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Original Research Article

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

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ABSTRACT

Background: The diagnostic like history, clinical examination and prejudiced role of white cell count and C-reactive protein (CRP) in acute appendicitis has been studied widely but still remains controversial. Therefore, the purpose of this study was to evaluate the diagnostic value of CRP, Total leucocytes count, bilirubin levels individually in cases of acute appendicitis and its complications.
Methods: This randomized prospective study was conducted in department of Surgery and our surgical hospital, Palanpur Gujarat. Total included 50 cases of clinically and radiologically diagnosed of acute appendicitis. The diagnostic value of these markers was predicted for the all groups in terms of sensitivity, specificity, PPVs and NPVs using sensitivity analysis and the diagnostic accuracy assessed.
Results: Acute appendicitis is the most common in female predominance with age group of 20-29 years and <20 years. The Inflamed appendix was diagnosed in 35 (70%) patients, Gangrenous appendix in 5 (10%) patients and Perforated appendix 4 (8%) patients. 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 ($p<0.001$). The CRP has highest sensitivity and specificity (74%, 52%) followed by bilirubin (65%, 70%), WBC count (60.2%, 89.5%).
Conclusions: TLC, CPR and bilirubin can be helpful in the diagnosis and decision-making of patients with suspected acute appendicitis.

Keywords: Appendicitis, Bilirubin, C-reactive protein, Nor-mal appendix, Perforated appendicitis, Total leucocytes count

INTRODUCTION

Acute appendicitis is the commonest source of "acute abdomen". Appendectomy is the most commonly performed emergency operation.[1] its diagnosis is established by surgeon's clinical impression depending on Presenting history, clinical evaluation and laboratory tests. Acute appendicitis with mutable expressions may suggest approximately any other acute abdominal circumstances and in revolve may be impersonated by a assortment of conditions.[2,3] The Incidence of acute appendicitis is about 8.6% in men and 6.7% women.[4] Acute unfussy appendicitis can be thorny to discriminate clinically from perforated appendicitis, especially in the elderly and in children.[5,6] The mortality associated with simple acute appendicitis is reported to be 0.3%, but raised to 6% in cases with perforation.[7] About 30–50% cases of Acute Appendicitis are known to have gangrene or perforation at the time of surgery. Only about 35-45% of patients present in a typical way. So accurate diagnosis and evaluation of severity in most of cases are problematic for surgeon.[8] It is estimated that the

accurateness of clinical diagnosis of acute appendicitis is insincere between 76% to 92%.[9] The rate of normal appendices without need removed remains high (15%-30%) despite a number of techniques. On one hand, a normal appendix at appendicectomy stand for a misdiagnosis; on the other hand, a late diagnosis of appendicitis may lead to augmented death and morbidity. Uniformly distressing is the actuality that perforation may take place in up to 35% of cases thus usually, surgeons have accepted a elevated incidence of needless Appendicectomies in order to diminish the incidence of perforation.[9,10] This approach is being gradually more questioned in today's epoch of proof based medicine. The elevated speed of negative explorations for appendicitis is a trouble faced not only by the general surgeon, but also the patient and the society as entire, since appendicectomy, like any other surgical operation, results in socio-economic impacts in the form of hospital operating expense, lost working days, and declined productivity.[11] The aim of surgical treatment is removal of an inflamed appendix before perforation with a minimum number of negative Appendicectomies. Most of the cases of acute appendicitis are diagnosed by Alvarado score 7 and above. Diagnosis of gangrenous and perforated appendix is challenging. CT scan abdomen can be helpful but it is cost effective and time consuming. Raised TLC, raised level of C - reactive protein and hyperbillirubinemia can be helpful in making diagnosis of gangrenous or perforated appendicitis.[12] C-reactive protein (CRP), an acute phase protein, is raised in tissue injury and inflammation and high levels are seen in AA and in gangreneous and perforated appendix, with reported sensitivity as high as 100%.[13] Severe sepsis results in damage to the hepatocytes and raised serum bilirubin level.14 Several studies have found bilirubin to be a useful serological marker for predicting an acute appendicitis.[14]

Though various imaging modalities like computed tomography (CT) scan, magnetic resonance imaging (MRI) and ultrasonography may help in early diagnosis of perforated appendix, they may not be readily available in many health centers of the third world and developing countries.[13] In such condition clinical and laboratory investigations may be the only, cheaper and readily available options for diagnosis. In view of the above context, this present study is an effort to establish the role of hyperbilirubinemia, total leucocytes count and CRP as predictive markers for complicated appendicitis with perforation, abscess formation or gangrenous transform.

METHODS

The proposed prospective study was carried out in the department of General surgery, General Hospitals Palanpur associated with Banas Medical College and Research Institute, Palanpur and our Surgical Hospital Palanpur Gujarat, India for the period of two years from November 2019 to November 2021. This study was performed on 50 patients who have clinically and radiologically diagnosed of having acute appendicitis and who were depurated for emergency appendicectomy in General Surgery Department and our surgical Hospital Palanpur. The written informed consent was obtained from each patients or patients relative. The present study was done on 50 cases satisfying inclusion and exclusion criteria. 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.

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.

