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The study of C-reactive protein as the most useful predictor of difficult laparoscopic cholecystectomy or its conversion

Nyage Lombi[1],Ankan Ghosh [2], Harish Manivannan [3],Khulem Stellone Singh[4]Fleming Nagarajan [5], Debaleena Goswami [6],Ranita Devi S [7]
[1,2,3,5,6]*(Postgraduate Trainee, Department of Surgery, Regional Institute of Medical Sciences, India)*
[4]*(Senior Resident, Department of Surgery, Regional Institute of Medical Sciences, India)*
[7]*(Professor,Department of Surgery, Regional Institute of Medical Sciences, India)*

Abstract: *Laparoscopic cholecystectomy (LC) can be the easiest or the most difficult laparoscopic operation. Conversion to open surgery has been a traditional marker of difficult laparoscopic cholecystectomy and anticipation of conversion can help in consenting patients and preparing them for longer stay and complications. In adopting laparoscopic cholecystectomy it must be realized that the need for conversion to open operation is 15–25% (5 times the conversion rate for chronic cholecystitis). The high conversion rate from laparoscopic to open surgery provoked an interest in studying the predictive factors for successful completion (without conversion to open surgery) of the early laparoscopic cholecystectomy in acute cholecystitisC-reactive protein is known to increase upto many folds in severe cases of inflammation and/or infection, and it is also known that levels drop as inflammation subsides, but its utility as a significant predictor indifficult laparoscopic cholecystectomy or need for conversion of laparoscopic cholecystectomy to open cholecystectomy still remains controversial.Therefore, this study which included 150 patients with cholelithiasis was conducted with an objective to understand and correlate preoperative C-reactive protein values with the intra-operative difficulty, This study has shown strong association between peak preoperative C-reactive protein level and gallbladder pathology related conversion of laparoscopic procedures. At a cut-off point of 42 mg/dl, C-reactive protein has a high positive as well as negative predictive value. So CRP on its own appears to be good independent predictor of conversion*

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I. Introduction

Cholelithiasis, a disease of hepatobiliary system, is rising in incidence all over the world including India, especially northern parts of India.Laparoscopic cholecystectomy has since long been the 'gold standard' for the treatment of symptomatic gallstones presenting as acute/chronic cholecystitis.However, the laparoscopic approach was initially considered to be relatively contraindicated or unsafe in acute cholecystitis. It was believed that inflammatory tissue reactions make the dissection difficult, thus increasing the hazard of serious complications as well as the conversion rate.The feasibility, safety and benefits of early laparoscopic surgery in acute cholecystitis were proved by several studies and it soon became the treatment of choice for acute cholecystitis.It must be realized that the need for conversion to open operation is 15–25% (5 times the conversion rate for chronic cholecystitis). The high conversion rate from laparoscopic to open surgery provoked an interest in studying the predictive factors for successful completion (without conversion to open surgery) of the early laparoscopic cholecystectomy in acute cholecystitis.The identification of these factors is aimed at better preoperative selection of patients for early laparoscopic cholecystectomy.C-reactive protein (CRP) an acute phase reactant, is known to rise to high levels within 4-6 hours following acute injurious conditions such as trauma, surgery, inflammation or infection. [9]

Although, there are various factors which are studied for prediction of difficult cholecystectomy e.g. age, sex, body mass index, chronic obstructive lung diseases, previous abdominal surgeries and other co morbid conditions etc. but these are inconsistent factors to rely upon for prediction of difficult cholecystectomy requiring need for conversion.Very few studies are available that have employed determining levels of high C-reactive protein and its association with difficult cholecystectomy. Therefore, this study was conducted with an objective to understand and correlate preoperative C-reactive protein values with the intra-operative difficulty, and, if possible , try to arrive at some definitive conclusions whether these values of high C-reactive protein would help a surgeon anticipate a difficult laparoscopic cholecystectomy, or else, prepare the surgeon better for imminent need of conversion to open cholecystectomy intraoperatively and reduce the time of surgery.

