Research Square

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Inflammatory Burden Rather Than Symptom Duration Predicts Operative Difficulty in Acute Cholecystitis

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Abstract

Background

Operative difficulty during emergency laparoscopic cholecystectomy (ELC) can vary substantially. This study evaluated whether peak pre-operative C-reactive protein (CRP) is a greater independent predictor of operative difficulty than symptom duration.

Methods

A retrospective multicentre cohort study was conducted within Wide Bay Hospital and Health Service (November 2021 - May 2024). Adult patients undergoing ELC were included. Operative difficulty was graded 1 to 4 using a validated intra-operative grading system. Multivariable logistic regression adjusted for covariates, and receiver operating characteristic analysis was used to determine optimal CRP threshold for predicting grade 4 difficulty.

Results

A total of 284 patients were included. CRP was independently associated with increasing operative difficulty (adjusted OR 2.24 per log unit, 95% CI 1.91–2.63; $p < 0.001$), while longer symptom duration was inversely related (adjusted OR 0.81 per day, 95% CI 0.73–0.90; $p < 0.001$). A CRP threshold of 92.5 mg/L predicted grade 4 difficulty with 76.2% sensitivity, 82.5% specificity, and 89.2% negative predictive value.

Conclusion

CRP is a strong independent predictor of operative difficulty in emergency laparoscopic cholecystectomy for cholecystitis and appears to reflect inflammatory burden more accurately than symptom duration. Incorporating CRP into pre-operative assessment may improve risk stratification and facilitate appropriate operative planning.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is the gold standard management of acute calculous cholecystitis, with international guidelines endorsing surgery within the first 72 hours following symptom onset.[1–3] It is thought that a more delayed presentation and subsequent intervention are associated with a higher risk of operative complications.[4] In light of this, patients with a more protracted duration of symptoms are believed to have a more severe grade of acute cholecystitis, as classified by the Tokyo Guidelines.

While early cholecystectomy is recommended for lower-grade disease, treatment for high-grade disease focuses on systemic therapy and drainage procedures.[5]

Despite an internationally recognised clinical grading system, there is significant variability in the operative difficulty of LC across these grades. The Japan-Korea-Taiwan Collaborative Project established intra-operative markers of operative difficulty, noting that increasing difficulty is associated with higher rates of intra-operative complications.[6] Wennmacker et al. sought to simplify the framework outlined by the Japan-Korea-Taiwan Collaborative Project. They proposed four grades of intraoperative difficulty, summarised in Fig. 1.[7] While this study provides a framework for characterising operative difficulty and offers techniques to enhance the safety of dissection, there remains limited consensus on how to predict operative difficulty prior to undertaking surgery.[6] Anticipating operative difficulty allows for better preparation, including ensuring appropriate theatre allocation and specialist surgeon availability.

Several studies have sought to identify variables that can serve as pre-operative markers of operative difficulty. C-reactive protein (CRP), an acute-phase reactant, is one such marker. Plasma CRP concentration rises within 8 hours of an inflammatory insult and has a half-life of 19 hours; therefore, declining levels can be reliably interpreted as a marker of resolving inflammation.[8,9] Ng et al. have demonstrated that peak preoperative CRP level correlates with operative difficulty.[10] While CRP has been independently associated with operative difficulty, no study has directly compared its predictive performance against symptom duration within the same multivariable model. This distinction is not incidental: current severity and management frameworks, including the Tokyo Guidelines, use symptom duration as a proxy for disease severity, yet CRP and symptom duration may not capture the same biological process.[1,5] Whether one measure provides independent, non-redundant information over the other has direct implications for how these frameworks are constructed and applied in practice.

The primary outcome of this study was to evaluate whether CRP is an independent predictor of operative difficulty after adjusting for other covariables. Secondary aims were to assess whether CRP is predictive of secondary markers of operative difficulty, and post-operative complications.

METHODS

A multi-site retrospective cohort analysis was conducted at Hervey Bay and Bundaberg Hospitals. Data were collected from patients who underwent an emergency LC between November 2021 and May 2024. The study was approved by the institutional ethics committee HREC/2024/QHFSS&PQ/113436 (Nov ver 2).

Adult patients who underwent LC for acute cholecystitis were included in the study. Patients were excluded if they had previous upper abdominal surgery, concurrent pancreatitis or choledocholithiasis, or had undergone an ERCP in the 4 weeks prior to surgery. Patients without intraoperative descriptions or images were excluded, as were those without a preoperative CRP. Patients were selected in reverse chronological order until the required sample size was reached.

Baseline clinicopathological characteristics were retrieved from medical records. Symptom duration was identified as the number of whole days from symptom onset to operation date. Pre-operative CRP was recorded as the highest value prior to surgery. Operative difficulty grading was calculated retrospectively, using the operation report and intraoperative photographs. Researchers were blinded to clinicopathological characteristics when calculating operative difficulty.

