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# **Original Research Article**

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# hsCRP levels as predictor of difficult laparoscopic cholecystectomycurrent status evaluation experience in a teaching institution

# Balvinder Singh Arora<sup>1\*</sup>, Poornima Sen<sup>1</sup>, Raj Kumar Singh<sup>2</sup>, Indu Biswal<sup>1</sup>, Shivani B. Paruthy<sup>2</sup>

<sup>1</sup>Department of Microbiology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi 110029, India

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## \*Correspondence:

Dr. Balvinder Singh Arora,

E-mail: dr\_arorabalvinder007@yahoo.com

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#### **ABSTRACT**

**Background:** CRP, an acute phase reactant, is known to increase up to 1000 folds following inflammation and/or infection, but it's utility as a significant predictor of difficult LC or need for conversion to OC still remains controversial. Limited studies on levels of hsCRP and its association with difficult cholecystectomy are available in literature, especially in Indian context. It is hypothesized that levels of hsCRP pre-operatively for a given population or an individual patient if high would help a surgeon anticipate better a difficult LC, avoid excessive intra-operative manipulations, go for conversion early, reduce time of surgery and hence also minimise post-operative complications. **Methods:** The present included 30 clinically diagnosed 'cholecystitis with cholelithiasis' patients, and 30 healthy individuals. For accurate comparison of hsCRP levels, a fasting and post-operative, 6 and 12 hours, blood samples were analyzed by ELISA test. Pre-and post-operative hsCRP values were recorded and analyzed using multi-user licensed SPSS- Version 21.0.

**Results:** The mean value of hsCRP in controls was 1.43mg/L. In study group, in pre-operative serum samples, the concentration was 20.46 mg/l. At 6 and 12 hours post-operative periods, the mean values observed were 24.4mg/L and 23.7 mg/L respectively. Compared with controls, the mean values are fairly high and statistically also significant (p-values <0.0001). For the study group comparison of hsCRP value pre-operative and post-operatively 6 hours, using Wilcoxon Signed Rank Test has given the p-value <0.001 indicating that the increased hsCRP concentration in patients' circulation is highly significant as a predictor of difficult laparoscopic cholecystectomy. Similarly, Comparison of hsCRP value pre-operative and post-operative 12 hours, using Wilcoxon Signed Rank Test revealed the p-value <0.007 showing it as highly significant and a predictor of difficult LC requiring conversion. The preoperative value of 20.46% is significant for an individual planned for LC who may require conversion.

Conclusions: The preoperative hsCRP value of 20.64mg/L, as per our study results, can be relied upon as predictors of difficult LC and/or need for conversion not only in the study group in the given population but also in individual cases. Such a value of 20.64mg/L is definitely important for an individual case management. Knowing the preoperative values beforehand and if found high, it places a surgeon on a cautious note to avoid too much of LC manipulations intra-operatively, take an early decision to go for conversion, reduce the time of surgery, minimise post-operative complications and hence also morbidity.

Keywords: Conversion, hsCRP, LC, OC

<sup>&</sup>lt;sup>2</sup>Department of Surgery, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi 110029, India

#### INTRODUCTION

C-reactive protein, an acute phase reactant, is known to rise to high levels within 4-6 hours following acute injurious conditions such as trauma, inflammation or infection.1 Cholelithiasis, a disease of hepatobiliary system, is rising in incidence all over the world including India, especially northern parts of India.<sup>2</sup> Laparoscopic cholecystectomy (LC), is now a widelyaccepted method of choice for symptomatic gall bladder disease. It has virtually become the gold standard for the treatment of symptomatic cholelithiasis. Currently, surgeons are taking high risks patients which were initially considered a relative contraindication for LC a couple of years back.3 With wider application of LC, even for anticipated technically difficult and high risk cases, it is expected that complication rates would rise leading to increase in the conversion rate from Laparoscopic cholecystectomy (LC) cholecystectomy (OC).<sup>3,4</sup> 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.<sup>4</sup> Very few studies are available that have employed determining levels of hsCRP and its association with difficult cholecystectomy. Although, CRP is known to increase up to 1000 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 of difficult LC or need for conversion of LC to OC still remains controversial.<sup>5,6</sup> We hypothesize that, "Levels of hsCRP help predict the need for conversion". Therefore, this study was conducted with an objective to understand and correlate the pre-operative hsCRP values with 6 and 12 hour post-operative values, and, if possible, try to arrive at some definitive conclusions whether these values of hsCRP would help a surgeon anticipate a difficult LC, or else, prepare the surgeon better for imminent need of conversion of LC to OC intraoperatively and reduce the time of surgery.

