International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 6|Issue 02 (March-April)|2023 Page: 410-416
Original Research Paper

A Study on the Role of C-Reactive Protein in Minimizing Negative Appendectomy in Clinically Diagnosed Cases of Acute Appendicitis.

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Article Received: 02-March-2023, Revised: 22-March-2023, Accepted: 01-April-2023

ABSTRACT:

Background: Acute appendicitis is one of the most common surgical emergencies. Its accurate diagnosis is based on careful history, physical examination, laboratory and imaging investigation. C-Reactive protein (CRP) is an acute phase reactant protein, which rises rapidly in response to tissue injury and inflammation. The aim of the study is to correlate the levels of serum CRP with the histopathology of the removed appendix. The study also emphasises minimizing the rate of negative appendectomy by using CRP in clinically diagnosed acute appendicitis. **Materials and methods**: This is a cross-sectional study, conducted in the Department of Surgery in collaboration with the Department of Biochemistry. The study population consisted of 100 clinically diagnosed acute appendicitis patients aged 13-65 years who were undergoing emergency appendectomy from August 2019 to July 2021. Pre-operative blood was sent for CRP estimation; and all the specimen were sent for histopathological evaluation postoperatively. **Results**: The level of CRP increased in case of acute appendicitis and the elevation was observed to correlate with the severity of the disease as the levels increased significantly in cases of a perforated appendicitis (62.96 ± 31.20 mg/L vs 200.00 ± 26.45 mg/l; p=<0.001). Serum CRP was also positively correlated with Total leucocyte count and appendicular perforation (p<0.01). **Conclusion**: Elevated serum CRP levels support the surgeon's diagnosis and reducing the possibility of possibility of negative appendectomy and, as such, recommended to include in diagnostic workup of acute appendicitis.

Keywords: appendicitis, C-Reactive protein, total leucocyte count

INTRODUCTION:

Acute appendicitis is the most common cause of acute surgical abdomen.[1] The diagnosis is established based on the surgeon's clinical impression depending on present history, physical examination, laboratory tests, and imaging studies if needed.[2] Approximately 7 % of the population will have appendicitis in their lifetime with peak incidence between the age of 10-30 years. In 70 % of cases, the clinical presentation is typically clinical and there is no difficulty in diagnosis. The remaining 30% have atypical clinical presentation and present a diagnostic dilemma, especially in patients at extreme of age, in women of reproductive age and with abnormal position of the appendix and thus have an uncertain preoperative diagnosis leading to unnecessary appendectomy.[3] A normal appendix at appendectomy is a misdiagnosis; on the other hand, a delayed diagnosis of appendicitis might result in perforation and peritonitis. Perforation may occur in up to 35% of cases.[4] Traditionally, a higher incidence of unnecessary appendectomies occur to decrease the incidence of perforation. This approach is being increasingly questioned in today's world of cost-effective health care. Since appendectomy, like any other operation, has socio-economic effects in the form of hospital costs, missed workdays and decreased productivity.[5] The high rate of unfavourable appendicitis explorations burdens both the general surgeon and the patient. A limited number of negative appendectomies is the philosophy behind surgical treatment, which aims to remove an inflamed appendix before perforation. C-Reactive protein (CRP), an annular pentameric protein, is an acute –phase reactant protein, which rises rapidly in response to tissue injury

and inflammation, and can be measured in serum 6-12 hours after the onset of the inflammatory process. Many studies have investigated the role of CRP in improving the diagnosis of acute appendicitis.[6] Despite advances in technology and imaging modalities, there is uneasiness in the diagnosis of acute appendicitis, however, histopathological examination remains the gold standard for the confirmation of appendicitis. CRP because of its easy availability, cost-effectiveness plays a definitive role in the diagnosis of these patients with suspected acute appendicitis and helps in reducing the number of negative laparotomies. In this study, we estimate pre-operative serum C-reactive protein level in patients with clinically diagnosed acute appendicitis and evaluate the importance of CRP in reducing the rate of negative appendectomy by correlating with WBC counts and final histopathological findings.