The minimum sample size was calculated as 228 participants to achieve 80% statistical power, based on effect size estimates from prior literature.[7,11] Statistical analyses were conducted using STATA v17 and Prism v11. Standard measures of central tendency were used to summarise the dataset. Differences in baseline characteristics across operative difficulty grades were assessed using the Pearson χ^2 test for categorical variables and the Kruskal–Wallis test or ANOVA for continuous and ordinal variables, depending on normality. Pair-wise testing using Dunn's test with Bonferroni correction was conducted for differences in pre-operative peak CRP between operative difficulty grades. Pre-operative CRP was log-transformed (log10 CRP) prior to regression modelling due to its skewed distribution.

Screening for predictors of operative difficulty (graded 1–4) was performed using Pearson χ^2 tests for categorical variables and the Jonckheere–Terpstra test for trend for continuous or ordinal variables. Variables demonstrating a trend on screening ($p < 0.10$) or considered clinically relevant were subsequently entered into univariate ordinal logistic regression models to estimate effect sizes. A multivariable model was then constructed to identify independent predictors of operative difficulty. Variables demonstrating a trend towards significance ($p < 0.10$) or considered clinically relevant were entered into the multivariable model. Collinear variables were avoided. The proportional odds assumption was assessed using the Brant test. The final multivariate model was tested for interactions between significant predictors of operative difficulty. Complete data were available for all variables included in the regression models.

Receiver operating characteristic (ROC) curve analysis was used to assess the discriminative ability of pre-operative CRP alone to differentiate a binary outcome of difficult cholecystectomy (difficulty grade 4 vs grades 1–3), using the Youden index and reporting subsequent diagnostic performance metrics.

RESULTS

Clinicopathological Cohort Characteristics

There were 284 patients included in the final analysis. Their baseline clinicopathological details stratified by operative difficulty are summarised in Table 1. There were significant differences in age at surgery, sex, ASA score, weight, and symptom duration prior to admission across operative difficulty grades. All biochemical markers, including peak white cell count and CRP prior to surgery, as well as serum albumin and bilirubin levels, were significantly different across operative difficulty grades.

Table 1
Baseline characteristics of participants, separated by operative difficulty grade.

	Difficulty Grade				p-value
	1	2	3	4	
Cohort size (%)	49 (17.3%)	79 (27.8%)	72 (25.3%)	84 (29.6%)	
Age at surgery, years	41.0 (30.0–56.0)	48.0 (36.0–60.0)	61.5 (44.5–70.0)	67.0 (52.0-75.5)	**< 0.001**‡
Sex					**< 0.001**†
Female	37 (76%)	55 (70%)	36 (50%)	33 (39%)	
Male	12 (24%)	24 (30%)	36 (50%)	51 (61%)	
ASA					**< 0.001**†
1	5 (10%)	7 (9%)	3 (4%)	1 (1%)	
2	30 (61%)	51 (65%)	27 (38%)	31 (37%)	
3	14 (29%)	19 (24%)	40 (56%)	43 (51%)	
4	0 (0%)	2 (3%)	2 (3%)	9 (11%)	
BMI, kg/m^2	31.1 (27.0-37.5)	30.1 (25.9–34.5)	31.5 (27.8–36.1)	31.4 (27.5–37.0)	0.33‡
Weight, kg	88.0 (71.0-105.0)	82.0 (72.0–98.0)	92.0 (73.5–104.0)	92.0 (82.5–104.0)	**0.033**‡
Duration of symptoms, days					
Prior to admission	1 (0–2)	0 (0–2)	1 (1–3)	1 (0–3)	**0.003**‡
Prior to surgery	4 (2–5)	2 (1–4)	3 (2–5)	3 (2–4)	0.058‡
WCC, $x10^9/L$	8.5 (7.5–11.4)	9.7 (7.2–12.4)	11.3 (9.2–13.1)	14.0 (10.9–18.1)	**< 0.001**‡
CRP, mg/L	5.8 (1.6–11.0)	15.0 (4.7–31.0)	40.5 (8.7–126.0)	201.5 (100.0-299.0)	**< 0.001**‡
Albumin, g/L	37.9 (± 4.4)	36.5 (± 5.0)	35.2 (± 5.3)	33.3 (± 5.5)	**< 0.001**§

Data are presented as mean (± SD) or median (IQR) for continuous measures, and No. (%) for categorical measures.

† Pearson χ^2 test; ‡ Kruskal-Wallis test; § ANOVA.

American Society of Anesthesiologists Physical Status Score (ASA); Body mass index (BMI); Peak pre-operative white cell count (WCC); Peak pre-operative C-reactive protein (CRP).

