C-Reactive Protein (CRP) as a Predictive Factor for Difficulty of Laparoscopic Cholecystectomy

FAWZY M. MUSTAFA, M.D.* and BAHAA SAEDA, M.D.**
The Departments of General Surgery* and Clinical Pathology**, Faculty of Medicine, Al-Azhar University

Abstract

Background: Acute cholecystitis with difficult laparoscopic surgery has impact on operating time and training of juniors. The clinical diagnosis of complicated acute cholecystitis (CAC) remains difficult with several pathological or ultrasonography criteria used to differentiate it from uncomplicated acute cholecystitis (UAC).

Aim of Study: Was to evaluate CRP (C-reactive protein) as a parameter that predict operative difficulty of LC (laparoscopic cholecystectomy) or conversion to open surgery.

Patients and Methods: A prospective randomized clinical trial was carried out on 150 Laparoscopic cholecystectomies performed from January 2019 to February 2022 at General Surgery Department, Al-Azhar University Hospitals (Cairo) Egypt. Association of intra-operative difficulties or conversion with the following factors was studied: Age, gender, CRP and white blood cell count (WBC).

Results: 150 patients were analysed [124 laparoscopic, 22 difficult laparoscopic cholecystectomy (LC) and 4 C (Conversion to open)]. All patients had a recorded CRP. Median CRP was highest for patients who were converted (280.5) compared to those who had difficult LC (67.40) or LC (7.05). High preoperative CRP, WBC and cholangiopancreatography, were predictors of conversion. These factors were only marginally better than CRP alone in predicting conversion.

Conclusion: C-reactive protein can be efficient predictor of conversion of Laparoscopic cholecystectomy (LC).

Key Words: C-reactive protein – Laparoscopic cholecystectomy – Complicated acute cholecystitis – Gangrenous cholecystitis.

Introduction

THE pathophysiology of acute cholecystitis is blockage of the cystic duct. Edema of the gallbladder wall will eventually cause ischemia of the wall and become gangrenous. That may be infected by gas-forming organisms, causing acute emphysematous cholecystitis which is a life-threatening condition with high rate of mortality [1].

1% to 2% of patients with asymptomatic cholelithiasis develop acute cholecystitis. This is a consequence of an impacted cystic duct causing distension of the gallbladder and increased tension on the gallbladder wall, accompanied by an associated inflammatory reaction [2,3]. Early diagnosis by physical examination, radiology and laboratory C-reactive protein [CRP], white blood cell [WBC] count is the cornerstone for management of acute cholecystitis [3].

Laparoscopic cholecystectomy (LC) can be the easiest or the most difficult laparoscopic surgery. Anticipation of conversion can help in consenting patients and preparing them for longer stay and complications [4].

Laparoscopic surgery conversion of LC was influenced by a lot of factors like patient characteristics (high body mass index, previous abdominal surgery), anatomical variations of extra-hepatic biliary system and gallbladder (GB) pathology (severe inflammation of GB or common bile duct [CBD]) [4].

The studies found significant association of conversion with old age, male gender, previous abdominal surgery, previous endoscopic retrograde cholangiopancreatography (ERCP), and ultrasonographic findings (USS) like GB wall thickness etc. With increasing experience in laparoscopic surgery and advancement of technology many of the difficulties due to anatomical and patient factors could be dealt with laparoscopically [5]. GB wall thickness on ultrasound scan was a strong predictor of conversion of LC [6].

C-reactive protein (CRP) is an acute phase reactant protein secreted by the liver in response to interleukin-6 and other pro-inflammatory cytokines in the context of inflammation, infection,
trauma, malignancy and tissue infarction. Its circulating concentration is determined by its rate of synthesis reflecting the intensity of the pathological process, and hence it is a good indicator of severity of inflammation. It was observed that many of the patients who had their LC converted to open surgery (either emergency or delayed) had very high CRP at the time of their index admission for GB pathology. Even for those who were not converted, LC was difficult if their preoperative CRP levels were moderately raised [7].

Our study hypothesised that high CRP level due to GB pathology (biliary colic or acute inflammation) is associated with difficulties and conversion.

The aim of this study was to evaluate CRP (C-reactive protein) as a parameter that predict operative difficulty of LC (laparoscopic cholecystectomy) or conversion to open surgery.

**Patients and Methods**

A prospective randomized clinical trial was carried out on 150 Laparoscopic cholecystectomies performed from January 2019 to February 2022 at General Surgery Department Al-Azhar University Hospitals (Cairo) Egypt performed by experience upper gastrointestinal surgeon.

**Inclusion criteria:** All the patients 18 years and above who had cholecystectomy.

**Exclusion criteria:** The study aims to look at the association between CRP and difficult cholecystectomy/conversion due to GB pathology; the following patients were excluded to avoid confounding effect of these factors:
- High BMI (>35).
- Previous abdominal surgery.
- Preoperative ERCP and pancreatitis
- Patient with concurrent non-biliary cause of raised CRP concentration (chest infection).