II. Material And Methods

This Cross-sectional study was conducted in the Department of Surgery, Regional Institute of Medical Sciences, Imphal, Manipur during a period of two calendar years with effect from 1st August 2017 to 31st July 2019 which included all patients (>12 years of age) admitted from casualty and OPD to the Department of Surgery, Regional Institute of Medical Sciences, Imphal, with cholelithiasis

Study Design: Prospective cross sectional study

Study Location: This was a tertiary care teaching hospital based study done in Department of General Surgery along with Department of Microbiology, at Regional Institute of Medical Sciences, Imphal

Study Duration: 1st August 2017 to 31st July 2019.

Sample size: 150 patients.

Subjects & selection method:Patient admitted in the surgical ward with cholelithiasis at Department of Surgery, RIMS were enrolled in the study after informed consent.

A complete history, physical/clinical examination and investigations according to the proforma were done for all patients.

Inclusion criteria:

All patients with cholelithiasis planned for surgery admitted in Department of Surgery, Regional Institute of Medical Science, Imphal, irrespective of age, sex, and religion.

Exclusion criteria:

1. Those who refused to give consent.
2. High BMI (>35).
3. Previous abdominal surgery.
4. Patient with significant immunosuppression
5. Patient with severe cardiac and pulmonary co-morbidities

Procedure methodology

Sampling:

All patient with cholelithiasis planned for surgery and admitted in Department of Surgery, Regional Institute of Medical Science, Imphal, irrespective of age, sex and religion that fulfilled the inclusion criteria were taken up for the study.

After taking the proposed informed consent, blood sample were collected in the ward and sent to laboratory for the analysis of WBC count and C-reactive protein especially along with other routine investigations.

Study tools:

- RHELAX-CRP reagent.
- Slide with six reaction circles, sample dispensing pipettes, mixing sticks, rubber teat, stopwatch, test tubes and isotonic saline.
- RHELAX-CRP (slide test for C-reactive protein) is a uniform suspension of polystyrene latex particles coated with anti–CRP antibodies. The reagent is standardized to detect CRP concentrations greater than 0.6mg/dl. The standardization of detection limit of RHELAX-CRP is traceable to WHO, international reference standard (85/506) for human C-reactive protein.
- Positive control, reactive with RHELAX-CRP reagent.
- Negative control, non reactive with RHELAX-CRP.
- RHELAX-CRP slide test for detection of CRP is based on the principle of agglutination. The test specimen is mixed with RHELAX-CRP reagent and allowed to react. If CRP concentration is greater than 0.6mg/dl a visible agglutination is observed. If CRP concentration is less than 0.6mg/dl, then no agglutination is observed.
- RHELAX-CRP manufactured by Tulip Diagnostics (P) Ltd. Tulip House Rego Bagh, Alto santacruz, Bambolim complex P.O, Goa-403 202, India.

Procedures:

- Bring reagent and samples to room temperature before testing.
- Using isotonic saline prepare serial dilutions of the test specimen positive in the quantitative method 1:2, 1:4, 1:8, 1:16, 1:32, 1:64 and so on.
- Pipette each dilution of the test specimen onto separate reaction circles.
- Add one drop of RHELAX-CRP latex reagent to the drop of test specimen on the slide.
- Using a mixing stick, mix the test specimen and the latex reagent uniformly over the entire circle.

- Immediately start a stopwatch. Rock the slide gently, back and forth, observing for agglutination macroscopically at two minutes.

Interpretation of results:

- Agglutination in the highest serum dilution corresponds to the approximate amount of CRP in mg/dl present in the test specimen. concentration of the CRP can be calculated as follows:

  CRP (mg/dl) = S x D

  Where, S= sensitivity of the reagent i.e. 0.6mg/dl

  D= Highest dilution of serum showing agglutination.

Methods:

The present study was a hospital based observational study conducted in Department of Surgery, Regional Institute of Medical Sciences, Imphal, Manipur. A total of 150 patients clinically diagnosed, admitted and planned for elective/emergency cholecystectomy were recruited and it formed the study group. A detailed history, general physical examination, and baseline investigation for the operative procedure were duly undertaken in all patients. A written informed consent was obtained and the study was approved by the institutional Research Review Board RIMS, Imphal. A Standard preoperative procedure were followed, and for each patient recent laparoscopic cholecystectomy technique were performed by experienced surgeon. Depending on surgeon's judgement –the case, in question, of difficult and inability to proceed was converted to open cholecystectomy.

