Research Square

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Stratification of Surgical Risk in Acute Cholecystitis: Preoperative C-Reactive Protein as an Independent Predictor of Difficulty and Conversion

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Abstract

Purpose

Anticipating the difficulty and clinical course of an emergency cholecystectomy relies heavily on intraoperative judgement. Preoperative C-reactive protein (CRP) has been proposed as a marker of surgical difficulty, but most studies test it against a single outcome in isolation. We assessed whether a single preoperative CRP value could predict three distinct outcomes: surgical difficulty, conversion to open surgery, and postoperative course

Methods

We analysed 221 prospectively enrolled, consecutive patients undergoing emergency laparoscopic cholecystectomy for acute cholecystitis at a single tertiary centre. Surgical difficulty was graded intraoperatively with the Parkland scale (grades 1–3 vs 4–5). CRP's association with difficulty was assessed with logistic regression; ROC-curve analysis evaluated discrimination for difficulty, conversion, and complications, and Spearman correlation assessed length of stay.

Results

CRP was higher in patients with a difficult gallbladder (median 166.0 vs 45.1 mg/L, $p < 0.001$) and remained an independent predictor after adjustment for baseline confounders (adjusted OR 1.006 per mg/L, $p < 0.001$; AUC 0.73). A higher threshold, approximately 304 mg/L, identified a high risk of conversion (AUC 0.76; specificity 89.4%; negative predictive value 96.9%); CRP was also weakly associated with any complication (AUC 0.64) and correlated with length of stay (rho = 0.37, $p < 0.001$); the small number of major complications precluded reliable modelling.

Conclusion

A single preoperative CRP value provides usable information on three distinct outcomes in acute cholecystitis, with different thresholds for anticipating difficulty and for conversion risk. These outcome-specific thresholds warrant prospective, multicentre validation.

Introduction

Acute cholecystitis is one of the most common reasons for emergency general surgery admission, and laparoscopic cholecystectomy performed within the first days of symptom onset remains its standard treatment. What varies enormously from one patient to the next is not whether the operation should be done, but how hard it will be. A gallbladder with dense adhesions, a friable wall, and an obliterated Calot's triangle has direct practical implications: a more experienced surgeon, a senior colleague available on standby, specific counselling about the risk of conversion, and closer postoperative observation. Several intraoperative scoring systems now describe this variability once the abdomen has been opened, among them the Nassar scale [1] and the five-tier Parkland grading scale, which classifies the gallbladder from a normal-appearing organ (grade 1) to one that has completely lost its anatomical planes (grade 5) [2, 3]. The obvious limitation of both is that they describe difficulty only once the decision to operate has already been made.

This has pushed a parallel line of research toward preoperative predictors: something a surgeon can look at the day before, or in the emergency department, and use to plan ahead. C-reactive protein (CRP) has repeatedly come up as a

candidate because it is cheap, fast, already drawn as part of routine work-up, and roughly tracks the intensity of the local and systemic inflammatory response that, mechanistically, is what makes a gallbladder hard to dissect (oedema, wall thickening, and pericholecystic inflammation). Several single-centre series have reported that CRP correlates with a difficult dissection [4–7], or with the Nassar difficulty grade specifically [8], with cut-offs that vary widely between studies, from around 11 mg/dL in elective, lower-severity cohorts [4, 5] to well over 200 mg/L in cohorts weighted toward emergency, more advanced disease [7]. A smaller number of studies have instead used conversion to open surgery as the outcome, generally reporting higher and more consistent thresholds in the order of 100–300 mg/L [7, 9–12], and fewer still have asked whether the same marker says anything about what happens after the operation: length of stay, complications, or readmission [6, 13].

What is missing from this literature, as far as we can tell, is a single cohort in which the same preoperative CRP value is tested against all three questions at once: how difficult will this be, will it need to be converted, and how will the patient do afterwards. Treating these as separate research questions has produced a fragmented evidence base with inconsistent cut-offs and little guidance on which threshold matters for which decision. Our group previously reported, in a case-control study comparing intraoperative indocyanine green (ICG) cholangiography with conventional laparoscopic cholecystectomy in acute cholecystitis, that the conventional arm carried roughly double the preoperative CRP of the ICG arm, alongside a higher conversion rate and a longer stay (an incidental finding that we did not formally test at the time, and that prompted the present study) [14]. Using an expanded cohort from the same institution's emergency cholecystectomy population, we set out to determine whether preoperative CRP independently predicts Parkland-graded surgical difficulty and, as secondary aims, whether it also predicts conversion to open surgery and postoperative morbidity, with the intention of proposing outcome-specific thresholds rather than a single all-purpose cut-off.

Materials and methods

Patients were prospectively and consecutively enrolled into a single-centre cohort of adults undergoing emergency laparoscopic cholecystectomy for acute cholecystitis in the General and Digestive Surgery Department of the Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain, between November 2023 and November 2025, as part of an ongoing case-control study of intraoperative indocyanine green (ICG) cholangiography [14]. The present study is a secondary analysis of that same prospectively maintained cohort, examining preoperative CRP as a predictor of surgical difficulty, conversion, and morbidity — a question not addressed in our original report. The cohort includes, and extends, the population previously reported in that study [14]; patients from it who met the criteria below were carried forward into the present analysis together with additional patients recruited afterwards. The study was approved by the Aragón Ethics Committee for Research (CEICA) for the collection of case-control data related to intraoperative ICG use, approval number PI24/478, and all patients provided written informed consent.

We included patients undergoing emergency laparoscopic cholecystectomy with a clinical, laboratory, and radiological diagnosis of acute cholecystitis consistent with at least grade I of the Tokyo Guidelines 2018 (TG18) criteria [15]. We excluded patients operated on electively, those managed by primary open (subcostal) surgery, and those in whom imaging was inconclusive for acute cholecystitis. Patients who received intraoperative ICG and those who did not were analysed together as a single cohort, since our hypothesis was that CRP's predictive value operates independently of intraoperative imaging technique; ICG use is reported descriptively across difficulty groups (Table 2) and examined separately in relation to conversion (see Results).