	Difficulty Grade				p-value
	1	2	3	4	
Bilirubin, μmol/L	8.0 (6.0–11.0)	10.0 (7.0–14.0)	13.0 (9.0–19.0)	15.0 (10.0–26.0)	**< 0.001**‡
Data are presented as mean (± SD) or median (IQR) for continuous measures, and No. (%) for categorical measures.					
† Pearson χ^2 test; ‡ Kruskal-Wallis test; § ANOVA.					
American Society of Anesthesiologists Physical Status Score (ASA); Body mass index (BMI); Peak pre-operative white cell count (WCC); Peak pre-operative C-reactive protein (CRP).					

Intra-operative and post-operative outcomes stratified by operative difficulty are presented in Table 2. Aside from conversion to an open procedure, all intra-operative characteristics were significantly different between the operative difficulty grades. While the overall and individual post-operative complication rates remained low, the composite measure of all post-operative complications was significantly different between operative difficulty grades. Additionally, the post-operative admission and total admission durations were significantly different across operative difficulty grades.

Table 2
Intra-operative findings and post-operative outcomes stratified by operative difficulty

	Difficulty Grade				p-value
	1	2	3	4	
Intra-operative					
Primary surgeon level					**< 0.001**†
Consultant	39 (80%)	58 (73%)	64 (89%)	81 (96%)	
Registrar	10 (20%)	21 (27%)	8 (11%)	3 (4%)	
Duration of surgery, hours	1.22 (1.05–1.47)	1.48 (1.25–1.75)	1.88 (1.58–2.17)	2.20 (1.78–2.57)	**< 0.001**‡
Gallbladder					
Gangrenous	0 (0%)	0 (0%)	8 (11%)	72 (86%)	**< 0.001**†
Perforated	0 (0%)	0 (0%)	0 (0%)	33 (39%)	**< 0.001**†
Subtotal cholecystectomy	0 (0%)	0 (0%)	1 (1%)	17 (20%)	**< 0.001**†
Conversion to open	0 (0%)	0 (0%)	1 (1%)	4 (5%)	0.081†
Drain placed	0 (0%)	11 (14%)	30 (42%)	73 (87%)	**< 0.001**†
Post-operative					
Post-operative complication	0 (0%)	2 (3%)	7 (10%)	12 (14%)	**0.005**†
Bile leak	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0.64†
Surgical site infection	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0.50†
Secondary infection	0 (0%)	1 (1%)	3 (4%)	6 (7%)	0.098†
Unplanned return to theatre	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.40†
Non-operative intervention	0 (0%)	0 (0%)	3 (4%)	2 (2%)	0.18†

Data are presented as median (IQR) for continuous measures, and No. (%) for categorical measures.

† Pearson χ^2 test; ‡ Kruskal-Wallis test.

	Difficulty Grade				p-value
	1	2	3	4	
Readmission within 30 days	0 (0%)	1 (1%)	3 (4%)	8 (10%)	**0.021**†
Duration of admission, days					
Post-operative	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	2.0 (2.0–4.0)	**< 0.001**‡
Total admission	3.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	4.0 (3.0–6.0)	**< 0.001**‡
Data are presented as median (IQR) for continuous measures, and No. (%) for categorical measures.					
† Pearson χ^2 test; ‡ Kruskal-Wallis test.					

Peak Pre-operative Serum C-Reactive Protein

Pre-operative CRP differed significantly across operative difficulty grades ($p < 0.001$), with all pairwise comparisons significant on post-hoc testing (Fig. 2).

Predictors of Operative Difficulty

The findings of the univariate and subsequent multivariate ordinal logistic regression model are summarised in Table 3. The proportional odds assumption was met for all variables except symptom duration ($p = 0.03$). Sensitivity analysis using a partial proportional odds model demonstrated a consistent inverse association across all operative difficulty thresholds, with no change in the direction or interpretation of the effect. Interaction between CRP and symptom duration was assessed a priori, with no significant interaction identified ($p = 0.08$).

Table 3
Univariate and multivariable ordinal logistic regression for predictors of operative difficulty

Variable	Jonckheere–Terpstra Trend / χ^2	Univariate regression		Multivariable regression	
		OR	p-value	Adjusted OR (95% CI)	p-value
Age	< 0.0001	1.05	< 0.001	1.03 (1.02–1.05)	< 0.001
Sex	< 0.001	2.95	< 0.001	1.77 (1.09–2.87)	0.02
ASA	< 0.001	2.56	< 0.001	—	—
BMI	0.28	—	—	—	—
Weight	0.038	1.01	0.015	—	—
Duration of symptoms, days					
Prior to admission	0.025	1.10	0.087	—	—
Prior to surgery	0.77	0.97	0.45	0.81 (0.73–0.90)	< 0.001
WCC×10^9/L	< 0.0001	1.19	< 0.001	—	—
log CRP (per log unit)	< 0.0001	2.18	< 0.001	2.24 (1.91–2.63)	< 0.001
Albumin g/L	< 0.0001	0.90	< 0.001	—	—
Bilirubin µmol/L	< 0.0001	1.03	0.002	—	—
Sex reference unit = female.					
American Society of Anesthesiologists Physical Status Score (ASA); Body mass index (BMI); Odds Ratio (OR); Peak pre-operative C-reactive protein (CRP); Peak pre-operative white cell count (WCC).					

