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Is C-reactive Protein an Independent Risk Factor for Complication of Laparoscopic Cholecystectomy for Acute Cholecystitis

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Abstract: *Background:* Acute cholecystitis (AC) is the most common complication of gall bladder stones. C-reactive protein (CRP) level is only used as a diagnostic criterion of AC. Because there is the lack of studies demonstrating a better discrimination power of CRP measurement on AC, The aim of this study was evaluate the discriminative power of CRP in AC management and treatment outcome. *Patients and methods:* The number of patients in this study was 30 patients presented with AC. After clinical examination, Laboratory and radiological investigations and resuscitation within 1st 24h. of admission, all patients treated by laparoscopic cholecystectomy (LC). *Results:* Out of total participants, 8 patients were males (26.7%) and 22 females (73.3%). There ages ranged from 21 to 66 years with mean ± SD 11.29. Higher levels CRP were found in cases of high grade fever, palpable tender RT. hypochondrial mass and pyocele cases with significant difference was 0.001, 0.001 and 0.005 respectively. Timing of intervention was within 7 days from 1st symptom day ranging 2-7 days with mean 4.37. Total operative time was ranging from 42-180 minutes with mean 109.57. Blood loss ranging from 50-200 cc with mean 95. Total hospital stay ranged from 4-6 days. *Conclusion:* High levels of CRP with male sex, high grade fever preoperatively, presence of palpable tender RT. hypochondrial mass, high total leucocytic count, cases of pyocele and presence of intra-operative adhesion and timing of intervention are risk factors for difficulty, complications, operative and postoperative out come in patients undergoing laparoscopic cholecystectomy for Acute cholecystitis.

Keywords: C-reactive Protein, Risk Factor, Acute Cholecystitis, Complication Laparoscopic Cholecystectomy

1. Introduction

Acute cholecystitis (AC) is the most common complication of gall bladder stones and one of the most frequently seen surgical diseases [1]. The Clinical diagnosis of AC is challenging and may result in misdiagnosis, delay in laparoscopic cholecystectomy (LC), or hospital discharge without operation [2-4]. Failure to perform cholecystectomy for AC at index admission is associated with an increased mortality, higher hospital readmission, and open cholecystectomy rates, and an increased health care costs [5].

To improve the sensitivity of the diagnosis of AC, the Japanese society of Hepato-Biliary Pancreatic Surgery developed 2007 and 2013 Tokyo Guidelines. According to these guidelines, diagnostic criteria for AC include physical examination findings. Laboratory results such as C-reactive protein (CRP) and white blood cell levels, as well as radiological evaluation [6, 7]. CRP level is only used as a diagnostic criterion of AC, and it is not part of determinant criteria of the severity assessment of the disease in the guidelines. On the other hand, Correlation between CRP levels and severity of AC is a well-known fact. Several studies have reported that CRP level is a reliable predictor of severe conditions of inflammation in AC [8, 9, 10].

Because there is the lack of studies demonstrating a better discriminative power of CRP measurement on AC, the aim of this study was evaluate the discriminative power of CRP in AC managements and treatment out comes.

2. Patients and Methods

2.1. Patients

This study was carried out in the gastrointestinal and laparoscopic surgery unit, General Surgery Department, Tanta University Hospitals in the period from April 2014 to January 2016. The number of Patients in this study was 30 Patients presented with AC. All Patients presented with acute cholecystitis were included and those with high CRP that could be due to associated condition e.g. acute pancreatitis were excluded from the study. Demographics, history, physical examination, laboratory, and imaging findings during admission were evaluated.

2.2. Methods

Patients were initially given intravenous fluids, antibiotics and analgesic till resuscitation and control of fever and pain, and then treated by LC after 24 hours, Histopathological examination of gall bladder was performed for all patients.

