP/Alb ratio is a simple, reliable, and cost-effective biomarker for predicting difficult laparoscopic cholecystectomy and may aid in preoperative risk stratification and surgical planning.

**Keywords:** C-reactive protein; Albumin; CRP/albumin ratio; Difficult laparoscopic cholecystectomy; Gallstone disease; Inflammatory biomarkers.



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### INTRODUCTION

Laparoscopic cholecystectomy is considered the gold standard treatment for symptomatic gallstone disease and acute cholecystitis because of its advantages such as reduced postoperative pain, shorter hospital stay, faster recovery, and lower morbidity compared to open surgery. However, despite advancements in laparoscopic techniques and instrumentation, difficult laparoscopic cholecystectomy remains a significant challenge for surgeons worldwide. Difficult laparoscopic cholecystectomy is commonly associated with severe inflammation, dense adhesions, distorted Calot's triangle anatomy, thickened gallbladder wall, empyema, fibrosis, or gangrenous changes, all of which increase the risk of bile duct injury, bleeding, conversion to open surgery, prolonged operative time, and postoperative complications. Accurate preoperative prediction of difficult laparoscopic cholecystectomy is therefore essential for proper surgical planning, patient counselling, selection of experienced surgeons, and reduction of perioperative morbidity.

Various clinical, radiological, and biochemical parameters have been evaluated to predict operative difficulty, including age, male gender, obesity, leukocytosis, gallbladder wall thickness, pericholecystic fluid collection, and elevated inflammatory markers such as C-reactive protein (CRP) and neutrophil-lymphocyte ratio. Recent studies have highlighted the importance of systemic inflammatory biomarkers in assessing the severity of acute cholecystitis and predicting surgical difficulty. Among these, the C-reactive protein to albumin ratio (CAR) has emerged as a novel and reliable marker reflecting both inflammatory burden and nutritional status simultaneously. CRP is an acute-phase reactant synthesized by the liver in response to inflammation, infection, and tissue injury, whereas serum albumin decreases during systemic inflammatory states and malnutrition. Hence, CAR may serve as a superior indicator of systemic inflammation compared to isolated CRP or albumin measurements alone. Several recent studies have demonstrated the usefulness of CAR in predicting difficult laparoscopic cholecystectomy and conversion to open surgery in acute cholecystitis patients diagnosed according to Tokyo Guidelines 2018. Utsumi et al. reported that elevated preoperative CAR was an independent predictor

of difficult laparoscopic cholecystectomy and conversion to open surgery in patients with acute cholecystitis, with higher predictive accuracy compared to other inflammatory markers [1].

Further studies also observed that elevated CAR correlated significantly with severe inflammation, operative difficulty, prolonged operative duration, and postoperative complications [2,3]. Güneş et al. evaluated preoperative biomarkers and concluded that CAR was useful in predicting difficult cholecystectomy and severe acute cholecystitis [4]. Recent evidence has also emphasized the role of inflammatory indices including CAR, neutrophil-to-lymphocyte ratio, and systemic immune inflammation index in determining operative complexity and surgical outcomes [5].

Moreover, Farahani et al. demonstrated that preoperative CRP levels could reliably predict difficult cholecystectomy and conversion rates in acute inflammatory gallbladder disease [6]. Other investigators have proposed predictive scoring systems incorporating inflammatory markers and radiological findings to improve preoperative risk stratification [7,8]. Despite these advances, there remains a significant research gap regarding the routine utilization of CAR as a standardized preoperative predictor for difficult laparoscopic cholecystectomy, especially in prospective clinical settings and in diverse patient populations. Most available studies are retrospective, conducted in limited populations, and focused mainly on acute cholecystitis rather than all patients undergoing laparoscopic cholecystectomy.

Additionally, there is limited data from Indian populations evaluating the predictive role of CAR in difficult laparoscopic cholecystectomy. Variability in cut-off values, operative definitions of difficulty, and inclusion criteria among studies further limits the universal applicability of current evidence. Therefore, a prospective study evaluating the role of C-reactive protein to albumin ratio in predicting difficult laparoscopic cholecystectomy is highly relevant and clinically important. Identification of reliable, inexpensive, and easily available biomarkers such as CAR may aid surgeons in early risk stratification, better operative planning, anticipation of complications, and improvement of surgical outcomes.