Sensitivity Analysis of Severe Operative Difficulty

To confirm the robustness of the ordinal regression findings, a binary logistic regression model was performed using grade 4 operative difficulty as the outcome. In this model, higher CRP remained strongly associated with increased odds of difficult surgery (adjusted OR 2.50, 95% CI 1.93–3.24, p < 0.001), while longer symptom duration was associated with reduced odds (adjusted OR 0.82 per day, 95% CI 0.70–0.96, p = 0.013). Increasing age was also associated with higher odds of difficult surgery (adjusted OR 1.03 per year, 95% CI 1.00–1.05, p = 0.016), while sex was not

significantly associated (p = 0.2).

The optimal CRP threshold identified using the Youden index was 92.5mg/L with diagnostic performance summarised in Table 4. Peak pre-operative CRP alone demonstrated good discrimination for severe operative difficulty (Fig. 3). The associated area under the curve (AUC) was 0.85. Incorporation of age, sex and symptom duration further improved model performance (AUC = 0.87).

Table 4
Diagnostic performance of CRP threshold (92.5mg/L) for predicting severely difficult cholecystectomy (grade 4).

Metric	Value (%) (95% CI)
Sensitivity	76.2 (65.7–84.8)
Specificity	82.5 (76.5–87.5)
Positive predictive value	64.6 (54.4–74.0)
Negative predictive value	89.2 (83.8–93.3)
Prevalence	29.6 (24.3–35.3)

The potential interaction between pre-operative CRP (dichotomised at 92.5mg/L) and symptom duration was assessed using an interaction term in multivariable logistic regression. There was no evidence of interaction between dichotomised CRP and symptom duration (Wald test for interaction, p = 0.72). In stratified multivariable logistic regression analyses, symptom duration was associated with reduced odds of difficult cholecystectomy in patients with CRP ≥ 92.5mg/L (adjusted OR 0.82 per day, 95% CI 0.67–0.99, p = 0.044), whereas no statistically significant association was observed in patients with CRP < 92.5mg/L. This likely reflects differences in statistical power rather than true effect modification.

Correlation of CRP with Secondary Markers of Operative Difficulty and Post-operative Complications

Table 5 summarises intra-operative and post-operative outcomes stratified by the pre-operative peak CRP threshold of 92.5 mg/L. Patients with a higher peak pre-operative CRP had a higher rate of secondary markers of operative difficulty than those with a low CRP. Similarly, the composite rate of post-operative complications and admission duration were higher for patients with a higher peak pre-operative CRP.

Table 5
Intra-operative findings and post-operative outcomes stratified by peak pre-operative threshold.

	Peak Pre-operative CRP		
	< 92.5 mg/L	**≥ 92.5mg/L**	**p-value**
Intra-operative			
Primary surgeon level			**< 0.001**†
Consultant	148 (80.0%)	94 (94.9%)	
Registrar	37 (20.0%)	5 (5.1%)	
Duration of surgery, hours	1.58 (1.22–1.97)	1.93 (1.48–2.35)	**< 0.001**‡
Subtotal cholecystectomy	5 (2.7%)	13 (13.1%)	**< 0.001**†
Conversion to open	1 (0.5%)	4 (4.0%)	**0.033**†
Drain placed	48 (25.9%)	66 (66.7%)	**< 0.001**†
Post-operative			
Post-operative complication	8 (4.3%)	13 (13.1%)	**0.007**†
Bile leak	0 (0.0%)	2 (2.0%)	0.052†
Surgical site infection	0 (0.0%)	1 (1.0%)	0.17†
Secondary infection	3 (1.6%)	7 (7.1%)	**0.018**
Unplanned return to theatre	0 (0.0%)	1 (1.0%)	0.17†
Non-operative intervention	3 (1.6%)	2 (2.0%)	0.81†
Readmission within 30 days	5 (2.7%)	7 (7.1%)	0.081†
Duration of admission, days			
Post-operative	1.00 (1.00–2.00)	2.00 (1.00–4.00)	**< 0.001**‡
Total admission	3.00 (2.00–4.00)	4.00 (3.00–6.00)	**< 0.001**‡
Data are presented as median (IQR) for continuous measures, and No. (%) for categorical measures.			
† Pearson χ^2 test; ‡ Mann-Whitney U test.			

