

A Prospective Observational Study to Assess the Diagnostic Efficacy of total TLC, CRP and Total Bilirubin in Acute Appendicitis

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Abstract

Aim: To study the diagnostic value of total leucocytes count, C-reactive protein and total bilirubin in acute appendicitis: a prospective study.

Methods: This study was performed on 45 patients who have clinically and radiologically diagnosed of having acute appendicitis. All patients fulfilled all the inclusion criteria like all clinically and radiologically diagnosed cases of acute appendicitis and its complications will be included in present study and Patients with hepatic disorders, a history of alcohol intake with AST/ALT >2, A history of hepatotoxic drug intake, HBsAg positive and or those with a past history of jaundice, concomitant conditions where CRP/leukocyte count/neutrophil count is elevated in acute appendicitis patients with associated diseases like rheumatoid arthritis, SLE, glomerular nephritis and gout were excluded from present study.

Results: The results for comparison of (Mean±SD) of predictive markers like TLC, CRP and total serum bilirubin levels between normal appendix and different type of appendicitis were done by using one way analysis of variance with post hoc analysis according to Tukey-HSD. As compared to those with a normal appendix patients with any appendicitis were older, mostly females and had higher TLC, CRP and total serum bilirubin levels. Patients with perforated appendicitis had higher total bilirubin, TLC and CRP levels as compared to patients with normal and inflamed appendix ($p < 0.001$) or a normal appendix ($p < 0.001$).

Conclusion: A combination of elevated levels of TLC, CRP and serum total bilirubin has high sensitivity and specificity to find out different types of appendicitis.

Keywords: TLC, CRP, Bilirubin, Appendicitis

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Introduction

The diagnosis of appendicitis remains essentially clinical, requiring a mixture of observation, clinical acumen and surgical science. Despite appendicitis being a common disease, its presentation is not always typical and misdiagnosis is therefore not uncommon.[1] Diagnostic difficulties may lead to negative

appendicectomies[2] or cases of missed appendicitis resulting in complications such as appendiceal perforation (AP) or abscess formation.[3]

Diagnostic scoring systems have been developed in an attempt to improve the diagnostic accuracy of acute

appendicitis(AA).[4,5] The most prominent of these scores, developed by Alvarado,5 gives points for symptoms (migration of pain, anorexia, and nausea), physical signs (right lower quadrant tenderness, rebound tenderness, and pyrexia), and laboratory values (leukocytosis and left shift). Although these scores can help guide clinical thinking, they do not markedly improve diagnostic accuracy.[6] Other diagnostic aids including ultra- sound(USG), computed tomography(CT)[7] or even magnetic resonance imaging [MRI]),[8] do exist in order to help confirm the diagnosis or to guide the surgeon's decision on operative management or a period of observation when appendicitis is suspected.[9] However, these diagnostic adjuncts may be ex- pensive, may involve high radiation exposure, and may not always have accurate and reproducible results.[9]

The diagnostic and discriminatory role of white cell count (WCC) and C-reactive protein (CRP) in AA has been studied expansively but still remains contentious.[10–14] Literature points that a rise in serum bilirubin level in patients with clinically suspected appendicitis may be a predictor for perforation of appendix.[15]

It is well established that when microbes invade the body, leukocytes defend it. This leads to increase in the leukocyte count. Bacterial invasion in the appendix leads to transmigration of bacteria and the release of pro-inflammatory cytokines such as TNF-alpha, IL6 and cytokines. These reach the liver via Superior mesenteric vein (SMV) and may produce inflammation, abscess or dysfunction of liver either directly or indirectly by altering the hepatic blood flow.

In view of the above context, the present study was undertaken to determine the diagnostic accuracy of WCC, CRP and bilirubin, either individually or when

combined, in the prediction of appendicitis and, especially, its complications (i.e. perforated appendicitis).

Material and methods

This prospective study was carried out in the Department of General Surgery, Shree Narayan Medical institute and Hospital Saharsa, Bihar, India for 1 year.