Patient demographics, radiological findings, duration of surgery, conversion to open, perioperative complications, readmissions and mortality will retrieved. Surgical difficulty is based on the Nassar scale [8] and a CRP level below 6mg/l is considered normal.

**Nassar difficulty grading scale:**

Surgeons were asked to grade the difficulty of the procedure using the Nassar scale (grades 1-4). This scale was published in 1995 and graded operative findings from the gallbladder, cystic pedicle and associated adhesions [8].

**The scale is as follows:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gallbladder-floppy, non-adherent. Cystic pedicle-thin and clear. Adhesions-Simple up to the neck/Hartmann's pouch.</td>
</tr>
<tr>
<td>2</td>
<td>Gallbladder-Mucocele, Packed with stones. Cystic pedicle-Fat laden. Adhesions-Simple up to the body.</td>
</tr>
<tr>
<td>3</td>
<td>Gallbladder-Deep fossa, Acute cholecystitis, Contracted, Fibrosis, Hartmans adherent to CBD, Impaction. Cystic pedicle-Abnormal anatomy or cystic duct-short, dilated or obscured. Adhesions-Dense up to fundus; Involving hepatic flexure or duodenum.</td>
</tr>
<tr>
<td>4</td>
<td>Gallbladder-Completely obscured, Empyema, Gangrene, Mass. Cystic pedicle-Impossible to clarify. Adhesions-Dense, fibrosis, wrapping the gallbladder, Duodenum or hepatic flexure difficult to separate.</td>
</tr>
</tbody>
</table>

The grading system is designed to be used as an overall summary of the operative conditions found, and the worst factor found in the individual aspect of either the 'Gallbladder', 'Cystic Pedicle' or 'Adhesions' should be used to define the final overall grade [8].

**Patient management:**

All patients with gall bladder stone by clinical and ultrasound findings are admitted to general surgery department. Laparoscopic cholecystectomy is performed after the patient is assessed as fit for general anesthesia. All cases undergo chest X-ray and urine analysis to exclude other causes of increased CRP.

CRP (mg/L), and white blood cell count (WBC) on admission were recorded for all the patients. Logistic analysis is used to assess predictors of high operative difficulty (grade III or above) versus low difficulty (grades I and II), and included the following variables: Age, sex, and CRP level.
Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro-Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi^2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples $t$-test was used to compare between two independent groups of normally distributed variables (parametric data). $p$-value <0.05 was considered significant.

Fig. (1): Illustrates laparoscopic images of each of the Nassar operative difficulties.

Results

150 laparoscopic cholecystectomies performed between 2019 and 2022, all patients had preoperative estimation of CRP concentration, but some cases were excluded owing to preoperative chest or urinary infection.

Table (1): Demographic parameter of patients who had LC with difficult dissection and conversion to open surgery groups.

<table>
<thead>
<tr>
<th>Demographic parameter</th>
<th>Laparoscopic cholecystectomy</th>
<th>Difficult Dissection</th>
<th>Conversion to open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td>Median (IQR)</td>
<td>47.5 (36.8-55.0)</td>
<td>59.0 (50.5-70.0)</td>
</tr>
<tr>
<td>Gender:</td>
<td>Male/female (%)</td>
<td>25/122 (20.16)</td>
<td>18/22 (81.81)</td>
</tr>
</tbody>
</table>

Fig. (2): Demographic parameter of patients who had LC with difficult dissection and conversion to open surgery groups.
**Clinical characteristics are summarized as:**
The admission diagnosis was biliary colic in 120 of the 150 patients (80%), acute cholecystitis in 30 (20%). A medical history of previous admission was recorded for 19 patients (12.67 per cent). All patients who had laparoscopic cholecystectomy were evaluated by ultrasound imaging of the abdomen.

The duration of surgical procedure ranged from 22 to 187 min. The median time for laparoscopic cholecystectomy was 75 min. There were 4 cases conversions to open surgery. Duration of hospital stay ranged from 1 to 15 (median 3) days.

No association was found between Nassar scale grades and the timing of laparoscopic cholecystectomy, but patients with a previous admission for had increased operative difficulty than those with a first admission.

Table (2): CRP and WBC comparison of patients who had LC with difficult dissection and conversion to open surgery groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laparoscopic cholecystectomy</th>
<th>Difficult Dissection</th>
<th>Conversion to open</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC:</td>
<td>7.75</td>
<td>9.50</td>
<td>12.35</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>(6.20-9.45)</td>
<td>(7.10-13.00)</td>
<td>(7.60-16.75)</td>
</tr>
<tr>
<td>CRP:</td>
<td>9.25</td>
<td>67.40</td>
<td>280.5</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>(7.05-62.20)</td>
<td>(18.95-300.55)</td>
<td>(201.48-320.50)</td>
</tr>
</tbody>
</table>

**C-reactive protein:**
All patients had a preoperative peak CRP level of more than 6 mg/l. The preoperative peak CRP level ranged from 7.05 to 320.50 mg/l. A statistically significant association was found between the proportions of patients with a CRP level greater than or equal to 6 mg/l and Nassar scale grades.