## **METHODS**

The present study was a hospital based observational study conducted in a city hospital with an attached teaching institution. A total of 30 patients clinically diagnosed as cholecystitis with cholelithiasis were recruited and it formed the study group while 30 healthy individuals- residents and technical staff formed control group. A detailed history, general physical examination, and baseline investigations for the operative procedure were duly undertaken in all patients. A written informed consent was obtained and the study was approved by Institutional Ethics Committee (IEC). All 30 cases diagnosed as cholecystitis with cholelithiasis were between the age group of 15-60 years. Standard preoperative procedures were followed and for each patient

standard laparoscopic cholecystectomy (LC) technique was performed by experienced surgeon. Depending upon surgeon's judgement- the case, in question, of difficult and inability to proceed was converted to open cholecystectomy (LC) method.

For accurate comparison of hsCRP levels, a fasting morning 5ml blood sample followed by blood sample (5ml) post operatively at 6 and 12 hours were obtained as per the standard procedures. Sera were stored immediately at -200°C till the test was put up. All the sera were analyzed by the kit CRP EIA made by XEMA Co. Ltd Moscow, Russia. It is based on two site sandwich enzyme immunoassay principle. Testing procedure was done according to manufacturer's instructions and optical density (OD) was directly related to the quantity of the measured analyte in the spectrum as per the manufacturer's instructions. Pre-and post-operative hsCRP values were recorded. Statistical analysis was performed using multi-user licensed SPSS - Version 21.0.

#### **RESULTS**

All cases and controls, 30 each, were categorized into five age and gender matched groups. Among 30 cases, 5 were males and 25 females. Among 30 healthy controls, 17 were males and 13 females. The gender and age distribution in cases was not statistically significant (p-value=0.110). No statistically significant difference between the gender and age distribution of the controls either was noticed (p-value=0.110) (Table 1).

Table 1: Age and gender distribution of study subjects.

Age	Study group			Control group		
group (Years)	Male	Female	Total	Male	Female	Total
21-30	1	7	8	0	1	1
31-40	0	10	10	3	1	4
41-50	3	7	10	4	3	7
51-60	1	1	2	10	8	18
Total	5	25	30	17	13	30

p-value 0.110 (using Fischer's exact test); p-value 0.755 (using Fischer's exact test)

Table 2: Comparison, in study group, n=30, of conversion of laparoscopic cholecystectomy (LC) to open cholecystectomy (OC) w.r.t age groups.

Age group (Years)	Converted to OC	Continued as LC
21-30	0	8
31-40	2	8
41-50	0	10
51-60	1	1
Total 30	3	27

0.079 p-value (Using Fischer's exact test)

Two cases in the age group 31-40 and one case from 51-60 years. required conversion to OC while remaining 27 were successfully completed for LC. Statistically, it is insignificant. It reflects, in present study, that the age group does not bear any significant relationship to need for conversion of LC to OC although the number of cases is a limitation here (Table 2). For hsCRP concentrations,

the mean value in controls was 1.43mg/L. In study group, in pre-operative serum samples, the concentration was 20.46mg/L. At 6 and 12 hours post-operative periods, the values observed were 24.4mg/L and 23.7 mg/L respectively. Compared with controls, the mean values are fairly high and statistically also significant (p-values <0.0001) (Table 3).

Table 3: Distribution of mean (M) and Standard deviation (SD) of the mean values of hs-CRP in cases at preoperative, post-operative 6 and 12 hours and controls.

hsCRP mean values (mg/L)							
Study group (n=30)							
Control group (n=30)	Pre-operative		Post-operative 6 hour		Post-operative 12 hour		
	Mean	SD	Mean	SD	Mean	SD	
Mean-value 1.43	20.64	4.909	24.40	1.542	23.70	4.580	
p value < 0.0001	< 0.0001		< 0.0001		< 0.0001		

Table 4: Sensitivity and specificity status using cut-off of hsCRP as >20 (in study group) predicting need for conversion to open cholecystectomy.