MATERIAL AND METHODS:

This cross-sectional study was carried out in the Department of General Surgery in collaboration with the Department of Biochemistry. A total of 100 clinically diagnosed acute appendicitis patients aged 13-65 years who were undergoing emergency appendectomy from August 2019 to July 2021 were enrolled. Exclusion criteria were: patients who were immune-compromised and on steroid therapy, interval appendectomies, pregnant women and patients with other co-morbidities or other acute infections. Written informed consent was obtained from all patients before sample collection. The study was approved by the Research Ethics Board, Institutional Ethics Committee (IEC), registered under Research Ethics Board number A/206/REB-Comm (SP)RIMS/2015606/84/2019.

Methods of data collection:

Detailed socio-demographic and clinical characteristics were recorded for each patients including age, gender, residence, patient history, investigations including serum CRP and TLC and histopathology of appendix post operatively. Serum CRP was performed before the operation but was not taken into account for the decision of appendectomy. WBC count was noted in all patients. After an appendectomy, the removed appendix was sent for histopathological examination.

Sample collection and laboratory measurements:

Five ml of venous blood was taken before the operation wand allowed to clot at room temperature. The clot was retracted, and serum separated by centrifugation at 2000 rpm for 10 minutes. Serum C-Reactive protein was determined by quantitative turbidimetric assay method.

Statistical analysis:

All statistical analysis were performed using IBM: SPSS Statistics Version 21. All the categorical variables were described as the number of cases and percentages. To establish an association between the mean of serum CRP level with the socio-demographic profiles as well as past history of illness, statistical tests like t-test (independent sample test) and F-test (ANOVA, analysis of variance ratio) were used. Further Karl Pearson's correlation coefficient "r" and Spearman's rho "p" were adopted to evaluate the correlation between means of serum CRP level with the socio-demographic profiles, past history of illness, and postoperative outcomes. All comparisons are two-sided and the p-value of < 0.05, <0.01, and <0.001 were taken as the cut-off values for significant, highly significant, and very highly significant respectively.

RESULTS:

In this study, there were 100 clinically diagnosed cases of acute appendicitis patients, there were 60% males and 40% females. The sample consisted of 91% rural dwellers as against only 9% urban dwellers (table-I).

As depicted in figure 1, the maximum number of cases were in the age group of 15-24 years followed by 25-34 years.

Figure 2 deals with the distribution of clinically diagnosed cases of acute appendicitis patients concerning their past history of illness. It was observed that 9 % of the patients had a past history of surgery whereas 5% had a past history of diabetes and another 5% had a past history of hypertension; 4% had a past history of Tuberculosis; and the lowest i.e.,3% had a history of appendicitis.

Independent sample t-test was applied for the comparison of means of S.CRP level according to sex, as seen from table-II. It suggests that the mean S.CRP level for males were found be 65.40mg/L which was a little less than that of counterpart female with a mean S.CRP level of 69.58mg/l. however the observed variation was not significant statistically(p-value =0.601).

Since the comparison was made among more than two means of S.CRP level according to age, F-value, commonly known as Analysis of Variance ratio (ANOVA) was applied; as shown in the table-III. It is worth mentioning that there was a significant statistical difference between the age groups of patients and S.CRP level. For instance, the mean S.CRP (54.12mg/L) increases from the age group of 15-24 years to 104.58 mg/L for the age group of 45 years and above. The observed variation was tested and found to be very highly significant (p=0.001).

It was observed from table-IV that the past history of surgery had a certain impact on S.CRP level as those having a past history of surgery have significantly higher mean S.CRP level (93.67mg/l, p=0.031). Similarly, there is a strong impact on the S.CRP level as those having a past history of diabetes had a very highly significant higher mean of S. CRP level than

that of those not having a past history of diabetes (131.20 mg/L vs 63.69mg/L, p=<0.001). On the contrary, past history of hypertension, TB, and appendicitis didn't have any significant association with the S.CRP level (p>0.05). Nonetheless, it was witnessed that those who were having a past history of hypertension, TB, and appendicitis had a higher mean S.CRP level than those who were not having a past history of these illness. It could be observed from the table-V that, appendicular perforation had significant association with S.CRP (p<0.001) as those who had appendicular perforation had a mean S.CRP level of 200.00mg/L as against S.CRP level of 62.96 mg/L for those who had not appendicular perforation. HPE positive had no significant impact on the S.CRP level. However, those having these outcomes had a higher mean than that those who didn't have such outcomes. The findings from table-VI shows that there was a positive or direct correlation of each of the pre and post-operative outcomes with S.CRP levels. However, correlation of TLC and appendicular perforations had very high significance with S.CRP level but no significant correlation was established with vomiting, fever and HPE positive.