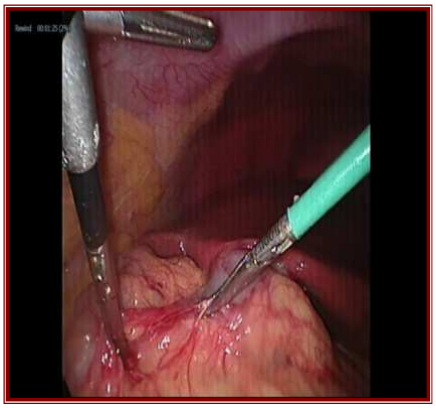

Figure 1. *Adhesion between gall bladder and surrounding structures.*

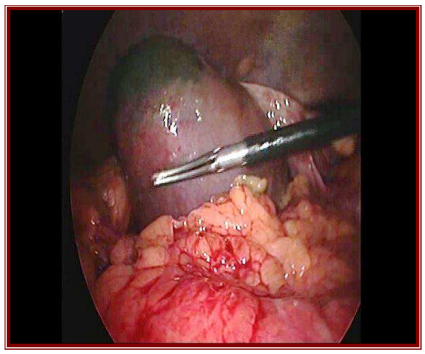

Figure 2. *Taking adhesions down.*

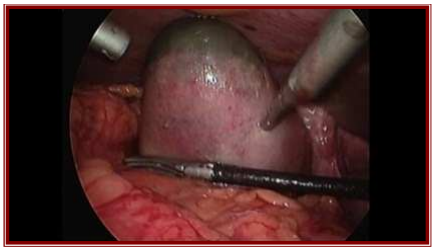

Figure 3. *Stapping a distended gall bladder by verrus needle.*

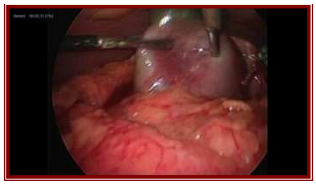

Figure 4. *After evacuation of distended gall bladder.*

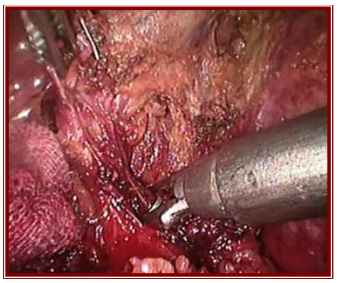

Figure 5. *Applying clip to artery.*

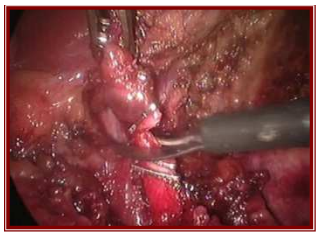

Figure 6. *Cutting cystic duct by scissor between proximal 2 clips and distal one.*

2.3. Statistical Analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS v.20

3. Results

Out of total participants, 8 patients were males (26.7%) and 22 females (73.3%).

Theirr ages ranged from 21 to 65 years with mean ± SD 11.29.

Table 1. *Laboratory investigations.*

Patients (n = 30)			
Parameter		**N**	**%**
TLC	Normal	9	30
	Elevated	21	70
Total bilirubin	Normal	28	93.3
	Elevated	2	6.7
SGOT	Normal	25	83.3
	Elevated	5	16.7
SGPT	Normal	23	76.7
	Elevated	7	23.3
H. pylori	No	17	56.7
	Yes	13	43.3
HCV Ab	No	22	73.3
	Yes	8	26.7
CRP	Range	9-96	
	Mean ± S.D	44.60 ± 35.08	
T.L.C	Range	4200-22700	
	Mean ± S.D	22700.48 ± 4534.06	

High total leucocytic count was found in cases of high grade fever with significant difference 0.001 and presence of palpable tender right hypochondrial mass with significant difference 0.001. "Table 2"

Table 2. *Total leucocytic count correlations.*

TLC		Range			Mean	±	S. D	t. test	p. value
Fever	High	12800	–	22700	15485.71	±	3357.85	29.110	0.001*
	Low	4200	–	12800	9106.25	±	3116.72		
Palpable tender right hypochondrial mass	Yes	12800	–	22700	15492.31	±	3494	22.650	0.001*
	No	4200	–	15400	9476.47	±	3381.85		