DISCUSSION

Peak pre-operative CRP is an independent predictor of LC difficulty for acute calculous cholecystitis. Furthermore, peak pre-operative CRP is also significantly associated with secondary markers of operative difficulty, post-operative complications and admission duration. A peak pre-operative CRP threshold of 92.5 mg/L predicts severely difficult cholecystectomy with a sensitivity of 76.2% and specificity of 82.5%. Patients with a CRP above this level can be anticipated to encounter a more difficult operation, with a higher rate of conversion to subtotal cholecystectomy, and a longer duration of hospital stay. These findings may facilitate more appropriate theatre allocation and anticipation of complex operative strategies.

The association between CRP and increased operative difficulty supports findings in existing literature. Wennmacker et al. and Ng et al. both identified CRP as an independent predictor of operative difficulty, with Ng et al. demonstrating a similar CRP cut-off value of 90mg/L to predict a difficult cholecystectomy with a sensitivity and specificity of 71.5% and 70.5%, respectively.[7,10] The present study extends these findings through a multicentre design spanning two regional Australian centres, using a validated four-tier intraoperative difficulty grading system applied independently of biochemical data. Importantly, this is the first study to directly compare the predictive value of CRP against symptom duration within the same multivariable model, demonstrating that inflammatory burden — rather than time since diagnosis — is the dominant determinant of operative difficulty.

Contrary to traditional assumptions, longer symptom duration was associated with lower operative difficulty. One possible explanation is that symptom duration is an imprecise surrogate for inflammatory burden. Patients with severe acute inflammation may present early due to symptom severity, whereas those with milder disease may delay presentation. In contrast, CRP directly reflects the biological inflammatory response and may therefore more accurately capture operative difficulty. Additionally, patients with prolonged symptom duration often receive a period of antibiotic therapy prior to surgery, which may partially attenuate the acute inflammatory response despite a longer clinical course. Finally, while symptom onset is clinically significant, it is a subjective measure and prone to recall bias. Peak pre-operative CRP was selected because it reflects maximal inflammatory burden rather than a single time-point measurement. Given the short half-life of CRP, peak values may better capture the biological severity of acute cholecystitis than admission values or symptom duration alone. This finding carries direct implications for guideline-based decision-making. The Tokyo Guidelines incorporate a symptom duration of greater than 72 hours as a criterion for moderate (Grade II) severity, a classification that subsequently informs the choice between early surgery, percutaneous drainage, and delayed interval cholecystectomy.[1,5] If symptom duration does not reliably correlate with — and in this cohort was inversely associated with — objective inflammatory burden and operative difficulty, its continued use as a severity criterion warrants re-examination. These findings raise the possibility that a subset of patients with short symptom duration but high inflammatory burden may be under-triaged by current duration-based frameworks, while patients with prolonged but lower-grade symptoms may be over-triaged.

The discrepancy between elapsed symptom duration and inflammatory burden highlights the limitations of using chronological measures as surrogates for disease severity. Symptom duration forms part of

contemporary management algorithms and contributes to clinical grading systems such as the Tokyo Guidelines. However, our findings suggest that elapsed symptom duration is a poor surrogate for operative difficulty and that inflammatory burden, as reflected by peak CRP, may provide a more objective measure of disease severity. Whether objective inflammatory biomarkers such as CRP should complement existing severity classification systems warrants further investigation.

Accurate pre-operative risk stratification has practical implications for theatre scheduling, consultant involvement, and resource allocation. A CRP threshold of 92.5 mg/L may identify patients who would benefit from early senior involvement, longer theatre allocation, and preparedness for bailout procedures such as subtotal cholecystectomy.

In addition to CRP, increasing age and male sex emerged as independent predictors of operative difficulty in the multivariable model. Older patients were more likely to have a more difficult operation, which may be indicative of premorbid functioning or delayed presentation. Male sex was independently associated with increasing operative difficulty in the ordinal model but was not significantly associated with grade 4 difficulty in the binary sensitivity analysis. This is consistent with prior observations that advancing age and male sex are associated with a more difficult operation.[12,13]

Strengths and Limitations

The strengths of this study include the use of a validated intra-operative difficulty grading system and a multicentre cohort, enhancing the reproducibility and generalisability of the findings. Operative difficulty was assessed independently of biochemical and baseline clinical characteristics to minimise bias, and complete data were available for all variables included in the regression models. Unlike previous studies, operative difficulty was defined by anatomical and inflammatory findings rather than operative duration, reducing the influence of surgeon experience and adjunctive procedures on the outcome measure.

This study is limited by its retrospective design and the potential subjectivity of operative difficulty grading, which relied on operation reports and intra-operative images and may have been affected by variability in documentation. The study was conducted in two regional Australian centres, which may limit generalisability to other settings. Although adequately powered for the primary analysis, the sample size restricted subgroup analyses and uncommon complications. Finally, peak pre-operative CRP was used to represent inflammatory burden, and changes in CRP over time or imaging findings incorporated within the Tokyo Guidelines were not assessed.