Preoperative CRP was measured on admission, before surgery, as part of routine blood work. Surgical difficulty was graded by the operating surgeon at the time of surgery using the Parkland scale [3], dichotomised, as in prior validation work, into an "easy" group (grades 1–3) and a "difficult" group (grades 4–5). Conversion to open surgery, any

postoperative complication (graded with the Clavien-Dindo classification), 30-day readmission, biliary complications requiring ERCP, and 30-day mortality were recorded prospectively in the departmental database. We additionally collected variables considered plausible confounders of surgical difficulty a priori: age, sex, body mass index, ASA physical status, Charlson comorbidity index, place of residence, anticoagulant use, previous abdominal surgery, prior biliary symptoms, duration of symptoms before admission, imaging modality (ultrasound versus CT), ultrasound findings (gallbladder wall thickening, distension, pericholecystic fluid, local complications, common bile duct dilation), lithiasic versus alithiasic disease, and preoperative Tokyo Guidelines severity grade.

Continuous variables are described as mean ± standard deviation or median [interquartile range] according to distribution, assessed with the Kolmogorov-Smirnov test, and compared between groups with Welch's t-test or the Mann-Whitney U test accordingly; categorical variables are described as counts and percentages and compared with the chi-square or Fisher's exact test as appropriate. Effect sizes are reported as the difference in means (Welch's t-test) or the Hodges-Lehmann estimate of the median difference (Mann-Whitney U test), with its 95% CI; for categorical variables we report the odds ratio (OR) with 95% CI by the Woolf method. Multivariable logistic regression, with Parkland difficulty as the dependent variable, included preoperative CRP together with a prespecified set of clinically plausible baseline confounders: age, sex, ASA class, Charlson comorbidity index, duration of symptoms, and body mass index. We assessed CRP's discriminative ability for each outcome (difficulty, conversion, any complication) with receiver operating characteristic (ROC) curve analysis, reporting the area under the curve (AUC) with its 95% CI, and identified the cut-off maximising the Youden index; sensitivity, specificity, and predictive values at this cut-off are reported with their 95% CI. As a further sensitivity analysis, given that CRP might simply be tracking overall clinical severity, we refitted the difficulty model with the addition of preoperative Tokyo Guidelines severity grade (II-III vs I). Given the small number of events, major complications (Clavien-Dindo ≥IIIa), 30-day readmission, biliary complications, and mortality were examined descriptively rather than with predictive models, since we judged formal regression or ROC analysis unreliable below approximately ten events per outcome. A two-sided $p<0.05$ was considered statistically significant throughout. All regression models were fitted on complete cases for the variables included; no imputation was performed.

All analyses were performed in jamovi (version 2.3, The jamovi project, Sydney, Australia).

Results

We analysed 221 patients (median age 65 years [IQR 49–76]; 102 women, 46.2%; median duration of symptoms 48 hours [IQR 24–72]), of whom 85 (38.5%) received intraoperative ICG cholangiography as part of the parent case-control study population [14]. Ninety-four patients (42.5%) had a difficult gallbladder by the Parkland scale (grade 4–5). Twelve patients (5.4%) required conversion to open surgery, 32 (14.5%) had at least one postoperative complication of any grade, and three patients (1.4%) died within 30 days. Median length of stay was 4 days [IQR 3–6]. Median preoperative CRP for the whole cohort was 100.8 mg/L [IQR 15.5–226.0], reflecting the wide range of inflammatory burden typical of an unselected emergency cholecystitis population.

Table 1 summarises preoperative characteristics stratified by Parkland difficulty. Patients with a difficult gallbladder were older (median 66 vs 61 years, $p=0.049$), more often men (66.0% vs 44.9%, $p=0.003$), had more comorbidity (CCI 2 vs 1, $p=0.035$), a longer duration of symptoms (72 vs 24 hours, $p=0.003$), and were more often diagnosed by CT rather than ultrasound (25.5% vs 6.3%, $p<0.001$). On ultrasound, pericholecystic fluid (47.6% vs 16.4%, $p<0.001$) and locally complicated disease (30.5% vs 11.5%, $p=0.001$) were both markedly more frequent in the difficult group. Preoperative CRP was more than three times higher in the difficult group (median 166.0 mg/L [IQR 72.8–285.3] vs 45.1 mg/L [IQR 11.2–142.0], $p<0.001$). Surgical difficulty was associated with worse outcomes across the board: conversion to open surgery occurred only among difficult gallbladders (12/94, 12.8%, vs none of the 127 easy cases; OR 37.17), any

postoperative complication was roughly three times more frequent (22.3% vs 8.7%; OR 3.03), and length of stay was two days longer (median 5 vs 3 days) (Table 2). A detailed breakdown of intraoperative pathological findings is given in Table 3.

On multivariable logistic regression adjusting for age, sex, ASA class, Charlson index, duration of symptoms, and body mass index, CRP remained an independent predictor of difficulty (adjusted OR 1.006 per mg/L, 95% CI 1.003–1.009, p<0.001, equivalent to roughly a 6% increase in the odds of a difficult gallbladder for every 10 mg/L rise in CRP), alongside male sex (OR 0.50 for female sex, 95% CI 0.26–0.94, p=0.031) (Table 4). ROC analysis identified an AUC of 0.73 (95% CI 0.66–0.80) for CRP alone, with an optimal cut-off of 56.5 mg/L (sensitivity 84.0%, specificity 58.7%, positive predictive value 60.3%, negative predictive value 83.1%) (Table 5, Fig. 1). An ordinal sensitivity analysis using the full five-grade Parkland scale produced a virtually identical estimate for CRP (OR 1.006 per mg/L, 95% CI 1.004–1.009, p<0.001), together with symptom duration and Charlson index as additional independent predictors of higher-grade difficulty (Table 6). When preoperative Tokyo Guidelines severity grade was added to the original model instead, it was itself a strong predictor of difficulty (adjusted OR 5.04, 95% CI 2.40–10.60, p<0.001; n=206), and CRP's own association attenuated to an adjusted OR of 1.003 (95% CI 1.000–1.006, p=0.096), no longer reaching significance.