Parameter using cut off 20	Difficult/converted to OC	Normal/continued as LC	Total	
HsCRP>20	1	15	16	PPV=6.7%
HsCRP ≤20	2	12	14	NPV=85.7%
Total	3	27	30	
	Sensitivity=33.3%	Specificity=44.4%		
HsCRP>22	1	11	12	PPV=8.33%
HsCRP ≤22	2	16	18	NPV=88.8%
Total	3	27	30	
	Sensitivity=33.3%	Specificity=59.2%		
HsCRP>23	1	10	11	PPV=9.1%
HsCRP ≤23	2	17	19	NPV=89.4%
Total	3	27	30	
	Sensitivity=33.3%	Specificity=62.9%		
HsCRP>24	1	9	10	PPV=10.0%
HsCRP ≤24	2	18	20	NPV=90.4%
Total	3	27	30	
	Sensitivity=33.3%	Specificity=66.7%		

As the cut off values are increased the specificity improves but sensitivity remains the same.

Table 5: Pre-operative hsCRP cases versus hsCRP 6 hours and 12 hours reading.

Pre-operative vs. post-operative	Mean rank	Sum of ranks	z-value	p-value
Cases- pre-operative CRP vs. Cases-	12.00	12.00	-3.615	< 0.0001
6 hr post-Operative hsCRP	According to negative ranks	12.00		
Cases- pre-operative CRP vs. Cases-			-2.679	0.007
12 hr post-Operative hsCRP	14.83 According to negative ranks	44.50	using Wilcoxon signe	d rank test

Since the pre-operative mean value in the study group is 20.6 mg/L and post-operatively these are 24.4 and 23.7 (6 and 12 hours post operatively), the cut off values of >20, 22, 23 and 24 were taken into consideration to find

sensitivity and specificities of such values, it was found that as we increase the cut off of hsCRP from 20 to 24, the specificity increases from 44.4% to 66.7% though the sensitivity remains same (33.3%). An improvement in the

positive predictive value as well as negative predictive value was also observed as the cut-off was raised to >20 to 24 (Table 4). For the study group comparison of hsCRP value pre-operative and post-operatively 6 hours, using Wilcoxon Signed Rank Test resulted in the p-value<0.001. It shows that the increased hsCRP concentration in patients' circulation is highly significant as a predictor of difficult laparoscopic cholecystectomy requiring conversion (Table 5). Similarly, comparison of hsCRP value pre-operative and post-operative 12 hours, using Wilcoxon Signed Rank Test provided the p-value<0.007. It shows that the increase hsCRP concentration in patients' circulation is highly significant

as a predictor of difficult laparoscopic cholecystectomy requiring conversion (Table 5). Keeping in view that the clinical samples collected at different time intervals are from the same study group, the Mann-Whitney-Wilcoxon (MWW), a nonparametric test of the null hypothesis was also employed to know the p value for comparisons of hsCRP values at pre- and post-operative- 6 and 12 hours' time points respectively. The p-value obtained is very small i.e. <0.0001. Such a small p-value again shows that the difference in hsCRP concentration is significant for the study group. It is also useful for an individual case management as predictor of difficult cholecystectomy requiring conversion to open cholecystectomy (Table 6).

Table 6: Comparison of control at each level of hsCRP with cases using Mann-Whitney U test.

Independent sample comparison no.	Group description	N	Mean rank	Sum of ranks	z-value	p-value
	Cases pre-operative CRP	30	45.50	1365.00		
Comparison 1	Control CRP	30	15.50	465.00	-6.680	<0.0001
	Total	60				
Comparison 2	Cases post-operative 6 hr CRP	30	45.50	1365.00	-6.880	<0.0001
	Control CRP	30	15.50	465.00		
	Total	60				
Comparison 3	Cases post-operative 12 hr CRP	30	45.50	1365.00	C 091	<0.0001
	Control CRP	30	15.50	465.00	-6.981	
	Total	60				