Inclusion and exclusion criteria

Clinically and radiologically diagnosed cases of acute appendicitis and its complications were included in present study.

Patients with hepatic disorders, a history of alcohol intake with AST/ALT >2, A history of hepatotoxic drug intake, HBsAg positive and or those with a past history of jaundice, concomitant conditions where CRP/leukocyte count/neutrophil count is elevated in acute appendicitis patients with associated diseases like rheumatoid arthritis, SLE, glomerular nephritis and gout were excluded from present study.

Methodology

This study was performed on 45 patients who have clinically and radiologically diagnosed of having acute appendicitis. The study protocol was approved by institutional ethics committee human Clinical diagnosis of acute appendicitis was done by in the Department of Surgery, based on symptoms of pain, migration, nausea and vomiting, anorexia, fever and signs of peritoneal inflammation like right iliac fossa tenderness, rebound tenderness and guarding. Once acute appendicitis suspected than patient was subjected to routine investigations as per the hospital etiquette. Urine microscopy was done in all cases. Old patients will be subjected to further investigations as part of preanesthetic work up including X-ray chest, ECG etc. CRP, Total leucocyte count and Total bilirubin was done in all cases. TLC count of more than 11,000/cumm was measured positive and total

bilirubin more than >1 mg was measured positive. Ultrasonography of abdomen was done in most of the cases to confirm diagnosis and rule out other causes of pain abdomen. CRP more than 6 mg/dl was measured to be positive. No special preparation of the patient will be required prior to sample collection by approved techniques. Patients with strong suspicion of acute appendicitis will be advised emergency appendicectomy. After obtaining consent, patients were operated, and the appendicectomy specimen will be sent for histopathological examination. The histopathology report was considered as the final diagnosis. The histopathologically positive cases among CRP positive group was measured true positives. The histopathologically negative cases in the same group were considered as false positives. The histopathologically positive case among CRP negative group was considering false negatives. The histopathologically negative cases in the same group were considered as true negatives. Similarly, TLC, Total bilirubin were also classified as true and false positives, and true and false negatives after correlating it with HPE reports. The

biochemical parameters like CRP, direct bilirubin, indirect bilirubin, total bilirubin, alkaline phosphates, and total protein were determined by enzymatic method using commercial available diagnostic kit on fully automated biochemical analyzer. The hematological parameters were estimated by five part hematological analyzer.

Statistical analysis

Data was analyzed using Statistical package for social sciences (SPSS), version 25.0 The level $p < 0.05$ was considered as significance.

Results

The present study was done on 45 patients with mean age \pm SD 25.56 ± 10.27 . Out of 45 patients, 24 (53.3%) were male and 21 (46.6%) are female, thus female high proportion is seen in the present study. Appendicitis is most frequent in the age group of 21-30 years and <20 years of age group in this study. Appendicitis reaches its climax frequency in the teens and before 20 years of age. In advancing age decrease the frequency of appendicitis (Table 1, 2)

Table 1: Age of patients

Age Groups	Numbers of patients	Percentage
10-20	17	37.7%
21-30	19	42.2%
30-31	6	13.3%
40-41	2	4.4%
>50	1	2.2%
Total	45	100%
Mean Age \pm SD	25.56 ± 10.27	

Table 2: Sex of patients

Gender/Sex	Numbers of Patients/cases	Percentage
Male	24	53.3 %
Female	21	46.6%
Total	45	100%

Histopathological examination was done in all 45 patients. Based on histopathology and intra-operative findings the Inflamed

appendix was diagnosed in 32 (71.1%) patients, Gangrenous appendix in 5

(11.1%) patients and Perforated appendix 4 (8.8%) patients while 4 (8.8%) patients did not have any evidence of appendicular perforation or inflammation (normal appendix). All histological findings are shown in Table 3.