DISCUSSION:

Acute appendicitis is the most common abdominal surgical emergency, but its diagnosis remains an enigmatic challenge, plagued by a high rate of negative explorations. There is no single reliable test with satisfactory sensitivity and specificity. Obstruction of the lumen is believed to be the major cause of acute appendicitis. Fecoliths are the usual cause of obstruction. Less-common causes are hypertrophy of lymphoid tissue, tumors and intestinal parasites.[7] The diagnosis of acute appendicitis is essentially clinical; however, a decision to operate based on clinical suspicion alone can lead to the removal of the normal appendix in 15-30% of cases. The premise that it is better to remove a normal appendix than to delay diagnosis does not stand up to scrutiny, particularly in the elderly. Hence, the diagnosis of appendicitis remains a dilemma despite the advances in various laboratory and radiological investigations. A new tool to help in the diagnosis of acute appendicitis would thus be welcomed. The present study established that acute appendicitis is slightly more common in males, with a male: female ratio of 1.5:1 (table-I). Also, young age is a risk factor, as nearly 43% of patients with acute appendicitis were <25 years of age. It was observed that the mean S.CRP level increases significantly as the age advances. This was similar to the study by Addiss DG et al.[8] The appendix during the 'teens is particularly liable to obstruct and hence to become inflamed because of the large proportion of lymphoid tissue which it contains.[9] Also ageing is thought to be related to inflammatory process, defining elevated vulnerability for disease and mortality with aging.[10] In our study patients having a past history of appendicitis, surgery, diabetes, hypertension, and TB had a higher mean S.CRP level than those who were not having a past history of these illnesses. These findings were supported by the study conducted by Lima LM et al[11] who suggested that patients with these illness have a more active inflammatory state. The inflammatory and metabolic factors associated with diabetes, such as high glucose, adipokines, modified lipoproteins and free fatty acids may trigger CRP production by endothelial cells, smooth muscle cells and monocytes/macrophages.[12] Experimental studies have unravelled an active direct participation of CRP in the development of endothelial dysfunction, vascular stiffness and elevated blood pressure. CRP has also been implicated as a mediator of vascular remodelling in response to injury and cardiac remodelling in response to pressure overload.[13]

In the present study, patient with appendicular perforation had significantly higher S.CRP than those without appendicular perforation (200.00mg/L vs 62.96 mg/L, p<0.001). This finding was supported by the result of Yamazaki S et al[14] who found CRP as an independent predictor of perforated appendicitis. In most cases, the risks of missing a case of acute appendicitis and resulting peritonitis or abscess formation outweigh those of complications brought on by a negative appendectomy.[15] Accurately identifying non-perforated acute appendicitis is currently important since new research suggests that acute appendicitis can be successfully controlled without surgery.[16,]

According to the study by Asfar S et al[6], C-Reactive protein is an acute phase reactant which rises rapidly in response to tissue injury and inflammation and can be measured in serum 6-12 hours after the onset of the inflammatory process. However, in this study, even if there was a significant rise in CRP levels of acute appendicitis case, no significant correlation of serum CRP was established with the history of symptoms like vomiting or fever.

In this study, we observed positive and significant correlation between S.CRP and TLC in acute appendicitis however no significant correlation was established with histopathological report. This was in par with the study conducted by David HB [17] and Mujahid AM et al[18] where mild leucocytosis ranging from 10,000 to 18,000 cells/cumm was found in patients with acute, uncomplicated appendicitis and is often accompanied by moderate polymorphonuclear leucocytosis.