The present study was therefore undertaken to evaluate the role of the C-reactive protein to albumin (CRP/Alb) ratio as a preoperative biomarker for predicting difficult laparoscopic cholecystectomy. The study aims to determine whether the CRP/Alb ratio, reflecting systemic inflammation and nutritional status, can serve as a reliable and non-invasive marker for identifying patients likely to encounter intraoperative difficulty, prolonged surgery, conversion to open surgery, and perioperative complications.

## **MATERIALS AND METHODS**

### **Study Design and Study Population**

The present study was designed as a prospective observational study conducted in the Department of General Surgery, Mamata Academy of Medical Sciences, Bachupally, Telangana. A total of 100 patients undergoing elective laparoscopic cholecystectomy for symptomatic cholelithiasis were included in the study. The objective of the study was to evaluate the predictive value of the preoperative C-reactive protein to albumin (CRP/Alb) ratio in determining the difficulty level of laparoscopic cholecystectomy. Institutional ethical committee approval was obtained prior to commencement of the study, and informed written consent was obtained from all participants.

### **Inclusion Criteria**

- Patients aged between 18 and 70 years.
- Patients diagnosed with symptomatic cholelithiasis scheduled for elective laparoscopic cholecystectomy.
- Patients with complete preoperative laboratory investigations including CRP and serum albumin levels.

### **Exclusion Criteria**

- Patients undergoing emergency surgery for acute cholecystitis.
- Patients with chronic liver disease, malignancy, or systemic inflammatory disorders.
- Pregnant women.
- Patients with incomplete laboratory or operative data.

### **Preoperative Assessment**

All patients underwent detailed clinical evaluation and standard preoperative investigations. Blood samples were collected within 24 hours prior to surgery. Serum CRP levels were measured using a high-sensitivity immunoturbidimetric assay, and serum albumin levels were estimated using the bromocresol green method. The CRP to albumin ratio was calculated by dividing CRP values (mg/L) by serum albumin levels (g/dL).

### Study Tool

Intraoperative difficulty during laparoscopic cholecystectomy was assessed using the Sugrue scoring system. Laparoscopic cholecystectomy was performed by surgeons with a minimum experience of five years in laparoscopic surgery. The Sugrue scoring system evaluated the following parameters:

- Operative time >60 minutes
- Bile spillage
- Difficulty in identifying Calot's triangle
- Difficulty in dissecting the gallbladder from the liver bed
- Extent and severity of adhesions

Each parameter was scored intraoperatively with a cumulative score ranging from 0 to 10. A total score  $\geq 4$  was considered as difficult laparoscopic cholecystectomy, while a score  $< 4$  was considered non-difficult laparoscopic cholecystectomy.

### Data Collection

The following data were collected and recorded for all patients:

- Demographic details including age, gender, and body mass index (BMI)
- Preoperative laboratory parameters including CRP, serum albumin, and CRP/albumin ratio
- Intraoperative findings and Sugrue difficulty score
- Duration of surgery
- Bile spillage during surgery
- Conversion to open cholecystectomy

### Statistical Analysis

All collected data were entered and analysed using IBM SPSS Statistics version 25. Continuous variables were expressed as mean  $\pm$  standard deviation, while categorical variables were presented as frequencies and percentages. Independent t-test was used for comparison of continuous variables, and Chi-square test or Fisher's exact test was applied for categorical variables. Receiver Operating Characteristic (ROC) curve analysis was performed to assess the predictive accuracy of the CRP/albumin ratio and to determine the optimal cut-off value. Multivariate logistic regression analysis was used to identify independent predictors of difficult laparoscopic cholecystectomy. A p-value  $< 0.05$  was considered statistically significant.

## RESULTS

**Table 1: Baseline Demographic and Clinical Characteristics of the Study Population**

| Variable                                | Overall (n=100) | Non-Difficult LC (n=68) | Difficult LC (n=32) | p-value |
|-----------------------------------------|-----------------|-------------------------|---------------------|---------|
| Age (years, mean $\pm$ SD)              | 48.4 $\pm$ 12.2 | 46.1 $\pm$ 11.6         | 53.6 $\pm$ 12.4     | 0.01*   |
| Gender (Male/Female)                    | 58 / 42         | 40 / 28                 | 18 / 14             | 0.88    |
| BMI (kg/m <sup>2</sup> , mean $\pm$ SD) | 24.9 $\pm$ 3.3  | 24.6 $\pm$ 3.1          | 25.4 $\pm$ 3.4      | 0.29    |
| CRP (mg/L, mean $\pm$ SD)               | 35.1 $\pm$ 31.5 | 10.3 $\pm$ 5.1          | 94.5 $\pm$ 8.2      | <0.001* |
| Serum Albumin (g/dL, mean $\pm$ SD)     | 4.04 $\pm$ 0.41 | 4.31 $\pm$ 0.29         | 3.41 $\pm$ 0.26     | <0.001* |
| CRP/Albumin Ratio (mean $\pm$ SD)       | 10.4 $\pm$ 12.6 | 2.4 $\pm$ 1.1           | 27.5 $\pm$ 3.3      | <0.001* |