Higher levels CRP was found in cases of high grade fever with significant difference 0.001, presence of palpable tender right hypochondrial mass with significant difference 0.001 and pyocele cases with significant difference 0.005. "Table 3"

Table 3. *CRP correlations.*

CRP		Range			Mean	±	S. D	t. test	p. value
Fever	High	9	–	96	70.71	±	32.28	28.179	0.001*
	Low	9	–	48	21.75	±	16.81		
palpable tender right hypo-chondrial mass	Yes	9	–	96	72.46	±	32.91	27.887	0.001*
	No	9	–	48	23.29	±	17.48		
Pyocele	No	9	–	48	38.89	±	32.16	9.173	0.005*
	Yes	9	–	96	96.0	±	0.0		

Both CRP and TLC were noticed to be directly proportion with amount of intra-operative hemorrhage. "Figure 1, 2"

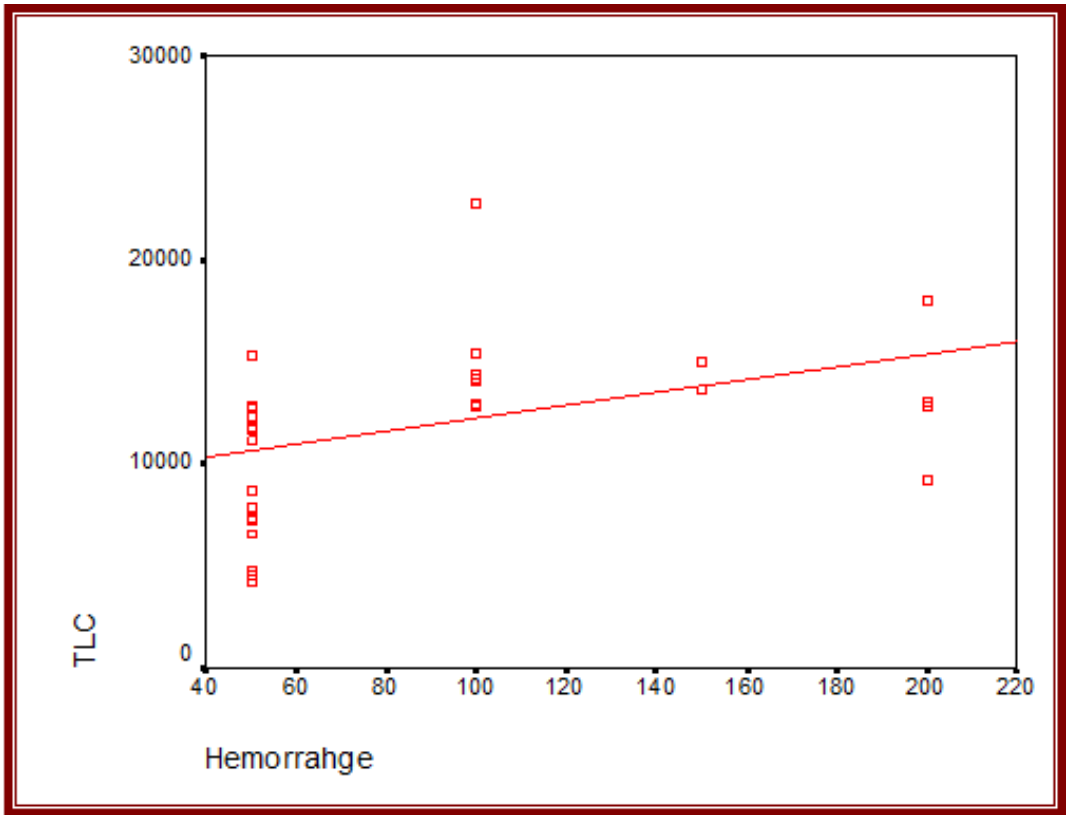