CONCLUSION

This study demonstrates that preoperative CRP is a statistically significant and clinically meaningful independent predictor of operative difficulty in emergency LC for acute cholecystitis. Higher CRP levels were associated with increased operative complexity, longer operative duration, prolonged length of hospital stay, and a greater likelihood of gangrenous or perforated cholecystitis, and were associated

with increased use of advanced operative strategies including subtotal cholecystectomy. A CRP threshold of 92.5mg/L demonstrated good discriminatory performance, with a negative predictive value of 89.2% supporting its use as a practical tool for preoperative risk stratification. This study supports the incorporation of peak pre-operative CRP into routine pre-operative assessment for acute cholecystitis, with the aim of optimising theatre scheduling, ensuring appropriate consultant involvement, and improving patient consent. Prospective studies incorporating serial inflammatory markers, radiological severity, and standardised assessment of operative difficulty are required to validate these findings.

Declarations

Author Contribution

BL: Conceptualization, Data curation, Investigation, Project administration, Visualization, Writing - Original Draft; RC: Formal analysis, Methodology, Project administration, Resources, Software, Visualization, Writing - Original Draft, Writing - Review & Editing; AB: Data curation, Writing - Review & Editing; MI: Conceptualization, Project administration, Supervision, Validation, Writing - Review & Editing;

Declaration of Competing Interests Statement

No conflicts of interest are declared by any author. No external funding was received for this study.

Data Availability

The datasets generated and analysed during the current study are not publicly available because they contain identifiable patient information but are available from the corresponding author on reasonable request, subject to institutional ethics approval and data sharing policies.

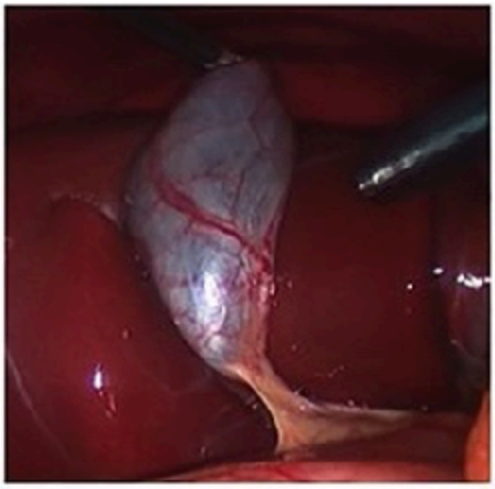
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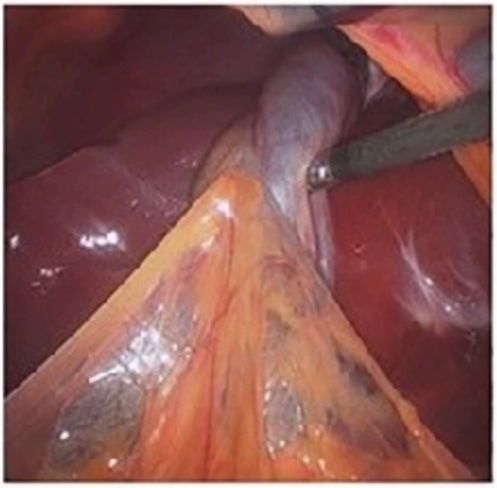
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Figures



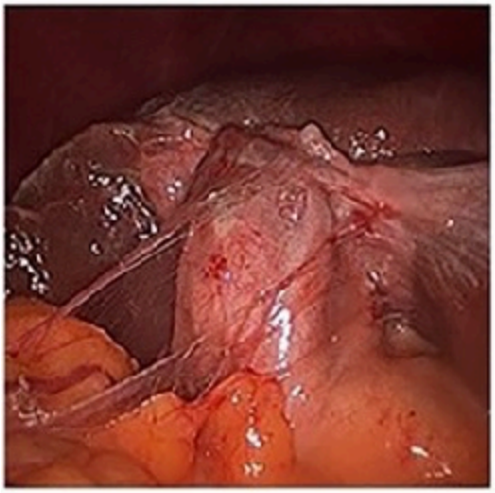
Grade 1

Thin walled, normal appearing GB
No adhesions



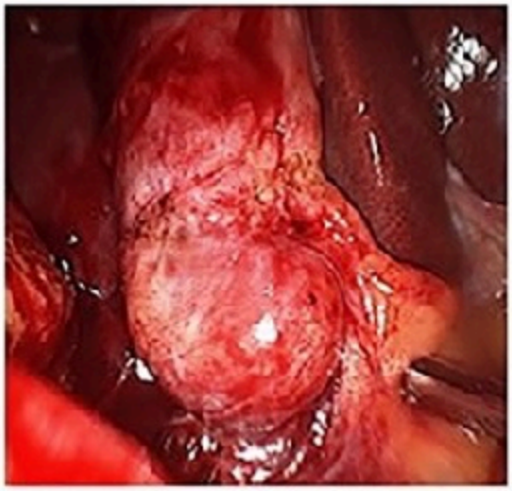
Grade 2

Mildly abnormal appearing GB
(slightly thick walled or distended)
And/or thin-filmy GB adhesion