## **DISCUSSION**

The failure rate of laparoscopic cholecystectomy in our study was only 10%. This is comparatively low but comparable with the failure rate of 15-25% in literature reported by Palanivelu C, Cuschieri A, and Mitchell et al in their study on 'Trends in the management of acute cholecyctitis".5-7 A relatively low failure rate is also attributable to the experience and surgical skills of the operating surgeon, albeit, among other variables like comorbidities, state of nutrition, etc. that can affect the outcome of such procedures. In a study done by Ibrahim S et al and Licciardello A et al presence of co morbidities were found as significant risk factor for conversion. 9,10 Among the three patients who required conversion to open cholecystectomy (OC), two were females and gender appears to have no relation to failure rate nor does it have any predictive value as per our results. It is in contrast to the reports that the male sex is associated with higher failure rates of laparoscopic surgery.<sup>8</sup> However; the number of patients recruited in the study was 30 and only three patients required conversion. Therefore, it is relatively difficult to comment precisely about the gender relationships to failure rate unless the number of patients recruited is large and more precise statistical significance is obtained. Two cases in the age group 31-40 and one in age group 51-60 years required conversion from LC to

OC while remaining 27 were successfully completed for LC. Statistically, it is insignificant. It reflects, as per our results, that the age group does not bear any significant relationship to need for conversion (of LC to OC) and the two groups are comparable (Table 3).

The mean value of hsCRP in controls was 1.43±0.88mg/L while in study group pre-operatively it was 20.64±4.90mg/L. At 6 and 12 hours post-operative periods the values observed were 24.37±1.54 and 23.70±4.58mg/L respectively. The mean values are fairly high compared with controls and statistically also significant (p-values<0.0001). The observation that preoperative levels are high as compared with the controls reflects that the process of inflammation has already set in. Post-operative high levels are suggestive of either aggravation of the inflammatory process already having set in preoperatively or surgical trauma. A decline in mean value to 23.70±4.58gm/L at 12 hours postoperative times' in study group, very judiciously, points to recovery from the underlying cause of inflammatory pathology or operative trauma that is inherent with any surgical procedure. To find out whether the difference in the values is significant or not, the cut off values of >20, 22, 23 and 24 were taken into consideration. It was found that, as increase the cut off value of hsCRP is increased from 20 to 24, the specificity increases though the

sensitivity remains the same (Table 4). Lack of improvement in sensitivity, as per the results obtained, show that the hsCRP levels although increase and can be easily detected qualitatively, but how well these correlates with the need for conversion is difficult to comment. The cut off values when raised from  $\geq 20$  to 24, an improvement in the positive predictive value as well as negative predictive value was observed. The specificity increased from nearly 45% to more than 66% (66.7%). The increase in specificity is important as it helps a laboratory physician to be more precise and predict the difficult cholecystectomy on a more definitive note. In the results of the study, it is also important to note that in the three patients who underwent conversionone patient (1) had a pre-operative value of 20mg/L; the second (2) had 14mg/L while the third had 25mg/L. In these three patients the post-operative values at 6 and 12 hours post-operatively increased to 25mg/L each and persisted. This persistent increased level of 25mg/L level, at and beyond 12 hours post-operative, however, reflects inflammation continuum, apparently due to the still active inflammatory process, and it may be attributable to aberrant immune response, especially, continuous release of the pro inflammatory cytokines or inadequate production of anti-inflammatory regulatory proteins that check the process of inflammation. A high hsCRP value in these three cases is again suggestive of the fact that need for conversion was imminent and of predictive value. There was no mortality and all the patients recovered well in time. Further, it is also important that the clinical samples collected at different time intervals are from the same study group, so the Mann-Whitney U test (also called the Mann-Whitney-Wilcoxon (MWW), a nonparametric test of the null hypothesis was employed to know the p value for comparisons of hsCRP values in pre-operative, post-operative- 6 and 12 hours. respectively as a group. The p-value obtained is <0.0001 and it shows the difference in hsCRP concentration is significant not only for the study group but also useful for an individual case management as predictor of difficult cholecystectomy requiring conversion to cholecystectomy (Table 6). Although other comorbid conditions and factors are, no doubt, important determinant of failure rates and hence need for conversion but it is an important conclusion that the preoperative hsCRP value of 20.64mg/L, as per present study results, can be relied upon as predictors of need for conversion. It is equally important for an individual case management also and it may serve as an important predictor of need for conversion, or else, at least it will put a surgeon on a cautious note to be extra vigilant

during surgery to avoid too much of LC manipulations intra-operatively, and take an early decision to go for conversion to OC reducing the time required for surgery and hence, in all probability, also reduce post-operative complications.

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