Additionally, further studies looking at the choice of the management strategy for acute appendicitis according to laboratory findings are required. Other limitation of our study includes small sample size and single centre based study. The level of CRP increased in case of acute appendicitis and the elevation was observed to correlate with the severity of the disease as the levels increased significantly in cases of a perforated appendix. The level of TLC was elevated in

case of acute appendicitis along with rising levels of serum CRP. In conclusion, we think that although elevated CRP level is a nonspecific inflammatory marker in most of the inflammatory diseases, a high CRP level is helpful in the diagnosis of perforated Acute Appendicitis. Further studies with adequate sample size and extended-time period are needed to confirm this study in the case of patients with clinically diagnosed acute appendicitis preparing for emergency appendectomy.

Acknowledgements: The authors thank the patients for their participation in the study

Funding: Not applicable

Conflict of interest: There is no conflict of interest.

TABLES

Table 1. Socio-demographic profiles of patients

Parameters		No. of cases (100)	Percentage
Sex	Females	40	40
	Males	60	60
Residence	Rural	91	91
	Urban	9	9

Figure 1: Percentage comparison of the number of patients according to age

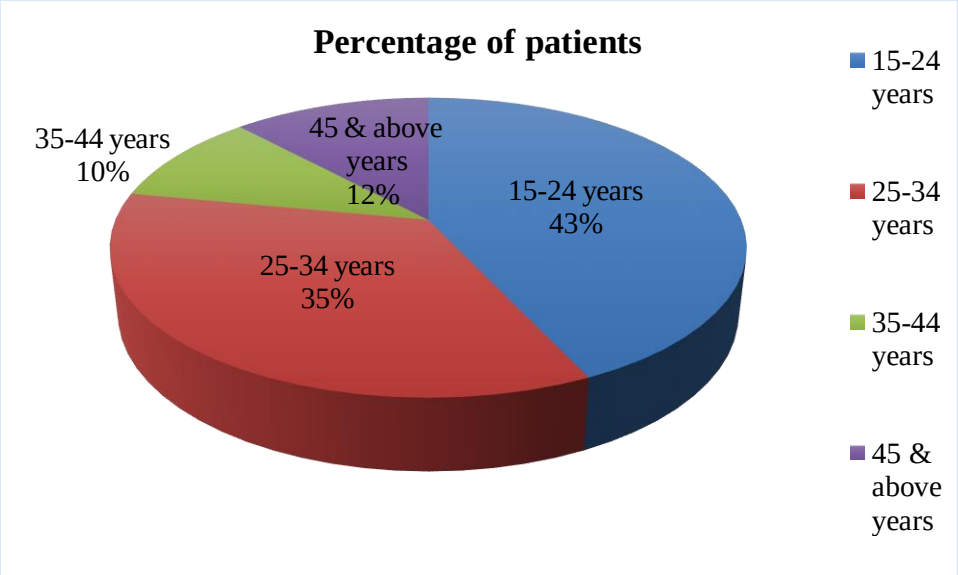

Figure 2: Percentage comparison of the number of patients according to the past history of illness.