Figure 7. *TLC correlation with hemorrhage.*

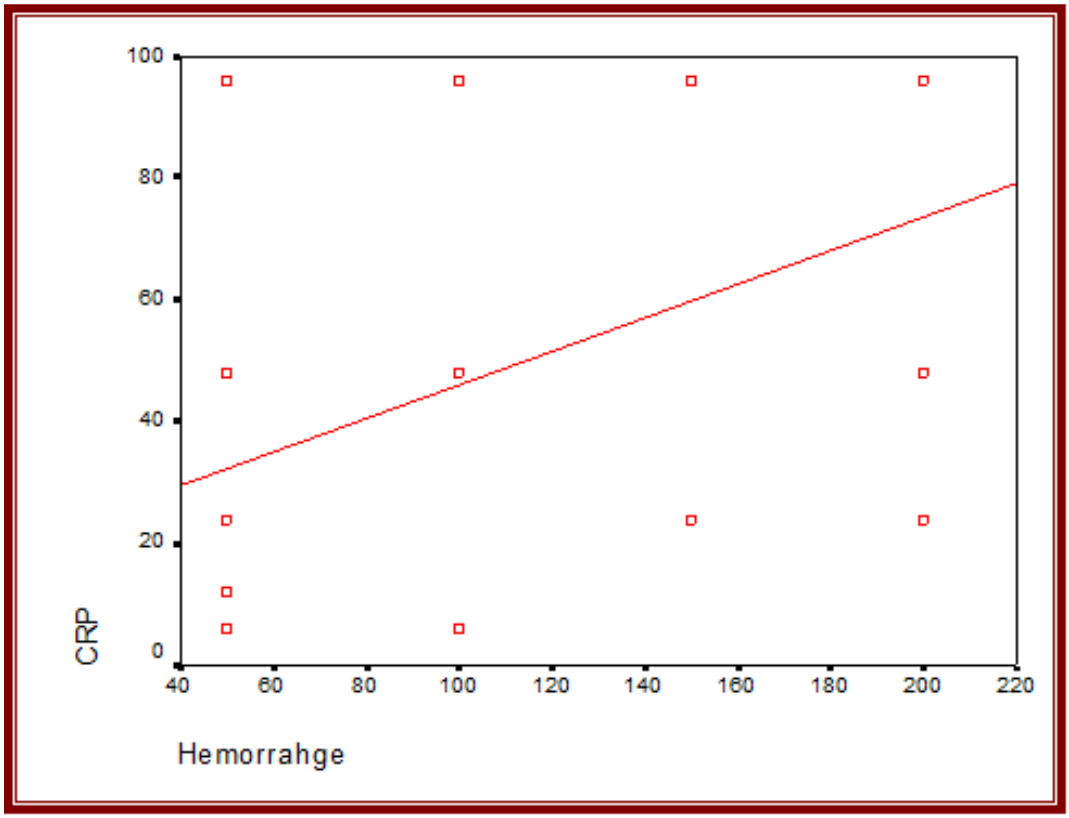

Figure 8. *CRP correlation with hemorrhage.*

Timing of intervention was within 7 days from 1st symptom day and ranging 2-7 days with mean 4.37.

Timing of intervention was directly proportion with hemorrhage and amount of drain post-operative with significant difference 0.006 and 0.035 respectively. "Table 4"

Table 4. *Timing of intervention correlation with hemorrhage and amount of drain.*

		Timing of intervention
Hemorrahge	r	0.492
	P value	0.006*
Drain bag amount	r	0.472
	P value	0.035*

Total operative time was ranging from 42-180 minutes with mean 109.57. Blood loss ranged from 50-200 cc with mean 95.