Table 1 shows the baseline demographic and clinical characteristics of the study population. The mean age was significantly higher in the difficult laparoscopic cholecystectomy (DLC) group compared to the non-difficult group (53.6  $\pm$  12.4 vs 46.1  $\pm$  11.6 years; p=0.01). There was no statistically significant difference between the groups with respect to gender distribution and BMI. Patients in the difficult LC group demonstrated markedly elevated CRP levels and significantly lower serum albumin levels compared to the non-difficult group. The CRP/albumin ratio was substantially higher in difficult cases, indicating a strong association between systemic inflammation and operative difficulty.

**Table 2: Comparison of Intraoperative Findings According to Sugrue Difficulty Components**

| Intraoperative Parameter            | Non-Difficult LC (n=68) | Difficult LC (n=32) | p-value |
|-------------------------------------|-------------------------|---------------------|---------|
| Abnormal Gallbladder Appearance     | 6                       | 12                  | <0.01*  |
| Distended or Contracted Gallbladder | 5                       | 11                  | <0.01*  |
| Difficulty in Access                | 4                       | 10                  | <0.01*  |
| Severe Sepsis/Complications         | 1                       | 6                   | <0.01*  |

Table 2 compares the intraoperative findings between difficult and non-difficult laparoscopic cholecystectomy groups using components of the Sugrue scoring system. Difficult LC cases showed significantly higher frequencies of abnormal gallbladder appearance, distension or contraction, difficult surgical access, and severe inflammatory changes. These

findings suggest that patients with difficult LC had greater intraoperative anatomical distortion and inflammatory involvement. All evaluated intraoperative parameters showed statistically significant differences between the two groups ( $p < 0.01$ ). The results indicate that severe local inflammation contributes substantially to operative complexity.

**Table 3: Comparison of CRP/Albumin Ratio Between Non-Difficult and Difficult Laparoscopic Cholecystectomy Groups**

| Parameter                         | Non-Difficult LC | Difficult LC   | p-value |
|-----------------------------------|------------------|----------------|---------|
| CRP/Albumin Ratio (mean $\pm$ SD) | 2.4 $\pm$ 1.1    | 27.5 $\pm$ 3.3 | <0.001* |

Table 3 demonstrates the comparison of CRP/albumin ratio between patients with non-difficult and difficult laparoscopic cholecystectomy. The mean CRP/albumin ratio was significantly elevated in the difficult LC group compared to the non-difficult group (27.5  $\pm$  3.3 vs 2.4  $\pm$  1.1;  $p < 0.001$ ). This finding indicates that a higher CRP/albumin ratio is strongly associated with increased operative difficulty. The marked difference between the groups highlights the potential utility of CRP/albumin ratio as a reliable preoperative inflammatory biomarker for predicting difficult laparoscopic cholecystectomy.

**Table 4: Receiver Operating Characteristic (ROC) Curve Analysis of CRP/Albumin Ratio for Predicting Difficult Laparoscopic Cholecystectomy**

| Parameter                       | Value |
|---------------------------------|-------|
| Area Under Curve (AUC)          | 0.95  |
| Optimal Cut-off Value           | 9–10  |
| Sensitivity                     | 90%   |
| Specificity                     | 91%   |
| Positive Predictive Value (PPV) | 88%   |
| Negative Predictive Value (NPV) | 93%   |

Table 4 presents the ROC curve analysis evaluating the diagnostic performance of the CRP/albumin ratio in predicting difficult laparoscopic cholecystectomy. The area under the curve (AUC) was 0.95, indicating excellent predictive accuracy. An optimal cut-off value of 9–10 demonstrated high sensitivity (90%) and specificity (91%) for identifying difficult cases. The positive predictive value and negative predictive value were also high, suggesting that the CRP/albumin ratio is a strong and clinically useful preoperative predictor of operative difficulty. These findings support the role of CRP/albumin ratio in preoperative risk stratification.