For accurate measurement of C-reactive protein level early morning fasting blood sample was taken and send to Biochemistry laboratory RIMS, Imphal. All the sera were analyzed by using kit PHALEX-CRP, manufactured by Tulip Diagnostic (P) Ltd, Goa, India. Testing procedure was done according to manufacturer's instructions and optical density was directly related to the quantity of the measured analyzed in the spectrum as per the manufacturer's instructions.

Statistical analysis

The data collected were analyzed at the end of the study by using mean, percentage and significance test using 't-test', 'chi-squared test' and receiver operating characteristic (ROC)curve with a P value of <0.05 as significant

III. Results

This is a Hospital base cross sectional study conducted at Regional Institute of Medical Sciences, Imphal, Manipur, from August 2017 to July 2019 in the Department of Surgery. All the patients admitted for laparoscopic cholecystectomy in the Department of Surgery, Regional Institute of Medical Sciences, Imphal, were recruited. This was to study the C-reactive protein level to predict the outcome of laparoscopic cholecystectomy and its possible conversion to open cholecystectomy. In this study age, sex, WBC count and ultrasonographic findings were included as other important parameters to predict the outcome of the Surgery. During the study periods, 150 patients were recruited and underwent laparoscopic cholecystectomy which formed the study groups.

AGE:

All the cases were categorized into six age groups, less than 20 years 12(8%) patients, 21 - 30 years 18 (12%) patients, 31-40 years 38 (25.3%) patients, 41-50 years 42 (28%) patients, 51-60 years 25 (16.7%) patients, and more than 60 years 15 (10%) patients (Table-1)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<20	12	8.0	8.0	8.0
	21-30	18	12.0	12.0	20.0
	31-40	38	25.3	25.3	45.3
	41-50	42	28.0	28.0	73.3
	51-60	25	16.7	16.7	90.0
	>60	15	10.0	10.0	100.0
	Total	150	100.0	100.0	

Table 1: Age distribution the patients

SEX:
Out of one hundred fifty patients who were recruited for the study, 29(19.3%) were male and 121(80.3%) were female as shown in (figure-1).

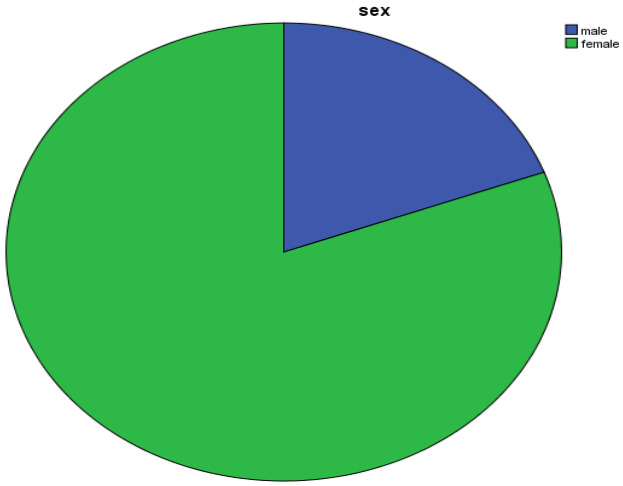


Figure 1: Sex Distribution of the participant**.**

COMPARISION OF SEX AND THE OUTCOME OF THE SURGERY:

		operation			Total[a]
		normal laparoscopic cholecystectomy	difficult lap cholecystectomy	conversion to open cholecystectomy	
sex	male	13	10	6	29
	female	105	13	3	121
Total		118	23	9	150

Figure 2: correlation between sex and outcome of surgery.

Out of one hundred fifty patients who were recruited for the study, 29(19.3%) were male and 121(80.7%) were female. Again, out of 121 female patients 118(97.5%) underwent laparoscopic surgery, and 3(2.5%) patients were converted to open surgery, and out of 29 male patients, 23(79.3%) underwent laparoscopic surgery, and 6(20.7%) patients were converted to open surgery. In this study more male patients (20.7%) were converted as compared to female patients (2.5%) to open surgery (Table-2). There was significant positive correlation between the sex of the patient and the outcome of the surgery with r(148)=421,p value=<0.05.