Long operative time was associated with male sex, high grade fever preoperatively, presence of palpable tender right hypo-chondrial mass, higher total leucocytic count and higher CRP levels with significant difference as follow 0.03, 0.001, 0.001,0.001, 0.002 respectively. "Table1 5"

Table 5. *Operative time correlation with demographic data.*

Operative time		Range			Mean	±	S. D	t. test	p. value
Sex	Male	70	–	170	139.5	±	32.75	5.207	0.03*
	Female	42	–	180	98.68	±	46.32		
Fever	High	78	–	180	139.43	±	29.73	16.835	0.001*
	Low	42	–	160	83.44	±	42.77		
RUQ mass	Yes	78	–	180	141.23	±	30.14	16.372	0.001*
	No	42	–	160	85.35	±	42.16		
TLC	r	0.675							
	P value	0.001*							
CRP	r	0.532							
	P value	0.002*							

Also, Some intra-operative findings has been noted to have longer operative time as cases of pyocele, presence of intraoperative adhesions and more intra-operative hemorrhage, with significant difference 0.029, 0.003 and 0.001 respectively. It was noted that delayed timing of intervention had no significant difference (0.145) on operative time. "Table 6"

Table 6. *Operative time correlations with timing of intervention and intra-operative findings.*

Operative time		Range			Mean	±	S. D	t. test	p. value
Pyocele	No	42	–	180	103.42	±	44.88	5.271	0.029*
	Yes	157	–	170	164.0	±	6.56		
Adhesion	No	42	–	105	65.86	±	20.82	10.879	0.003*
	Yes	42	–	180	122.87	±	43.85		
Hemorrhage	r				0.573				
	P value				0.001*				
Timing of intervention	r				0.273				
	P value				0.145				

Total hospital stay ranged from 4-6 days. It has noted that hospital stay increased with male, pyocele cases and delayed timing of intervention with significant difference of 0.035, 0.016 and 0.011 respectively.

Table 7. *Hospital stay correlations.*

Total hospital stay			4	5	6	X2	P-value
Sex	Male	N	0	5	3	6.684	0.035*
		%	.0%	23.8%	75.0%		
	Female	N	5	16	1		
		%	100.0%	76.2%	25.0%		
Fever	High	N	1	10	3	2.726	0.256
		%	20.0%	47.6%	75.0%		
	Low	N	4	11	1		
		%	80.0%	52.4%	25.0%		
RUQ Mass	Yes	N	1	9	3	2.774	0.254
		%	20.0%	42.9%	75.0%		
	No	N	4	12	1		
		%	80.0%	57.1%	25.0%		
Pyocele	No	N	5	20	2	8.307	0.016*
		%	100.0%	95.2%	50.0%		
	Yes	N	0	1	2		
		%	.0%	4.8%	50.0%		

Table 8. *Hospital stay correlations.*

Total hospital stay		Range			Mean	±	S. D	F. test	p. value
CRP	4	9	–	96	33.60	±	39.02	0.424	0.659
	5	9	–	96	45.14	±	33.01		
	6	9	–	96	55.50	±	47.34		
TLC	4	4800	–	15300	10160.00	±	4147.05	1.068	0.358
	5	4200	–	22700	12066.67	±	4810.96		
	6	11700	–	18000	14575.00	±	2653.77		
Timing of intervention	4	2	–	3	2.60	±	0.55	5.321	0.011*
	5	2	–	7	4.62	±	1.47		
	6	4	–	7	5.25	±	1.50		
Operative time	4	56	–	160	113.40	±	44.07	0.168	0.846
	5	42	–	180	106.52	±	47.44		
	6	70	–	170	120.75	±	54.12		
Hemorrahge	4	50	–	50	50.00	±	0.00	3.180	0.058
	5	50	–	200	97.62	±	55.85		
	6	50	–	200	137.50	±	62.92		

4. Discussion

According to Tokyo Guidelines 2007, 2013, high plasma level of C - reactive protein is one of the diagnostic criteria in acute cholecystitis (AC). In previous studies, regarding the grading of the disease according to Tokyo Guidelines, no cut-off values of CRP have been proposed so far. In a study by Nikfarjam et al., CRP valve >94 was found to be a significant risk factor for Gangrenous gall bladder [8]. Mok et al., reported that CRP of 200 appears to be the best cut off point for predicting for gangrenous gall bladder [10]. Asaiet. al reported a significant correlation between high risk bactobilia and advanced age, high levels of CRP, and the evidence of significant gall bladder infection. In their study, the cut-off value was found to be 134 mg/L for bactobilia [11]. Esin et al, concluded that CRP, a well known acute phase reactant that increases rapidly in various inflammatory processes, can be accepted as a strong predictor in classifying grades of the disease, and treatment can be reliably planned according to this classification [12].