Grade 3

Moderately abnormal appearing GB
(thick walled, oedematous, with
mucocele, or large distended
gallbladder)
And/or overlying moderate adhesions



Grade 4

Severely inflamed or grossly abnormal
appearing GB (e.g. necrotic or perforated)
And/or extensive or dense adhesions

Figure 1

Laparoscopic cholecystectomy intra-operative difficulty grading system.

Grades are subclassified into straightforward (Grades 1-2) and complicated (Grades 3-4). Reproduced from Wennmacker SZ, Bhimani N, van Dijk AH, Hugh TJ, de Reuver PR. Predicting operative difficulty of laparoscopic cholecystectomy in patients with acute biliary presentations. ANZ J Surg.

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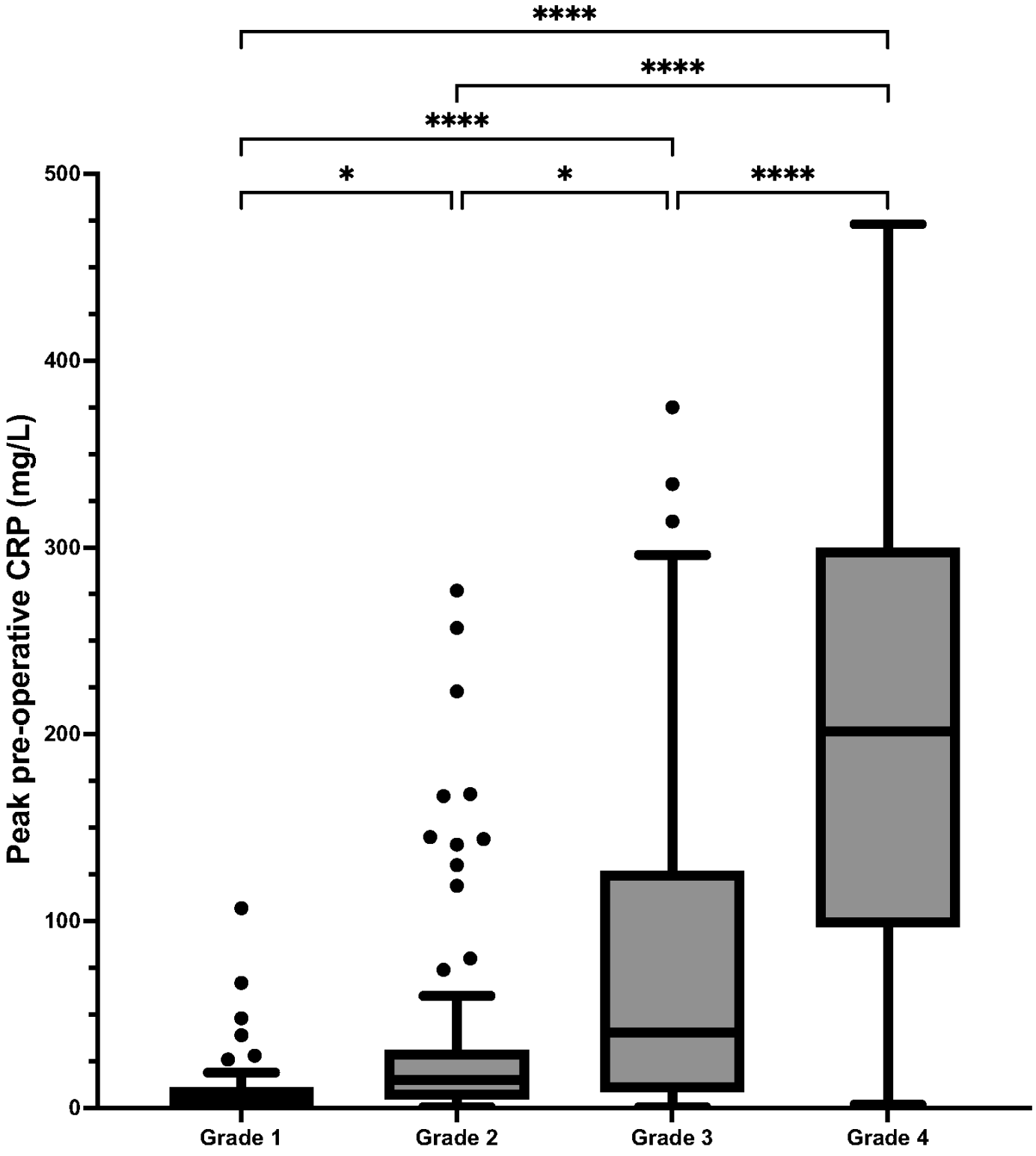


Figure 2

Distribution of preoperative C-reactive protein (CRP) levels (mg/L) according to operative difficulty grade.