Statistical analysis

Data was analyzed using Statistical package for social sciences (SPSS), version 20 (SPSS Inc., Chicago, IL). Results for continuous variables are presented as mean±standard deviation, and analysis of variance (ANOVA) with post hoc analysis according to Tukey (HSD) was used to compare mean data among different types of appendicitis. Chi-square test and Fischer's exact chi square test were used for the comparison of categorical variables and presented as percentage. The level $p<0.05$ was considered as significance.

RESULTS

The present study was done on 50 patients with mean age±SD 24.54±9.25 at our surgical hospital, Gujarat, India who has been clinically, radiologically and histopathologically diagnosed of acute appendicitis. Out of 50 patients, 24 (48%) were male and 26 (52%) 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 wise distribution of patients.

Age Groups	Numbers of patients	Percentage
10-20	18	36%
21-30	20	40%
30-31	7	14%
40-41	3	6%
>50	2	4%
Total	50	100%
Mean Age ± SD	24.54±9.25	

Table 2: Sex wise distribution of patients.

Gender/Sex	Numbers of Patients/cases	Percentage
Male	24	48 %
Female	26	52%
Total	50	100%

Histopathological examination was done in all 50 patients. Based on histopathology and intra-operative findings the Inflamed appendix was diagnosed in 35 (70%) patients, Gangrenous appendix in 5 (10%) patients and Perforated appendix 4 (8%) patients while 6 (12%) patients did not have any evidence of appendicular perforation or inflammation (normal appendix). All histological finding are shown in Table 3.

Table 3: Distribution of patients according to histopathology of appendix.

Histopathology	Numbers of Patients/cases as per gender		Total cases (n=50)	Level of significance As per chi-square test
	Male	Female		
Normal appendix	2	4	6	p>0.05 (p=0.547) Not Significant
Inflamed appendix	19	16	35	
Gangrenous appendix	3	2	5	
Perforated appendix	2	2	4	
Total	26	24	50	

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 appen¬dicitis 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 acquiesce

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=6)	Inflamed Appendicitis (n=35)	Gangrenous Appendicitis (n=5)	Perforated Appendicitis (n=4)	p value (ANOVA) post hoc analysis according to Tukey-HSD
Age (Years)	19.29± 3.15	24.16±6.25	25.66±6.45	28.26 ±7.37	<0.001* ,<0.001$^{\#}$,<0.007$^{\$}$
TLC	5.96±1.21	11.25±3.16	13.45±2.27	14.25 ± 2.48	<0.001*, <0.001$^{\#}$,<0.001$^{\$}$
CRP	4.85± 0.45	10.36±3.15	12.56±3.80	14.85±5.08	<0.001*, <0.001$^{\#}$, <0.001$^{\$}$
Bilirubin	1.10±0.43	1.66±0.58	2.89±0.35	3.56± 0.56	<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	(%)	Level of significance (Chi-square test- fisher exact test)
		Positive	Negative			
Total leucocytes count (TLC)	Positive	27	1	SEN	60.2%	p<0.05(p=0.024) TLC count is significant in diagnosis of acute appendicitis
				SPE	89.5%	
	Negative	17	5	PPV	96.5%	
				NPV	24.5%	
C-Reactive Protein (CRP)	Positive	31	3	SEN	74%	p<0.05(p=0.020) Serum C-RP level is significant in diagnosis of acute appendicitis
				SPE	52%	
	Negative	13	3	PPV	94%	
				NPV	15%	
Serum Total Bilirubin	Positive	28	1	SEN	65%	p<0.05(p=0.001) Total serum Bilirubin level is significant in diagnosis of acute appendicitis
				SPE	70%	
	Negative	18	3	PPV	93%	
				NPV	16%	

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

DISCUSSION

Acute Appendicitis, an inflammation of the vestigial vermiform appendix, is one of the most frequent reasons for acute abdomen and for evolving surgery. A group of history, physical signs, radiographic investigation, and laboratory analysis is used to diagnose an acute appendicitis. The most vital step in the supervision of patients with alleged appendicitis is attainment the judgment about operative intervention and its timing so that both negative appendicectomies and complicated appendicitis rates are kept to a minimum.[15]

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 35 (70%) patients, Gangrenous appendix in 5 (10%) patients and Perforated appendix 4 (8%) patients while 6 (12%) 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 appendicectomies.[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 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). Our results are in accordance with other studies done by previous authors.[10,14,15] 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.[16] 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.[20]

In our study, serum CRP estimation in diagnosis of acute appendicitis acquiesce 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 and specificity in our study are considered by other studies.[7,15,16] Study done by Oosterhuis et al, showed that serial CRP measurement can improve the accuracy of diagnosing acute appendicitis.[21] 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.[22] 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 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. 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.[23] Khan et al, in his study said that elevated total serum bilirubin good indicator of acute appendicitis.[24]

Limitations of study

In our study, TLC and CRP are non-specific inflammatory mediators. A pre-disease TLC and CRP position of patients in our study was not known, which otherwise would have helped in making enhanced decision regarding increased reason for increased levels of these mediators. Additionally, levels of direct and indirect bilirubin were not separately measured. Such information would have helped in a more specific analysis.

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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