Our study comprised 30 patients their ages ranged from 21 to 65 with mean ± S.D of 42.5 ± 11.29. There was 8 males (26.7%) and 22 female (73.3%). All patients presented with

elevated CRP ranging from 6-96 mg/L with mean 44.6 while 21 patients had elevated TLC with mean 22700. 45. 7(23.37%) and 5 (16.7%) patients should elevated SGPT and SGOT respectively and 2 cases (6.7%) should elevated bilirubin level.

Pre-operative CRP in Shinke and his colleagues' study was slightly high in the late phase group (4-7 days) compared with the early phase group (first 3 days) and WBC count was almost identical between the groups and on performing laparoscopic cholecystectomy in late phase did not influence operative, post operative complications or post operative hospital stay [13]. Timing of intervention in our study was with 7 days from 1st symptom day ranging 2-7 days with mean (4.37). In our study male and pyocele had a delayed time of intervention. Delayed timing of intervention was directly proportion to the intra-operative hemorrhage, amount of drain postoperative and hospital stay, however it had no significant value on operative time.

Teckchondani et al, reported that among patients with varying intra-operative severity of AC, there was significant difference in mean values of duration of Symptoms before surgery [14]. Ohata et al, reported that there was no significant difference between timing intervention and peri-operative outcomes of conversion rate to open surgery, operative time, Blood loss, postoperative morbidity, operative and post operative complications [15].

Operative time in this study was ranging from 42-180 minutes with mean 109.57. Longer operative time was associated with male, high grade fever pre-operatively, presence of palpable tender right hypochondrial mass, higher total leucocytic count, higher, CRP levels, cases of pyocele presence of intra-operative adhesions and more intra-operative blood loss. Ambe and Kohler reported that surgery lasted significantly longer in male patients [16]. While Bansal et al, reported longer duration of surgery is due to time required for removal of inflammatory pericholecystic adhesion, intra-operative gall bladder decompression and longer learning curve [17].

In the present study, there was neither conversion to open surgery nor bile duct injury. Total hospital stay in this study ranged from 4-6 days. It has noted that hospital stay increased with male, cases of pyocele and delayed timing of intervention with significant difference. Ambe and Kohler reported that the length of post operative hospital stay was significant longer in male patients [16]. Alqahtani found no significant difference in hospital stay between early (First 72 hours) and late group (after 72 hours) [18]. Also Farooq et al, reported that there was no significant difference in median post-operative hospital stay between early group and late group [19]. Popkharitov preformed a study of timing of surgery for AC. Three groups were compared, acute (72 hours), intermediate (4-7 days), and delayed (8 days) and no significant differences could be found in postoperative hospital stay between the three groups [20].

Andrei et al, concluded that CRP measurement does not influence management of patients with AC. To improved the quality of care and to minimize health care provider costs, Fit patients with more advanced forms of AC and higher values of CRP should have their operation performed earlier than patients with mild AC and a lower concentration of CRP [21].

5. Conclusion

High levels of CRP with male sex, high grade fever preoperatively, presence of palpable tender RT. Hypochondrial mass, high total leucocytic count, cases of pyocele and presence of intra-operative adhesion and timing of intervention are risk factors for difficulty, complications, operative and postoperative outcome in patients undergoing laparoscopic cholecystectomy for AC. We need to expand the number of patients for detection of cut-off level of CRP for grading of AC.

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