Data are presented as box-and-whisker plots showing the median, interquartile range, range, and outliers identified using the Tukey Outlier test. * p-value = 0.01 - 0.05; ** p-value = 0.001 to 0.01; *** p-value = 0.0001 to 0.001; **** p-value < 0.0001

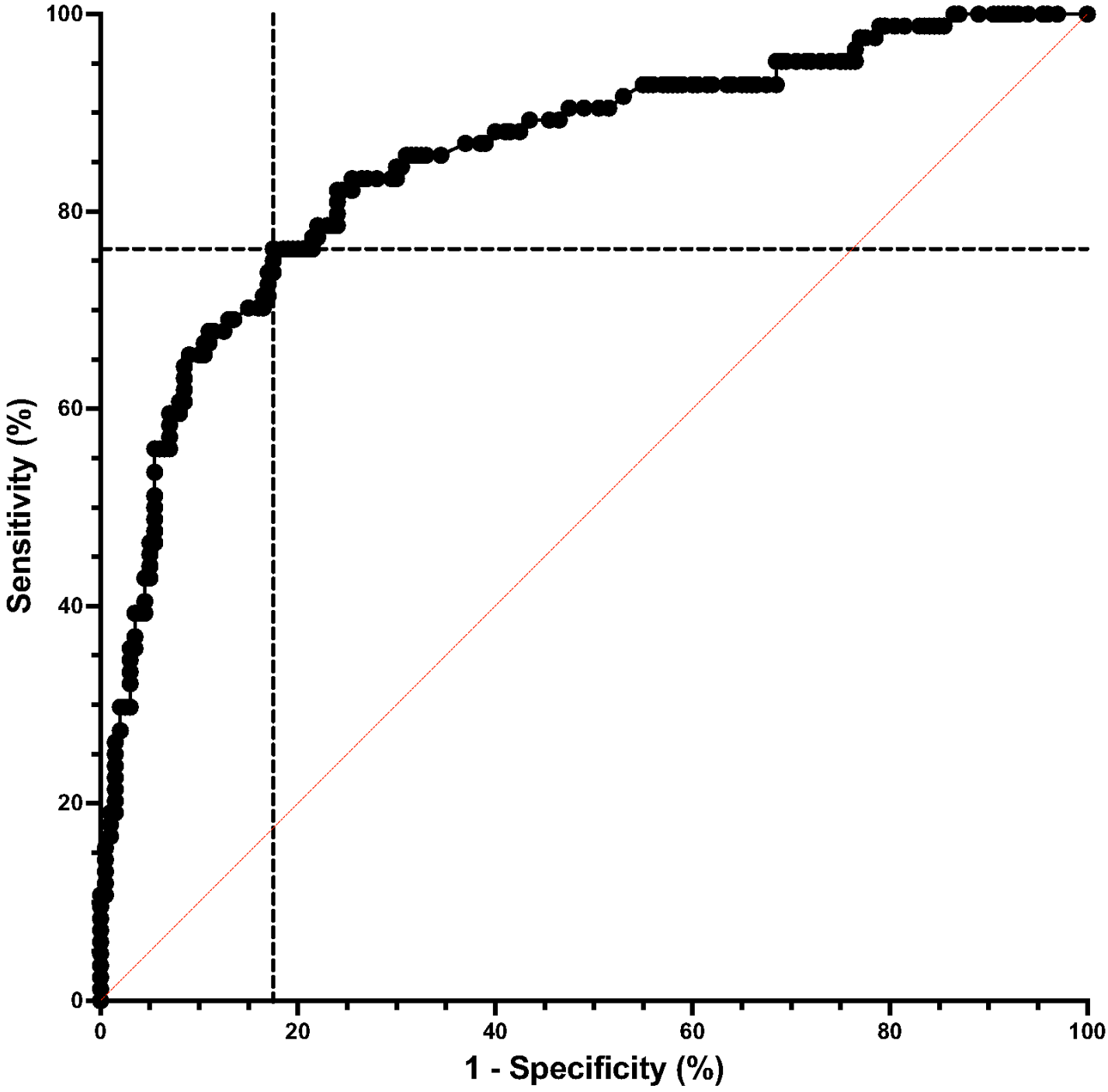


Figure 3

Receiver operating characteristic curve for preoperative CRP predicting severely difficult cholecystectomy.

The optimal CRP threshold identified by the Youden index was 92.5 mg/L, indicated on the curve at the intersection of the dotted lines, with corresponding sensitivity 76.2% and specificity 82.5%.