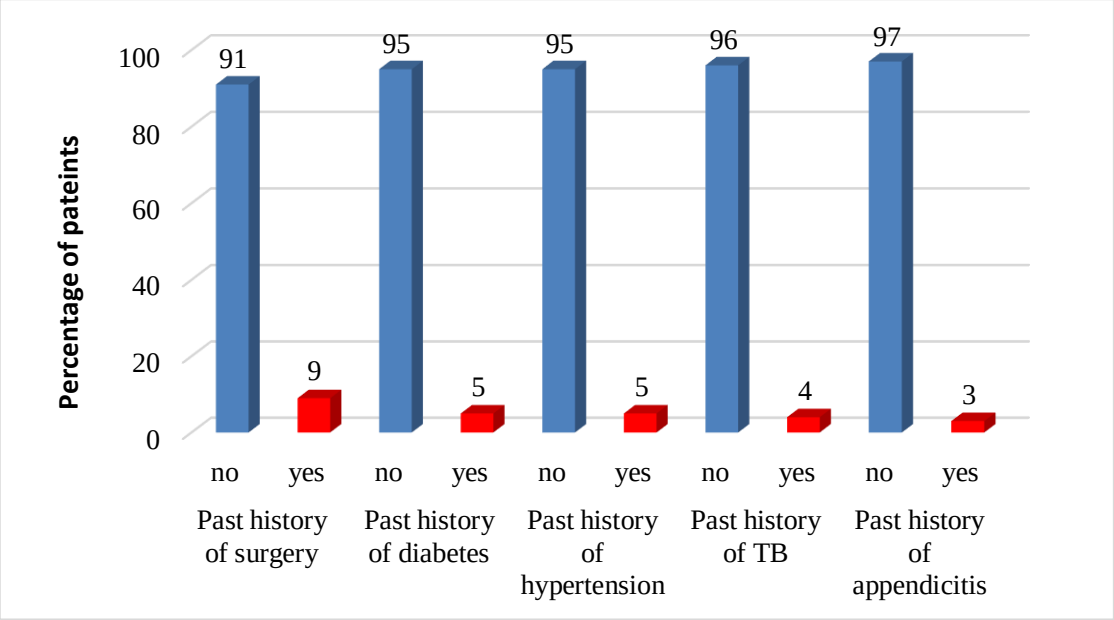

Table. 2: Mean ± SD of CRP level mg/L according to sex.

Parameters		N	Mean±SD (mg/dl)	t-value	df	p-value
Sex	Male	60	65.40±38.93	0.524	98	.601
	Female	40	69.58±39.10			

SD: Standard deviation; t-value: independent sample test; df: degree of freedom; p-value: probability due to chance factor

Table. 3: Mean ± SD of CRP level mg/L according to age.

Parameters		N	Mean±SD (mg/l)	df	F-value	p-value
Age in years	15-24	43	54.12±28.48	3.96	6.277	.001
	25-34	35	68.43±29.20			
	35-44	10	73.00±36.47			
	45 & above	12	104.58±67.38			
	Total	100	67.81±46.10			

Table 4. Mean ± SD of CRP level mg/l according to the past history of illness

Parameters		N	Mean±SD (mg/L)	t-value	df	p-value
Past history of surgery	Yes	9	93.63±57.95	2.193	98	0.031
	No	91	64.44±35.84			
	Total	100	67.07±38.86			
Past history of diabetes	Yes	5	131.20±77.3	4.073	98	<0.001
	No	95	63.69±33.25			
	Total	100	67.07±38.86			

Past history of hypertension	Yes	5	74.20±30.68	.419	98	.676
	No	95	66.69±39.34			
	Total	100	67.07±38.86			
Past history of Tuberculosis	Yes	4	93.75±86.73	1.408	98	.162
	No	96	65.96±36.12			
	Total	100	67.07±38.86			
Past history of appendicitis	Yes	3	73.33±18.14	.282	98	.778
	No	97	66.88±39.36			
	Total	100	65.86±38.86			

Table 5: Mean ± SD of CRP level mg/l according to intra and postoperative outcomes

Parameters		N	Mean ± SD(mg/l)	t-value	df	p-value
Appendicular perforations	Present	3	200.00±26.45	7.514	98	<0.001
	Absent	97	62.96±31.20			
	Total	100	67.07±38.86			
HPE positive	Present	96	67.58±39.41	.645	98	.520
	Absent	4	24.75±20.82			
	Total	100	65.86±38.86			

Table VI: Correlation between S.CRP and pre and post-operative outcomes

Variables	S.CRP (mg/L)	
	Correlation coefficient	p-value
Vomiting	.051	.410
Fever	.184	.083
TLC	.301**	<.001
Appendicular perforation	.296**	<.001
HPE-positive	.056	.540

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How to Cite:
Sandeep Samson, Khuraijam Gojen Singh, Niketa Ashem, & Davina Hijam. (2023). A study on the role of C-Reactive protein in minimizing negative appendectomy in clinically diagnosed cases of acute appendicitis: Study of CRP in minimizing appendectomy. *International Journal of Medical Science in Clinical Research and Review*, *6*(02), Page: 410–416. Retrieved from https://ijmscrr.in/index.php/ijmscrr/article/view/510

http://doi.org/10.5281/zenodo.7796684