Table 3: histopathology of appendix

Histopathology	Numbers of Patients/cases as per gender		Total cases (n=45)	Level of significance As per chi-square test
	Male	Female		
Normal appendix	1	3	4	p>0.05 (NS)
Inflamed appendix	18	14	32	
Gangrenous appendix	3	2	5	
Perforated appendix	2	2	4	
Total	24	21	45	

The results for comparison of (Mean±SD) of predictive markers like TLC, CRP and total serum bilirubin levels between normal appendix and different type of appendicitis were done by using one way analysis of variance with post hoc analysis according to Tukey-HSD. As compared to those with a normal appendix patients with any appendicitis were older, mostly females and had higher TLC, CRP and total serum bilirubin levels. Patients with perforated appendicitis had higher total bilirubin, TLC and CRP levels as compared to patients with normal and inflamed appendix ($p<0.001$) or a normal appendix ($p<0.001$). All significance of level between all different types of appendicitis was shown in table 4.

The subsequently part of the analysis related to choosing cut-off values for calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TLC, CRP and total bilirubin for diagnosis of appendicitis. This was done by doing sensitivity analysis. The value with highest value of sensitivity and specificity was finally chosen as the cut-off. Table 5

shows the sensitivity, specificity, predictive value of positive test and predictive value of negative test of TLC in our study is 60.2%, 89.5%, 96.5% and 24.5% respectively. In our study association of TLC count and acute appendicitis has shown to be significant with P value (0.024). Appendicitis and TLC count has been variously reported as either being reliable or unreliable, and hence where TLC count is in variance with clinical features the latter should take precedence. TLC count is statistically significant ($p<0.05$) in diagnosis of acute appendicitis in our study, serum CRP estimation in diagnosis of acute appendicitis acquires sensitivity of 74%, specificity of 52%, positive predictive value of 94%, predictive value of negative test 15%. Therefore, serum CRP levels are statistically significant ($p<0.05$) in diagnosis of acute appendicitis. The sensitivity, specificity, positive predictive value, negative predictive value was 65%, 70%, 93% and 16% respectively for predictive marker of serum total bilirubin. Total serum bilirubin level is statistically significant ($p<0.001$) in diagnosis of acute appendicitis. (Table 5).

Table 4: Predictive markers in normal appendix and different types of appendicitis

Predictive Markers (Mean ±SD)	Normal Appendix (n=4)	Inflamed Appendicitis (n=32)	Gangrenous Appendicitis (n=5)	Perforated Appendicitis (n=4)	p value (ANOVA) post hoc analysis according to Tukey-HSD
Age (Years)	20.31±4.17	25.18±7.27	26.68±7.47	29.28 ±8.39	<0.001* ,<0.001# ,<0.007\$
TLC	6.98±2.23	12.27±4.18	14.47±3.29	15.27 ± 3.50	<0.001* ,<0.001\$
CRP	5.87± 0.47	11.38±4.17	13.58±4.82	15.87±6.10	<0.001* ,<0.001# ,<0.001\$
Bilirubin	2.12±0.45	2.68±0.60	3.91±0.37	4.58± 0.58	<0.725* ,<0.001# ,<0.001\$

*: Normal Appendix versus Inflamed Appendicitis, **: Normal Appendix versus Perforated Appendicitis, ***: Inflamed Appendicitis versus Perforated Appendicitis

Table 5: Predictive markers in diagnosis of acute appendicitis and association with histopathology

Predictive markers	Status of predictive markers	Histopathological Status (HPE)		values	(%)	p-value
		Positive	Negative			
Total leucocytes count	Positive	25	1	SEN	61.2%	0.024 (Sig.)
				SPE	90.5%	
	Negative	15	4	PPV	97.5%	
				NPV	25.5%	
C-Reactive Protein	Positive	28	2	SEN	75%	0.001 (Sig.)
				SPE	53%	
	Negative	13	2	PPV	95%	
				NPV	16%	
Serum Total Bilirubin	Positive	26	2	SEN	66%	p=0.001 (Sig.)
				SPE	71%	
	Negative	14	3	PPV	94%	
				NPV	17%	

* SEN; Sensitivity, SPE; Specificity, PPV; Positive Predictive Value, NPV; Negative Predictive Value