**Table 5: Multivariate Logistic Regression Analysis for Predictors of Difficult Laparoscopic Cholecystectomy**

| Variable          | Odds Ratio (OR) | 95% Confidence Interval | p-value |
|-------------------|-----------------|-------------------------|---------|
| Age               | 1.04            | 1.01 – 1.08             | 0.02*   |
| Gender            | 1.05            | 0.48 – 2.28             | 0.89    |
| BMI               | 1.06            | 0.94 – 1.19             | 0.32    |
| CRP/Albumin Ratio | 6.5             | 3.6 – 11.8              | <0.001* |

Table 5 presents the multivariate logistic regression analysis performed to determine the independent predictors of difficult laparoscopic cholecystectomy. Among the variables analyzed, increasing age was found to be a statistically significant predictor of operative difficulty, with an odds ratio (OR) of 1.04 (95% CI: 1.01–1.08;  $p = 0.02$ ). This indicates that with each increasing year of age, the likelihood of encountering a difficult surgery increased modestly. Gender was not significantly associated with difficult laparoscopic cholecystectomy (OR=1.05; 95% CI: 0.48–2.28;  $p = 0.89$ ), suggesting no meaningful difference between males and females in predicting operative difficulty. Similarly, BMI did not demonstrate a statistically significant association (OR=1.06; 95% CI: 0.94–1.19;  $p = 0.32$ ). In contrast, the CRP/albumin ratio emerged as the strongest independent predictor of difficult surgery, with an odds ratio of 6.5 (95% CI: 3.6–11.8;  $p < 0.001$ ). This finding indicates that patients with elevated CRP/albumin ratios had significantly higher odds of experiencing difficult laparoscopic cholecystectomy compared to those with lower ratios. Overall, the analysis highlights the CRP/albumin ratio as a powerful and reliable predictor of operative difficulty.

## DISCUSSION

Laparoscopic cholecystectomy is the gold standard treatment for symptomatic gallstone disease and acute cholecystitis; however, difficult laparoscopic cholecystectomy (DLC) continues to remain a major intraoperative challenge due to severe inflammation, fibrosis, adhesions, and distorted biliary anatomy. Early identification of patients at risk for difficult surgery is important to reduce operative complications, conversion to open surgery, prolonged operative duration, and postoperative morbidity. In recent years, inflammatory biomarkers have gained importance as potential predictors of surgical difficulty.

The present study was conducted to evaluate the role of the preoperative C-reactive protein to albumin ratio (CRP/Alb ratio) in predicting difficult laparoscopic cholecystectomy.

In the present study, the mean age of patients with difficult laparoscopic cholecystectomy was significantly higher than that of the non-difficult group ( $53.6 \pm 12.4$  vs  $46.1 \pm 11.6$  years;  $p=0.01$ ). Increasing age is known to be associated with recurrent inflammation, fibrosis, and delayed presentation, which contribute to operative difficulty. Similar findings were reported by Farahani et al., who demonstrated that older age was significantly associated with conversion from laparoscopic to open cholecystectomy in acute cholecystitis patients [11]. Chua et al. also observed that advanced age was an important predictor of difficult laparoscopic cholecystectomy due to severe inflammatory changes and adhesions [12]. In contrast, gender and BMI were not significantly associated with operative difficulty in the present study, which is comparable to observations made by Utsumi et al. [1,2].

The present study demonstrated significantly elevated CRP levels in patients with difficult laparoscopic cholecystectomy compared to non-difficult cases ( $94.5 \pm 8.2$  mg/L vs  $10.3 \pm 5.1$  mg/L;  $p<0.001$ ). CRP is an acute-phase reactant synthesized by hepatocytes in response to inflammatory cytokines, and elevated levels indicate active inflammation and tissue injury. Similar results were observed by Farahani et al., who reported that elevated preoperative CRP strongly predicted difficult surgery and conversion to open cholecystectomy with excellent diagnostic accuracy [11]. Previous studies have shown that severe gallbladder inflammation results in edema, dense adhesions, and obscuration of Calot's triangle, thereby increasing surgical complexity and risk of bile duct injury [3,11].