Median CRP was markedly higher among the 12 patients who required conversion than among those who did not (271.0 mg/L [IQR 136.8–338.0] vs 87.8 mg/L [IQR 14.7–204.2], p=0.003). CRP discriminated conversion with an AUC of 0.76 (95% CI 0.62–0.89) (Table 5, Fig. 2), at a higher optimal cut-off than for difficulty alone (304 mg/L), reflecting specificity (89.4%) and negative predictive value (96.9%) rather than sensitivity (50.0%). In clinical terms, a CRP below this threshold made conversion unlikely, while a value above it identified approximately one in five patients requiring conversion. All 12 conversions occurred in patients who had not received ICG; restricting the ROC analysis to this subgroup (135 patients with available preoperative CRP) gave a similar estimate (AUC 0.73, 95% CI 0.59–0.86, cut-off 301 mg/L).

CRP was also higher in the 32 patients who developed any postoperative complication (171.5 mg/L vs 79.2 mg/L, p=0.013; AUC 0.64, 95% CI 0.53–0.74) (Fig. 3), with the 56.5 mg/L cut-off performing best. When restricting the outcome to major complications (Clavien-Dindo grade ≥IIIa, n=5), CRP showed no discernible difference (109.0 vs 98.6 mg/L, p=0.954); with only 5 events this comparison is uninformative, and we report it purely descriptively. Preoperative CRP correlated modestly with length of stay (Spearman’s rho=0.37, p<0.001).

Thirty-day readmission (n=8), biliary complications requiring ERCP (n=2), and mortality (n=3) were too infrequent in this cohort for reliable statistical modelling and are reported descriptively in Table 2; both patients with a biliary complication requiring ERCP and two of the three deaths occurred in patients with an above-median preoperative CRP, but with n=3 and n=2 these numbers do not support any inference and we report them only for completeness.

Discussion

In this cohort of 221 patients undergoing emergency cholecystectomy for acute cholecystitis, a single preoperative CRP measurement carried usable information about three different surgical questions, each with its own threshold. A relatively modest elevation, around 56 mg/L, flagged a gallbladder that was likely to be difficult to dissect and, to a lesser extent, one more likely to be followed by some degree of postoperative complication. A much higher value, around 300 mg/L, flagged a real risk of conversion to open surgery. These are not the same clinical decision, and treating CRP as a single-cut-off test, as much of the existing literature implicitly does, probably undersells what the marker can do.

Our findings on surgical difficulty fall within the range reported elsewhere, although the exact cut-off varies considerably between series. Anees et al. and Díaz-Flores et al., working with elective cohorts and defining difficulty by

operative time or intraoperative complications rather than a validated anatomical grading scale, reported thresholds around 11 mg/dL (110 mg/L) [4, 5]. Ng et al., in a considerably larger emergency cohort (n = 804) graded by the Nassar scale, reported an AUC of 0.78 with a cut-off of 90 mg/L for grade IV–V disease [8]. Our own cut-off of 56.5 mg/L for Parkland-graded difficulty (AUC 0.73) is lower than both; we attribute part of this gap to the different definitions of difficulty across studies (operative time, Nassar grade, and Parkland grade are related but not interchangeable constructs) and part to the smaller size of our own cohort, which limits the precision of any data-derived threshold. A similar range of associations has emerged whenever difficulty grading itself has been prospectively examined: in a 206-patient Nepalese validation of the Parkland scale, operative time, conversion, and postoperative fever all rose stepwise with grade [16], and in the original multicentre validation of a Nassar-type difficulty grade across more than 12,000 UK patients, complication rates rose from 7.6% to 24.4% between the lowest and highest grades [1, 17]. What is more consistent across studies, including ours, is the direction and independence of the CRP association: it predicts difficulty after adjustment for age, sex, comorbidity, and symptom duration, which argues against it being a simple proxy for how sick or how late-presenting a patient is. That said, CRP's association attenuated once we additionally adjusted for preoperative Tokyo Guidelines severity grade, itself a strong independent predictor of difficulty. This is not surprising (Tokyo grading already incorporates much of the clinical, laboratory, and imaging information that also drives CRP, even though CRP is not itself one of its severity criteria) and some shared variance between the two is expected. We see this as clarifying rather than undermining our main finding. Tokyo grading and CRP answer different questions: Tokyo grade, once the imaging and organ-function assessment behind it are complete, describes systemic risk, while CRP reflects local inflammatory burden and is available earlier, from a single, inexpensive test most patients already have on admission. Its practical value lies in informing decisions that cannot wait for the full work-up, such as surgeon allocation or counselling about conversion risk, not in outperforming Tokyo grade once that fuller picture is assembled.