COMPARISION OF AGE AND OUTCOME OF THE SURGERY:

		operation			Total
		normal laparoscopic cholecystectomy	difficult lap cholecystectomy	conversion to open cholecystectomy	
age	<20	12	0	0	12
	21-30	12	5	1	18
	31-40	29	7	2	38
	41-50	31	7	4	42
	51-60	19	4	2	25
	>60	15	0	0	15
Total		118	23	9	150

Table 3 : comparison of age of the patient with operation outcome

In this study the patient age was placed into six different groups as shown in (Table-3), to correlate with the outcome of the surgery. There was no significant positive correlation between the age of the patient and the outcome of the surgery in this study with r (148)= - .017, p value=.837.

COMPARISION OF WBC COUNTS WITH OPERATION OUTCOME:

		operation			Total
		normal laparoscopic cholecystectomy	difficult lap cholecystectomy	conversion to open cholecystectomy	
WBC	4-11	92	5	0	97
	12-15	25	14	5	44
	>16	01	4	4	9
Total		118	23	9	150

Table 4; correlation of WBC count with operation outcome

The WBC counts of the patients were divided into three categories. In first groups, WBC counts of 97 (64.6%) patients were normal, and 92 (94%) patients underwent normal laparoscopic surgery,5 (6%) patients underwent difficult laparoscopic surgery, and no any conversion to open cholecystectomy. Among second groups 44 (29.3%) patients were high WBC count range from 12-15 mm^3/dl, of which 25 (56.8%) patients underwent normal laparoscopic, 14 (31.8%) patient had difficult laparoscopic surgery, and 5 (11.3%) patients were converted from laparoscopic to open cholecystectomy. In third groups, 9 (6%) patients were WBC counts more 16 mm^3/dl with and among them 1 (11%) patient had normal laparoscopic surgery, 4 (44.4%) patient with difficult laparoscopic surgery, and 4 (44.4%) patients were converted to open surgery (Table-4). It shows that there is significant correlation between the raised WBC level and the outcome of the surgery with r(148)= .349, p value=0.001.

COMPARISION OF USG FINDING WITH OPERATION OUTCOME:

		operation			Total
		normal laparoscopic cholecystectomy	difficult lap cholecystectomy	conversion to open cholecystectomy	
USG	normal	101	9	1	111
	wall thickened >4mm	17	14	6	37
	pericholecystic collection	0	0	2	2
Total		118	23	9	150

Table 5: correlation of USG finding with operation outcome

Ultrasonography is one of the parameters which help in predicting the outcome of laparoscopic cholecystectomy in cholecystitis. In present study it was categorized into three groups, and of which 111 (74%) patients were normal USG findings, gallbladder wall thickness more than 4mm in diameter 37 (24.6%) patients, and pericholecystic collection 2 (1.3%) patients. In the first group it was found that 101 (90%) patients underwent normal laparoscopic cholecystectomy, 9 (8.1%) underwent difficult laparoscopic surgery, and 1 (1.9%) was converted to open. In the second group, out of 37(24.6%) patients with Gallbladder wall thickness >4mm, 17(45.9%) patients had normal laparoscopic surgery, 14 (37.8%) had difficult laparoscopic surgery, and 6 (16.2%) underwent conversion to open cholecystectomy. In the third group, 2 (1.3%) patients with pericholecystic fluid collection, all 2 (100%) patient were converted to open surgery (Table-5). This studies shows that a preoperative USG finding has significant correlation with the outcome of the surgery with r(148)= .567, p value=0.001.