**Discussion**
Due to the variability of operative findings, laparoscopic cholecystectomy is one of the most unpredictable operations in general surgery, this can be due to anatomical reasons, but is mainly due to the effect of cholecystitis and fibrosis on the dissection planes in Calot's triangle [9].

A recent study for AC found that CRP level at admission (≥3.6 mg/dL) and male gender were strongly related to conversion of emergency LC. In this study, the measurement of CRP in predicting a DD or conversion to open surgery was investigated alone for the subset of patients [10].

Two studies have been done previously to predict difficult LC rather than predicting conversion [11,12]. Randhawa and Pujahari looked at 15 factors that make the operation difficult, but not necessarily requiring conversion [11]. The other study by Sakuramoto et al., is the only study that looked at “difficult LC due to GB pathology” a concept similar to this study, but required 41 factors to predict intraoperative difficulties [12].

Previous studies in this field reported an association between a raised CRP level and cholecys-
titis, although with limited results in relation to duration of symptoms or timing of laboratory test evaluation. Another study found a CRP concentration above 200mg/l to be a good predictor of gangrenous cholecystitis, consistent with the present findings and Nassar scale grading [13].

In this study, patients were treated by experience surgical team despite CRP levels. However, the median hospital stay of 3 days was due to the exclusion criteria of another factor.

Some authors have acknowledged the importance of grading the difficulty of cholecystectomy and the use of operative risk predictive scores. The Nassar scale has been suggested to optimize the perioperative management of patients with gallstone disease [14].

In this study, the Nassar scale grade was higher when the preoperative peak CRP concentration was raised. An increased CRP level can be a predictor of a high operative difficulty grade, and this finding could be of use in planning surgical management and also to select patients appropriate for surgical training.

Although a number of important clinical applications of the Nassar grading system have been reported, the scale has yet to be validated and validated in large cohorts of patients such as the present study [8].

All Difficult Dissection/Conversions cases in this study group refer to difficulty in getting satisfactory views of the Calot’s triangle. The rate of conversion was higher in patients with preoperative CRP than those without. Median CRP was highest for patients who were converted to open surgery from laparoscopic.

Patients in the DD group were significantly older, had significantly higher CRP and WBC, and a higher percentage of males compared with patients in the LC group. Patients in the Conversion group were significantly older, had significantly higher CRP and WBC, a higher percentage of males.

In this study, the median CRP was significantly higher in the patients converted to open operation (286.2) compared to those with difficult LC (67.4) and laparoscopic group (7.05). This is the first study to assess value of CRP as a single predictor of difficult surgery.

Conclusion:
C-reactive protein can be efficient predictor of conversion of Laparoscopic cholecystectomy (LC).

Financial support and sponsorship: Nil.

Conflict of interest: Nil.

References
CRP as a Predictive Factor for Difficulty of Laparoscopic Cholecystectomy


البروتين سي التفاعل كعامل تنبؤي لصعوبة استئصال المرارة بالمنظار

خلاصة الدراسة: التهاب المرارة الحاد مع الجراحة التنظيرية الصعبة له تأثير على وقت التشغيل وتدريج العمر. لا يزال التشخيص السريري لإلتهاب المرارة الحاد المعقد صعبًا مع العديد من المعايير المرمية أو الموجات فوق الصوتية المستخدمة لتمييزه عن التهاب المرارة الحاد غير المعقد.

الهدف من الدراسة: تقييم البروتين سي التفاعل كعامل يتنبأ بصعوبة استئصال المرارة بالمنظار أو التحويل إلى الجراحة المفتوحة.

المرجع للدراسة: أجريت دراسة سريرية عشوائية مستقلة على 150 عملية استئصال مرارة بالمنظار في فبراير 2019 إلى فبراير 2020 في قسم الجراحة العامة، مستشفى جامعة الأزهر (القاهرة) مصر. تم دراسة ارتباط الصعوبات أثناء العملية أو التحويل مع العمليات التالية: العمر، الجنس، بروتين سي التفاعل، وعدد خلايا الدم البيضاء.

نتائج الدراسة: تم تحليل 100 مريضاً [124 بالمنظار، 22 استئصال المرارة بالمنظار الصعب و 50 درجات متوسطة (التحول إلى الفتح)]. كان لدى جميع المرضى بروتين سي التفاعل المسجل. كان متوسط بروتين سي التفاعل على النسبة للمريض الذي تم تحويلهم (500) مقارنة بذويه الذين لديهم حساب في استئصال المرارة بالمنظار (294) أو استئصال المرارة بالمنظار (27). كان ارتفاع بروتين سي التفاعل قبل الجراحة، وبعد خلايا الدم البيضاء، وتصوير الفيبراس والأنبوبية الصفراوية، عوامل تنبؤ بالتحول. كانت هذه العوامل أفضل بشكل هامشي من بروتين سي التفاعل وحده في توقع التحويل.

الاستنتاج: يمكن أن يكون بروتين سي التفاعل مؤشراً فعالاً لتحويل استئصال المرارة بالمنظار.