The conversion analysis is, we think, the more clinically actionable of the two primary findings, if only because the decision it informs (whether to block extra time, ensure a second experienced surgeon is available, or discuss conversion explicitly during consent) has to be made before the patient enters the operating theatre. Mok et al. and Kaushik et al. both described a stepwise rise in CRP from simple, through difficult, to converted cases, with Mok reporting an AUC as high as 0.93 for conversion in a cohort with a conversion rate broadly comparable to ours [6, 7]; Wevers et al. and Bouassida et al. reported broadly similar independent associations, at a threshold of 165 mg/L and in a large 556-patient prospective series respectively [9, 11], and a recent multicentre nomogram from Wu et al., built on more than 3000 patients across eight centres, retained CRP as one of five variables with a validation AUC above 0.83 [10]. Vaccari et al., in a two-centre Italian series of over 1300 patients, likewise found CRP among the independent predictors of conversion alongside age and comorbidity [18], and Utsumi et al. proposed a CRP-to-albumin ratio as a refinement of the same idea [12]. Our own cut-off of roughly 304 mg/L sits at the high end of this range, which we would attribute partly to our comparatively low overall conversion rate (5.4%) and partly to the coexistence of intraoperative ICG cholangiography in a large part of the cohort, an intervention that, in our own prior work, was itself associated with a lower conversion rate [14]. That every conversion in this series occurred in a patient who had not received ICG, and that the CRP-conversion association survived when we restricted the analysis to that subgroup alone, argues that CRP is not merely tracking ICG allocation; but we would still flag this interaction as something that needs testing in a cohort where ICG use is not concentrated in a way that creates near-complete statistical separation, before the 304 mg/L figure is treated as fixed.

The morbidity findings are the weakest part of this analysis, and we report them as such rather than overstate them. An AUC of 0.64 for any complication is a real but modest signal; this degree of discrimination is unlikely to support CRP as a standalone decision threshold for postoperative management. Sato et al., using the POSSUM score in a Japanese cohort, and Serban et al., comparing CRP with the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, both found inflammatory burden linked to postoperative complications without any single marker being decisive on its own

[19, 20], and at a much larger scale, the international AMBROSE cohort found that an operative difficulty grade conceptually parallel to Parkland was among the five strongest predictors of 30-day morbidity across more than 21,000 patients, at least consistent with the idea that whatever drives difficulty also drives part of what happens afterwards [21]. We found no discernible CRP difference for major complications specifically (Clavien-Dindo ≥IIIa, n = 5; 109.0 vs 98.6 mg/L, p = 0.954); with so few events this comparison carries no interpretable signal, and we report it for completeness rather than as a finding. The correlation with length of stay (rho = 0.37) is consistent with Kaushik et al.'s stepwise gradient and with Ljuca's more recent finding that CRP was the only laboratory value to remain an independent predictor of prolonged stay after multivariable adjustment [6, 13], although a correlation of this size explains only a modest share of the variance in an outcome shaped by many things besides inflammatory burden (bed pressure, surgeon availability, and social factors among them) none of which we captured in this database. Farahani et al., in a mixed 180-patient Iranian cohort of which only 76 (42%) had acute cholecystitis, similarly tested CRP against difficulty, conversion, and complications together, and reported higher discrimination than we found for all three outcomes [22]; This discrepancy is not readily explained, beyond the general caution that single-centre AUC estimates of this kind do not always reproduce; both their results and ours should be regarded as requiring external validation rather than as an upper bound. Readmission, biliary complications, and mortality were all too rare in our cohort (8, 2, and 3 events respectively) to model with any confidence, and we report the raw numbers mainly so that a future, larger or pooled analysis can use them, rather than because we believe they show anything on their own.

This study has the limitations expected of a secondary analysis within a broader, prospectively planned research programme. The cohort was recruited consecutively and prospectively as part of a case-control study centred on intraoperative ICG cholangiography [14], and although the wider aim of that programme was always to extend the same dataset toward other perioperative markers, the specific hypothesis tested here (that preoperative CRP predicts surgical difficulty) was not written into the original protocol as a prespecified primary endpoint. These findings should therefore be regarded as hypothesis-generating pending prospective validation. Difficulty grading was performed by the operating surgeon rather than by independent video review, which introduces some subjectivity even though the Parkland scale was designed to minimise it. A meaningful fraction of the cohort received intraoperative ICG cholangiography, which we have argued does not explain the CRP-conversion association but which we cannot fully exclude as an effect modifier given the small number of events. The CRP thresholds we report, particularly the 304 mg/L cut-off for conversion (based on only 12 events), were derived and evaluated in the same dataset and should be regarded as exploratory and internally derived rather than validated clinical thresholds. As in most series on this topic, the rarer outcomes (biliary complications requiring ERCP and death) occurred too infrequently for CRP, or indeed anything else, to be tested against them with statistical confidence. The strength of this analysis, we think, lies less in any single number than in the fact that all three questions were asked of the same patients using the same blood test, which better reflects how a single CRP value is actually used in clinical practice than three separate studies in three separate cohorts would.

Conclusion

In this cohort, a single preoperative CRP measurement carried independent, clinically distinguishable information about three separate outcomes in acute cholecystitis: a threshold near 56 mg/L was associated with a difficult gallbladder and, more weakly, with postoperative morbidity, while a threshold near 304 mg/L helped rule out a high risk of conversion when CRP fell below it (NPV 96.9%), though its low sensitivity and PPV mean it cannot be used to reliably rule conversion in. Given how inexpensive and widely available CRP already is, we believe these outcome-specific thresholds are worth validating prospectively, ideally in a multicentre cohort large enough to also examine the rarer, higher-stakes outcomes that our sample could not support.

Declarations

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Conflicts of interest:

The authors declare no conflicts of interest.

Ethics approval: This study was performed in accordance with the Declaration of Helsinki and was approved by the Aragón Ethics Committee for Research (CEICA), approval number PI24/478.

Consent to participate: All patients provided written informed consent.

Consent to publish: Not applicable — no identifiable individual data or images are included.

Data availability:

Data are available from the corresponding author on reasonable request.

Author contributions:

Rubén Carramiñana-Nuño: conceptualization, methodology, investigation (patient recruitment), data curation, formal analysis, writing, review & editing.