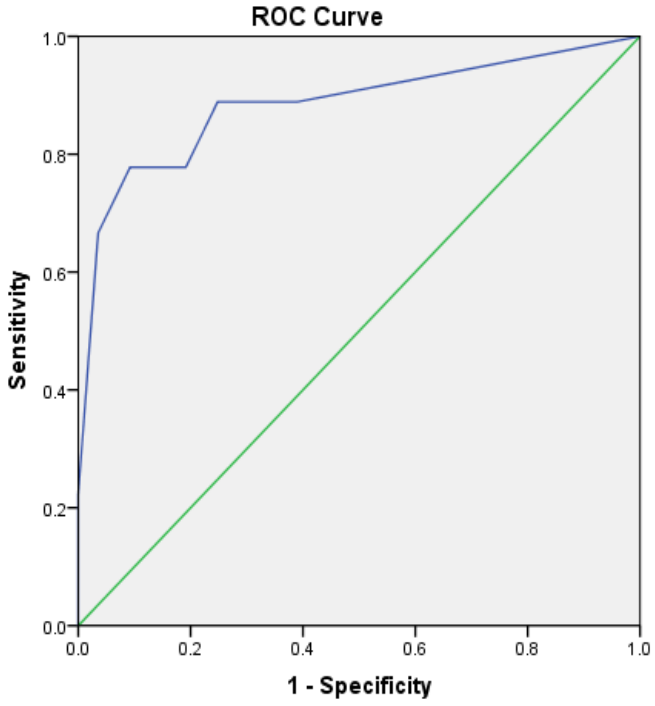
COMPARISION OF C-REACTIVE PROTEIN WITH OPERATION OUTCOME:

		operation			Total
		normal laparoscopic cholecystectomy	difficult lap cholecystectomy	conversion to open cholecystectomy	
CRPlevel	Normal 1-3	82	4	1	87
	4-10mg	20	0	0	20
	11-20mg	8	0	1	9
	21-30mg	7	1		8
	31-40mg	1	5	0	6
	41-50mg	0	8	1	9
	51-60mg	0	5	4	9
	>60mg	0	0	2	2
Total		118	23	9	150

Table 6: correlation of C-reactive protein with operation outcome

In this study, a C-reactive protein level was placed into eight categories as shown in (Table 6) with mean value of 2.33. Out of one hundred fifty patients 87(58%) were having normal range of CRP and 63(42%) patients were raised CRP level. Among 63(42%) patients who had raised CRP level 36(57%) patients undergone normal laparoscopic cholecystectomy, 19(30%) patients with difficult laparoscopic surgery, and 9(14%) patients were converted from laparoscopic to open cholecystectomy. Most of the patient who were having difficulty laparoscopic surgery and needs conversion were at the C-reactive protein level 41-60 mg/dl

The diagnostic accuracy of CRP on its own in predicting a conversion to open surgery was modeled for the patients who had a recorded preoperative CRP (n=150, Difficult=23, Conversion=9). Univariate analysis showed that CRP was found to be significant in predicting whether patient would be converted to open surgery with r(148)=.755, p value=<0.001.



The AUROC was .883, with a 95% confidence interval of 0.862-0.927 (Figure-2). This showed that C reactive protein was outstanding at separating patients who are likely to have a conversion to open cholecystectomy from laparoscopic surgery. The sensitivity of C-reactive protein was 42.63% with 95% CI 18.68%-65.24%, specificity was 90.2% (82.4-94.6%) positive predictive value (PPV) was 48.6% and negative predictive value (NPV) 91.2% .

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.883	.075	.000	.736	1.000

Figure 7: Area under the curve(Test result variables: CRP level

The test result variable(s): CRP level has atleast one tie between the positive actual state group and the negative actual state group. Statistic may be biased.

a. Under the non parametric assumption
b. Null hypothesis: true area=0.5

IV. Discussion

Today, laparoscopic cholecystectomy is accepted as safe and feasible surgical procedure of an experienced surgeon in the treatment of acute/chronic cholecystitis due to the gallbladder stone, although there is increased risk of bile duct injury due to the inflammation of the (GB) gallbladder wall, altered or unclear anatomy in calot's triangle. The intensity of inflammatory changes in the gallbladder affects the degree of surgical difficulties, increases possibility of conversion to open procedure. In early phase of cholecystitis submucosal edema facilitates dissection of gallbladder from the lodge and the anatomy of the calot's triangle is not significantly altered. Progression of inflammation is characterized by multiple adhesion of surrounding anatomic structure of gallbladder, fibrosis, or necrosis of GB wall eventually leading to scaring of structures near to the gallbladder. Aspiration of the GB has to be done for the decompression of edematous thickened GB wall to allow placement of grasper and for better visualization of the calot's triangle- reducing the risk of injury to biliovascular structures.