Discussion

In our study, female high proportion is seen in the present study. Appendicitis is most frequent in the age group of 21-30

years and <20 years of age group in this study. Appendicitis reaches its climax frequency in the teens and before 20 years of age. Based on histopathology and intra-operative findings Inflamed appendix was diagnosed in 32 (71.1%) patients, Gangrenous appendix in 5 (11.1%) patients and Perforated appendix 4 (8.8%) patients while 4 (8.8%) patients did not have any evidence of appendicular perforation or inflammation (normal appendix). This finding supported in study by Goonroos et al, in their study 62% female and 38% male patients had negative appendectomies.[16] The diagnostic accuracy of acute appendicitis in women of child bearing age group was low because of thus numerous circumstances mimicking appendicitis. Among the 80 patients reported positive on HPE examination, 70 cases were reported to have inflamed appendix, rest 18 cases were reported to have complication of acute appendicitis.

In our study, As compared to those with a normal appendix patients with any appendicitis were older, mostly females and had higher TLC, CRP and total serum bilirubin levels. Patients with perforated appendicitis had higher total bilirubin, TLC and CRP levels as compared

to patients with normal and inflamed appendix ($p < 0.001$) or a normal appendix ($p < 0.001$). This observation is supported by Patel et al, who found that the mean bilirubin levels in patients diagnosed with complicated appendicitis were higher as compared to that in patients with acute uncomplicated appendicitis.[17] This is in contrast to the findings of Sengupta A et al, who have suggested that normal TLC with normal CRP levels decrease the possibility of AA and that the patient can be discharged without more reviews.[18] Riazi et al, reports that the possibility of negative appendectomy in patients with both positive tests has been less than 10.0%.[19] In our case series, the

sensitivity, specificity, predictive value of positive test and predictive value of negative, test of TLC in our study is 61.2%, 90.5%, 97.5% and 25.5% respectively. In our study association of TLC count and acute appendicitis has shown to be significant with P value (0.024). Our results are in accordance with other studies done by previous authors.[20-22] According to study done by Goonroos et al, WBC was the test of choice in diagnosing uncomplicated acute appendicitis; however it's a poor predictor of protracted inflammation.[23] The WBC count when done individually distinguishes normal appendix from uncomplicated acute appendicitis whereas does not differentiate uncomplicated from complicated appendicitis. Coleman et al, reported that WBC is a poor predictor of severity of disease.[24] In our study, serum CRP estimation in diagnosis of acute appendicitis acquiesce sensitivity of 75%, specificity of 53%, positive predictive value of 95%, predictive value of negative test 16%. Therefore, Serum CRP levels are statistically significant ($p < 0.05$) in diagnosis of acute appendicitis. The sensitivity and specificity in our study are considered by other studies.[25,22,23] Study done by Oosterhuis et al, showed that serial CRP measurement can improve the accuracy of diagnosing acute appendicitis.[26] Gurleyiket al in their study found that mean CRP level was 33.8 mg/l in patients with non-perforated appendix (range, 5-85.1) mg/l and 128.5 (range, 79.2-230) mg/l in patients with perforated appendix these differences were highly significant.[27] Similarly in our study 88.8% of complicated appendix had very high value of CRP. In the present study, the sensitivity, specificity, positive predictive value, negative predictive value was 66%, 71%, 94% and 17% respectively for predictive marker of serum total bilirubin.[28] Total serum bilirubin level is statistically significant ($p < 0.001$) in

diagnosis of acute appendicitis. Similarly study done by Sander et al, in his study found the mean bilirubin levels in patients with Appendicle perforation to be significantly higher than those with a non-perforated appendicitis.

Conclusion

The outcomes of this study showed that in addition to history and physical examination, some basic laboratory findings like TLC, CPR and Bilirubin may be helpful in the diagnosis and decision making of patients with suspected appendicitis. A combination of elevated levels of TLC, CRP and serum total bilirubin has high sensitivity and specificity to find out different types of appendicitis.

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