Pilar Palacios-Gasós: supervision, writing, review & editing.

Vicente Manuel Borrego-Estella: conceptualization, supervision, writing, review & editing.

All authors read and approved the final manuscript.

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Tables

Table 1. Preoperative characteristics by surgical difficulty (Parkland grading scale)

Preoperative variable	n	Easy (Parkland 1-3)	Difficult (Parkland 4-5)	p	Effect (95% CI)*
Age (years)	221	61.0 [46.0-74.5]	66.0 [55.0-77.0]	0.049	5.0 (0.0 to 9.0)
Female sex, n (%)	221	70 (55.1%)	32 (34.0%)	0.003	OR 0.42 (0.24-0.73)
Nursing-home residence, n (%)	220	5 (4.0%)	6 (6.4%)	0.535	OR 1.65 (0.49-5.58)
BMI (kg/m^2)	208	28.8 [25.6-33.6]	29.4 [26.3-32.1]	0.913	-0.1 (-1.4 to 1.3)
ASA III-IV, n (%)	221	33 (26.0%)	30 (31.9%)	0.368	OR 1.34 (0.74-2.40)
Charlson comorbidity index	221	1.0 [0.0-3.0]	2.0 [0.0-4.0]	0.035	0.0 (0.0 to 1.0)
Anticoagulant use, n (%)	221	18 (14.2%)	15 (16.0%)	0.708	OR 1.15 (0.55-2.42)
Previous abdominal surgery, n (%)	221	33 (26.0%)	37 (39.4%)	0.041	OR 1.85 (1.04-3.28)
Previous biliary symptoms, n (%)	220	57 (45.2%)	44 (46.8%)	0.891	OR 1.07 (0.62-1.82)
Duration of symptoms (hours)	221	24.0 [24.0-72.0]	72.0 [24.0-72.0]	0.003	12.0 (0.0 to 24.0)
Diagnosis by CT (vs ultrasound), n (%)	221	8 (6.3%)	24 (25.5%)	<0.001	OR 5.10 (2.17-11.97)
Acalculous (vs calculous) cholecystitis, n (%)	219	2 (1.6%)	6 (6.5%)	0.072	OR 4.36 (0.86-22.12)
Gallbladder wall thickening (US), n (%)	204	121 (99.2%)	80 (97.6%)	0.566	OR 0.33 (0.03-3.71)
Gallbladder distension (US), n (%)	204	108 (88.5%)	80 (97.6%)	0.018	OR 5.19 (1.15-23.46)
Pericholecystic fluid (US), n (%)	204	20 (16.4%)	39 (47.6%)	<0.001	OR 4.63 (2.42-8.83)
Locally complicated disease (US), n (%)	204	14 (11.5%)	25 (30.5%)	<0.001	OR 3.38 (1.63-7.01)
CBD dilation (US), n (%)	204	4 (3.3%)	1 (1.2%)	0.650	OR 0.36 (0.04-3.32)
Tokyo Guidelines grade II-III (vs I), n (%)	220	31 (24.4%)	65 (69.9%)	<0.001	OR 7.19 (3.94-13.10)
Haemoglobin (g/dL)	221	13.6 [12.3-14.6]	13.7 [12.4-15.0]	0.408	0.2 (-0.3 to 0.7)
White cell count (x10^3/uL)	221	12.6 [8.5-15.4]	14.8 [11.5-18.6]	<0.001	2.6 (1.2 to 3.8)
AST (U/L)	211	26.0 [19.0-46.5]	30.0 [20.5-58.0]	0.146	3.0 (-1.0 to 7.0)
ALT (U/L)	208	26.0 [19.0-50.5]	29.5 [19.0-69.2]	0.219	3.0 (-2.0 to 10.0)
GGT (U/L)	209	40.0 [25.0-129.0]	57.5 [27.5-174.0]	0.212	7.0 (-4.0 to 22.0)

Preoperative variable	n	Easy (Parkland 1-3)	Difficult (Parkland 4-5)	p	Effect (95% CI)*
Alkaline phosphatase (U/L)	207	86.0 [66.0-111.2]	94.0 [71.5-142.0]	0.064	11.0 (-1.0 to 23.0)
Total bilirubin (mg/dL)	75	0.6 [0.4-0.9]	1.0 [0.9-1.5]	<0.001	0.5 (0.2 to 0.7)
Preoperative CRP (mg/L)	220	45.1 [11.2-142.0]	166.0 [72.8-285.3]	<0.001	94.0 (59.0 to 125.0)
Lactate (mmol/L)	181	1.5 [1.2-2.1]	1.6 [1.3-2.2]	0.194	0.1 (-0.1 to 0.3)

** Difference in means (Welch's t-test) or Hodges-Lehmann estimate of the median difference (Mann-Whitney U test) (difficult minus easy group) for continuous variables, according to normality (Kolmogorov-Smirnov test); odds ratio (difficult vs easy) with 95% CI by the Woolf method for categorical variables. Continuous variables expressed as mean ± SD or median [IQR] according to normality. Ultrasound and Tokyo-grade variables have n=204-220 owing to a subgroup diagnosed primarily by CT.*

Table 2. Surgical and postoperative outcomes by surgical difficulty

Outcome variable	n	Easy (Parkland 1-3)	Difficult (Parkland 4-5)	p	Effect (95% CI)*
Operative time (min)	221	88.0 [60.0-95.0]	117.0 [90.0-127.0]	<0.001	30.0 (25.0 to 36.0)
Conversion to open surgery, n (%)	221	0 (0.0%)	12 (12.8%)	<0.001	OR 37.17 (2.17-637.83)
Length of hospital stay (days)	218	3.0 [3.0-5.0]	5.0 [4.0-7.0]	<0.001	2.0 (1.0 to 2.0)
Locally complicated cholecystitis (pathology), n (%)	221	68 (53.5%)	92 (97.9%)	<0.001	OR 39.91 (9.42-169.07)
Any postoperative complication, n (%)	221	11 (8.7%)	21 (22.3%)	0.006	OR 3.03 (1.38-6.66)
Biliary complications, n (%)	221	0 (0.0%)	2 (2.1%)	0.180	OR 5.52 (0.25-123.87)
30-day readmission, n (%)	221	6 (4.7%)	2 (2.1%)	0.472	OR 0.44 (0.09-2.22)
Intraoperative ICG use, n (%)	221	42 (33.1%)	43 (45.7%)	0.069	OR 1.71 (0.99-2.95)