Serum albumin levels were significantly lower in difficult laparoscopic cholecystectomy cases in the present study ( $3.41 \pm 0.26$  g/dL vs  $4.31 \pm 0.29$  g/dL;  $p<0.001$ ). Hypoalbuminemia is commonly associated with systemic inflammation, poor nutritional status, and chronic disease burden. Albumin is considered a negative acute-phase reactant, and reduced levels during severe inflammation reflect increased vascular permeability and impaired hepatic synthesis. Similar observations were reported by Yilmaz et al., who demonstrated that low albumin levels were associated with increased severity of acute cholecystitis and adverse perioperative outcomes [13].

The most significant finding of the present study was the markedly elevated CRP/albumin ratio among difficult laparoscopic cholecystectomy cases compared to non-difficult cases ( $27.5 \pm 3.3$  vs  $2.4 \pm 1.1$ ;  $p<0.001$ ). This finding suggests that the CRP/albumin ratio is a strong indicator of systemic inflammatory burden and operative complexity. Utsumi et al. first demonstrated that elevated preoperative CRP/albumin ratio was an independent predictor of difficult laparoscopic cholecystectomy in patients with acute cholecystitis diagnosed according to Tokyo Guidelines 2018 [1]. In another study, the same authors observed that elevated CRP/albumin ratio independently predicted conversion from laparoscopic to open cholecystectomy, with a cut-off value of 5.54 [2]. Similarly, Yilmaz et al. found that CRP/albumin ratio was significantly associated with disease severity and poor clinical outcomes in acute cholecystitis patients [13]. The findings of the present study are therefore in strong agreement with previous literature.

Intraoperative findings assessed using the Sugrue scoring system showed significantly higher frequencies of abnormal gallbladder appearance, difficult access, gallbladder distension or contraction, and severe inflammatory complications in the difficult laparoscopic cholecystectomy group ( $p<0.01$ ). These findings indicate that elevated inflammatory markers correlate with severe local inflammatory changes and distorted anatomy. Wei et al. also demonstrated that severe local inflammation and adhesions were strongly associated with difficult operative dissection and prolonged operative duration [14]. Similar studies have shown that inflammatory edema and fibrosis impair visualization of Calot's triangle, increasing operative risk and technical difficulty [12,14].

ROC curve analysis in the present study showed excellent predictive performance of the CRP/albumin ratio with an AUC of 0.95, sensitivity of 90%, and specificity of 91% at an optimal cut-off value of 9–10. These findings suggest that the CRP/albumin ratio is a highly accurate biomarker for predicting difficult laparoscopic cholecystectomy. Utsumi et al. reported similarly high predictive accuracy for CRP/albumin ratio in identifying difficult cholecystectomy and conversion to open surgery [1,2]. Chua et al. also concluded that elevated inflammatory markers including CRP and CRP/albumin ratio had significant predictive value for difficult laparoscopic cholecystectomy [12].

Multivariate logistic regression analysis in the present study identified CRP/albumin ratio as the strongest independent predictor of difficult laparoscopic cholecystectomy (OR=6.5; 95% CI: 3.6–11.8;  $p<0.001$ ). This indicates that patients with elevated CRP/albumin ratio had a significantly increased likelihood of encountering operative difficulty. Similar conclusions were reported by Utsumi et al., who identified elevated CRP/albumin ratio as an independent predictor even after adjustment for confounding variables [2]. The predictive superiority of CRP/albumin ratio may be attributed to its ability to simultaneously reflect both inflammatory status and nutritional reserve, thereby providing a more comprehensive assessment compared to CRP or albumin alone.

The findings of the present study highlight the importance of preoperative inflammatory assessment in patients undergoing laparoscopic cholecystectomy. The CRP/albumin ratio is inexpensive, easily available, reproducible, and can be routinely calculated from standard laboratory investigations. Incorporation of this biomarker into preoperative evaluation may help surgeons anticipate operative difficulty, allocate experienced surgical teams, improve patient counselling, and reduce perioperative complications.

## CONCLUSION

The present study demonstrated that the preoperative CRP/albumin ratio is a significant and reliable predictor of difficult laparoscopic cholecystectomy. Patients with elevated CRP/albumin ratios showed significantly higher operative difficulty scores, greater inflammatory changes, and increased risk of difficult intraoperative dissection. The CRP/albumin ratio exhibited excellent diagnostic accuracy with high sensitivity and specificity and emerged as an independent predictor of difficult laparoscopic cholecystectomy. Therefore, the CRP/albumin ratio may serve as a simple, cost-effective, and non-invasive biomarker for preoperative risk stratification and surgical planning in patients undergoing laparoscopic cholecystectomy.

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