In this study, 150 patients have been recruited to study the level of C- reactive protein as predictor of difficult laparoscopic cholecystectomy and its conversion to open cholecystectomy. Variables like age, sex, WBC counts, and USG finding were included along with C-reactive protein in the study because it also affects the outcome of the surgery. In a study done by Ibrahim S et al and Licciardello A et al presence of co-morbidities and variables were found as significant risk factor for conversion[34].

In this study C reactive protein level of all the patients (150) were evaluated at the time of admission before the surgery, of which 87(58%) patients were within the normal range, and level was raised in 63(42%) patients of different age group with C-reactive protein ranging from 3.6mg/dl to 58mg/dl, The cut-off value were found to be 42mg/dl,

This study comprises of 150 patients with 29 male patients and 121 female patients with varying age difference ranges from less than 20 years to more than 60 years of age and the youngest patient was 14 years old female and the oldest was 64 years old male. In this study, the age of the patient has no positive significant correlation with the outcome of the surgery with p value=.837, and the sex of the patient has significant positive correlation with the outcome of the surgery, as 6 (20.7%) male patients were converted from laparoscopic to open cholecystectomy in compared to 3(2.5%) female patient who were converted to open cholecystectomy.

A USG finding like thickened gallbladder(GB) wall more than 4mm was statistically significant indicator of operational difficulties. Thickened gallbladder wall at preoperative USG is a sign of present inflammation or fibrosis due to cholecystitis[41]. Jantsch et al claimed that gallbladder wall thickness > 4mm is a frequent finding in acute cholecystitis. Inflammation progression is characterized by multiple adhesions of surrounding anatomic structures with gallbladder fibrosis or necrosis which creates difficulties when dissecting calot's triangle. In their studies 84% of the thickened gallbladder wall more than 4mm had difficulties laparoscopic cholecystitis.

In present study, preoperative USG finding like gallbladder wall thickness and pericholecystic fluid collection has predictive indicator of possible difficult laparoscopic cholecystectomy. Out of 150 patients, 37(24.6%) patients had thickened gallbladder wall of which 14 patients had difficult laparoscopic cholecystectomy and 6 patients were converted to open cholecystectomy. This study also shows positive correlation between preoperative USG findings and the outcome of the surgery with r(148)= .567, p value=0.001.

Pericholecystic fluid collection (PFC) is a ultrasonographic sign of acute inflammation. In this study, a multivariate analysis showed that PFC was significant predictor of a number of operational difficulties as shown in table-5, with all 2 patient of PFC were converted to open cholecystectomy. This correlate with many published studies which state that the PFC is a ultrasonographic sign of acute inflammation, and is an important predictor of operational difficulties and its possible conversion.

In present study WBC count was raised in 53(35%) of the patients of which 40(26%) patient had successfully completed laparoscopic cholecystectomy although 18 patient had a difficult dissection, 9 patient were converted to open cholecystectomy. It was found that raised WBC count has a significant positive predictor in terms of outcome of laparoscopic cholecystectomy with r(148)=.349, p value=<0.05

V. Conclusion

This study has shown strong association between peak preoperative C-reactive protein level and gallbladder pathology related conversion of laparoscopic procedures. At a cut-off point of 42 mg/dl, C-reactive protein has a high positive as well as negative predictive value. So CRP on its own appears to be good independent predictor of conversion. Considering strong correlation of C-reactive protein, WBC count, and gallbladder wall thickness on USG with conversion, it may be possible to develop a simple system for preoperative prediction of difficult laparoscopic cholecystectomy and its conversion.

A preoperative prediction of difficulties helps surgeon to assess his operations, to accelerate the decision for the conversion, to timely inform patients for better psychological preparation and obtaining approval for prior possible open cholecystectomy surgery. Patients with a higher number of predictors of difficulties also need to be operated by competent and rested surgical team and must have priority in making operation programs in order to reduce health care cost and increase safety of surgery outcome.

In this study, C-reactive protein along with other parameters have shown a positive predictive value of difficult laparoscopic cholecystectomy and its possible conversion. It is found that 19% of patients were converted to open surgery, and the minimum cut-off points were found to be 42mg/dl. This study was a single hospital base observational study with small sample size and a short period of time, so needs more validation and research before bring it for practical use.

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