**Same method as Table 1. No conversions occurred among Parkland 1-3 patients (0/127) so a 0.5 continuity correction was applied to this empty cell to estimate the odds ratio, whose 95% CI is accordingly very wide.*

Table 3. Intraoperative pathological findings by surgical difficulty (Parkland grading scale)

Intraoperative pathological finding	Easy (Parkland 1-3)	Difficult (Parkland 4-5)
Oedematous (uncomplicated)	59 (46.5%)	2 (2.1%)
Gangrenous	62 (48.8%)	69 (73.4%)
Perforated	4 (3.1%)	13 (13.8%)
Haemorrhagic	2 (1.6%)	4 (4.3%)
Emphysematous	0 (0.0%)	1 (1.1%)
Acalculous	0 (0.0%)	2 (2.1%)
Biliary peritonitis	0 (0.0%)	3 (3.2%)

Descriptive only: individual category p-values are not reported given the small sample size of several subcategories (cells with n<5), which precludes a reliable statistical comparison. The aggregated inferential comparison ("locally complicated cholecystitis", edematous vs all other categories) is reported in Table 2.

Table 4. Multivariable logistic regression for surgical difficulty (Parkland 4-5 vs 1-3)

n=207 (complete cases across the seven covariates).

Variable	Adjusted OR	95% CI	p
Preoperative CRP (per mg/L)	1.006	1.003-1.009	<0.001
Age (per year)	1.011	0.989-1.035	0.328
ASA III-IV (vs I-II)	0.592	0.232-1.515	0.274
Charlson index (per point)	1.119	0.904-1.386	0.302
Symptom duration (per hour)	1.009	1.000-1.018	0.061
Female sex (vs male)	0.499	0.265-0.940	0.031
BMI (per kg/m2)	0.988	0.927-1.052	0.701

Table 5. Association between preoperative CRP and surgical difficulty, conversion, postoperative complications, and length of stay

Outcome	n (events)	CRP no event	CRP event	p	AUC (95% CI) / rho	Cut-off	Sens.	Spec.	PPV	NPV
Surgical difficulty (Parkland 4-5)	220 (94 events)	45.1 [11.2-142.0]	166.0 [72.8-285.3]	<0.001	0.731 (0.663-0.798)	56.5 mg/L	84.0% (75.0-90.8)	58.7% (49.6-67.4)	60.3% (51.4-68.7)	83.1% (73.7-90.2)
Conversion to open surgery	220 (12 events)	87.8 [14.7-204.2]	271.0 [136.8-338.0]	0.003	0.755 (0.624-0.887)	304.0 mg/L	50.0% (21.1-78.9)	89.4% (84.4-93.3)	21.4% (8.3-41.0)	96.9% (93.3-98.8)
Any postoperative complication	220 (32 events)	79.2 [14.7-200.2]	171.5 [65.3-303.5]	0.013	0.638 (0.532-0.744)	56.5 mg/L	81.2% (63.6-92.8)	44.1% (36.9-51.6)	19.8% (13.4-27.7)	93.3% (85.9-97.5)
Major complications (Clavien-Dindo >=IIIa)*	219 (5 events)	98.6 [15.2-226.0]	109.0 [56.5-146.0]	0.954	not modelled (too few events)	-	-	-	-	-
Length of hospital stay (Spearman rho)	217	-	-	<0.001	rho = 0.374	-	-	-	-	-

AUC = area under the receiver operating characteristic curve, with 95% CI; cut-offs derived by the Youden index; sensitivity, specificity, PPV and NPV reported with 95% CI. Major complications and length of stay were not modelled with ROC analysis owing to too few events (major complications) or a non-binary outcome (length of stay, reported as Spearman's ρ instead).

Table 6. Ordinal logistic regression for surgical difficulty across the full Parkland scale (grades 1-5)

n=207. Proportional-odds model; OR interpretable as the increase in the odds of belonging to a higher Parkland difficulty category per unit of the variable.

Variable	OR (per Parkland grade)	95% CI	p
Preoperative CRP (per mg/L)	1.006	1.004-1.009	<0.001
Age (per year)	1.008	0.990-1.028	0.385
ASA III-IV (vs I-II)	0.542	0.244-1.203	0.132
Charlson index (per point)	1.246	1.034-1.502	0.021
Symptom duration (per hour)	1.011	1.003-1.018	0.006
Female sex (vs male)	0.474	0.280-0.800	0.005
BMI (per kg/m2)	1.021	0.970-1.074	0.436

Figures

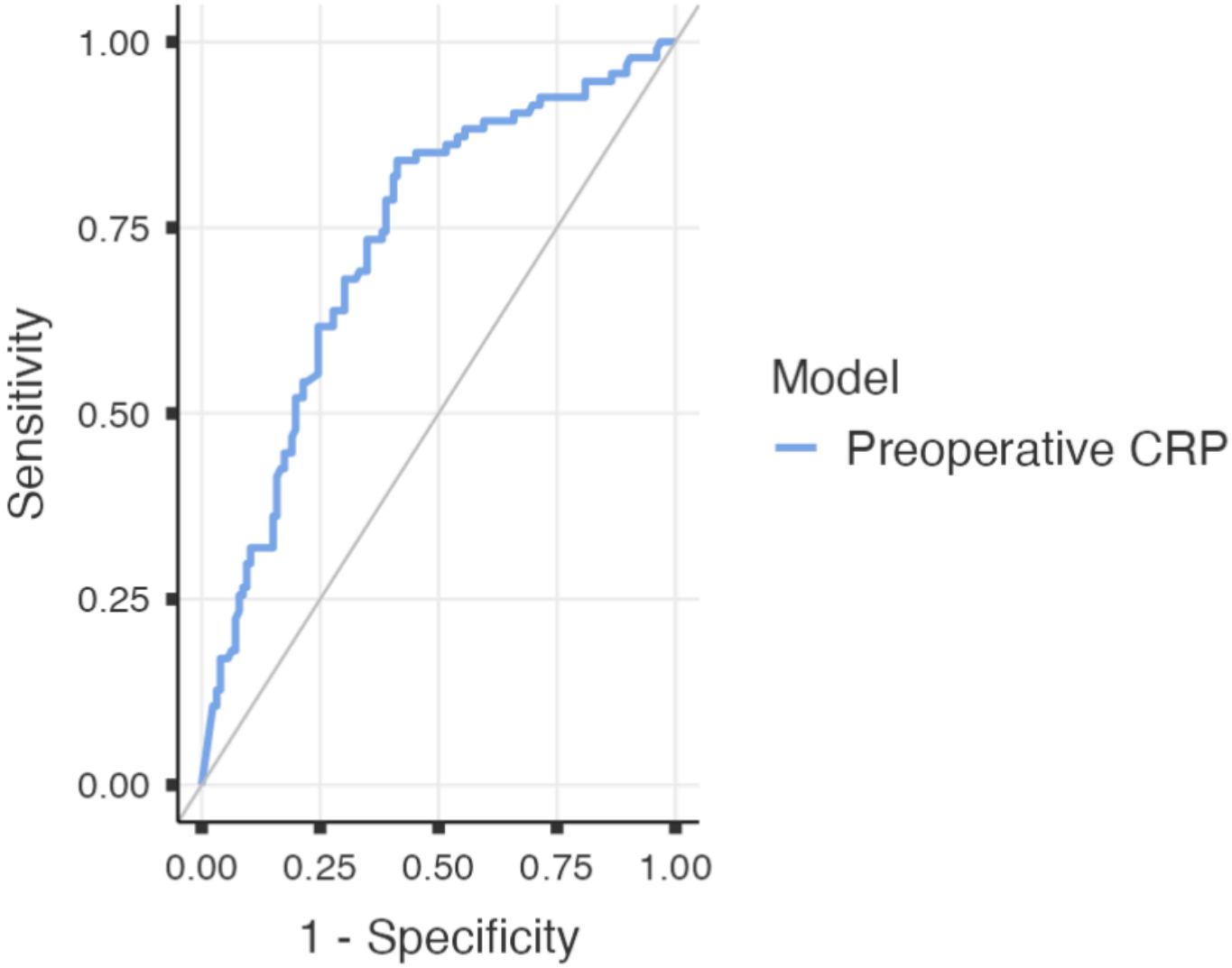

Figure 1

Receiver operating characteristic curve for preoperative C-reactive protein predicting surgical difficulty (Parkland grade). Area under the curve 0.73 (95% CI 0.66–0.80); optimal cut-off 56.5 mg/L (Youden index)

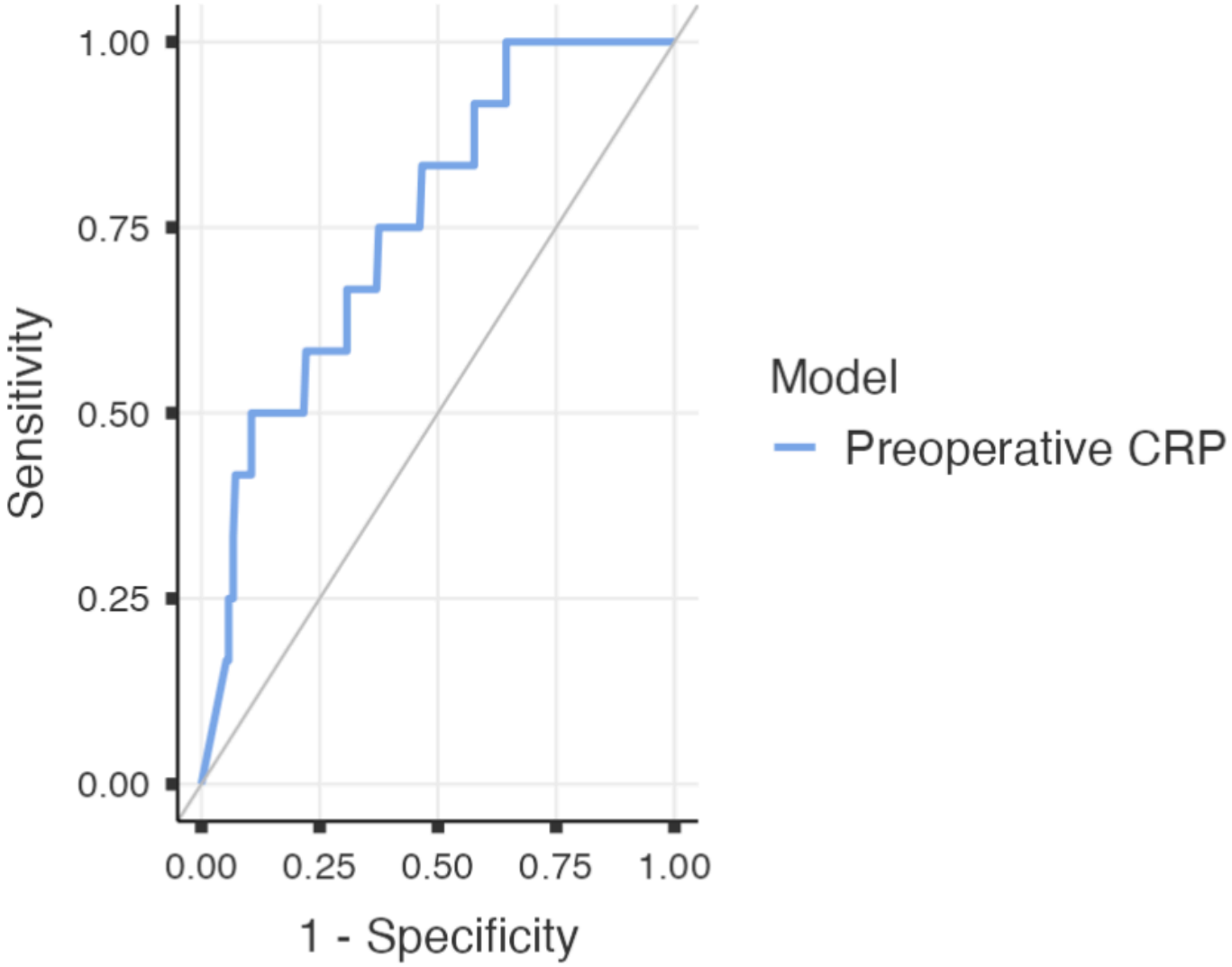

Figure 2

Receiver operating characteristic curve for preoperative C-reactive protein predicting conversion to open surgery. Area under the curve 0.76 (95% CI 0.62–0.89); optimal cut-off 304 mg/L

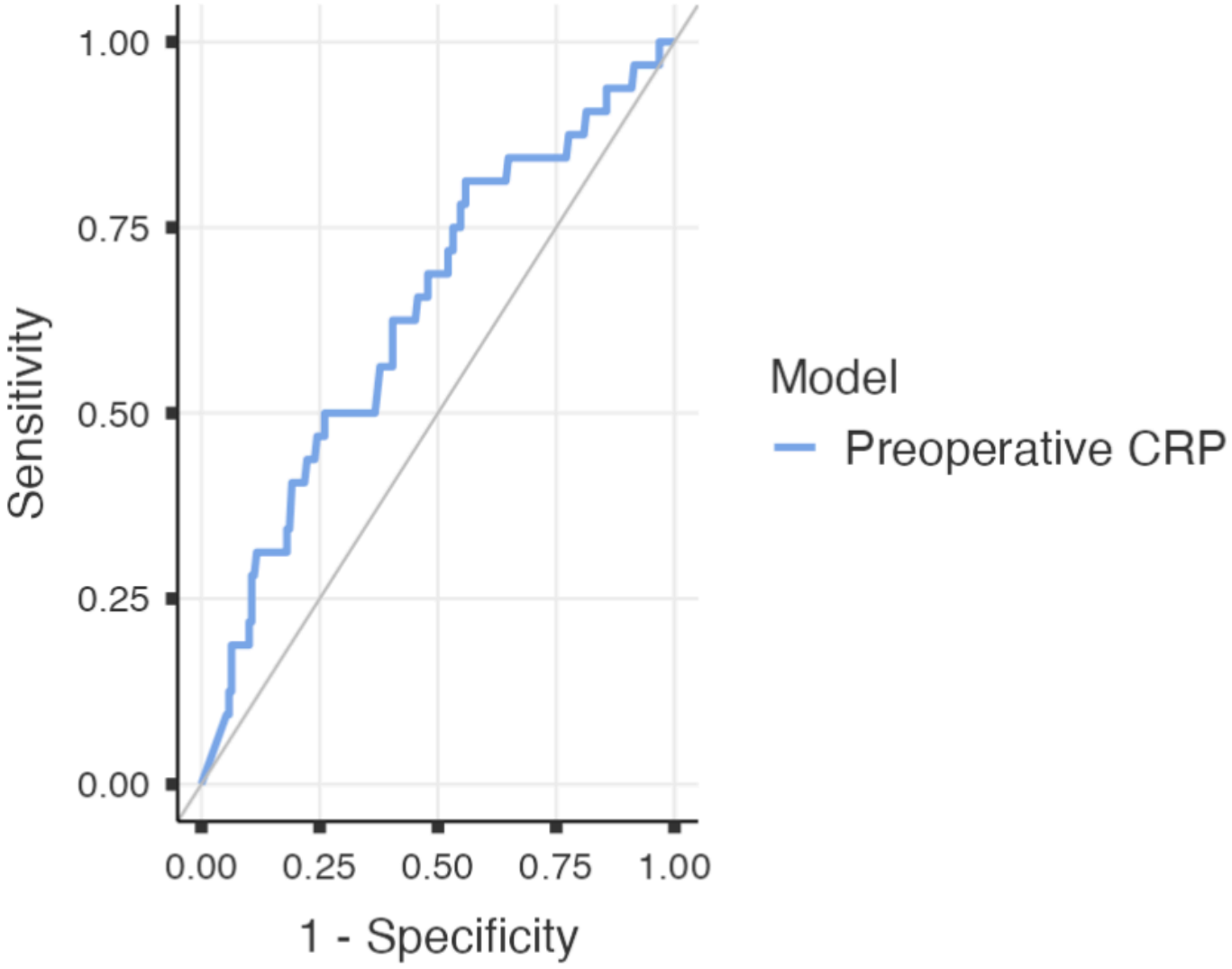

Figure 3

Receiver operating characteristic curve for preoperative C-reactive protein predicting postoperative complications. Area under the curve 0.64 (95% CI 0.53–0.74); optimal cut-off 56.5 mg/L