ORIGINAL ARTICLE

The Value of Raised Total Leukocyte Count, C-Reactive Protein and Serum Total Bilirubin in Assessing the Clinicopathological Severity of Acute Appendicitis

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ABSTRACT

Background: The outcome of acute appendicitis mainly depends upon its severity. While simple appendicitis is usually associated with quick convalescence, complicated appendicitis (with gangrene or perforation) can cause significant morbidity. Means to identify markers which can reliably predict the severity of acute appendicitis have been sought exhaustively.
Aim: We wanted to determine the accuracy with which these three serological markers can predict the clinico-pathological severity of Acute Appendicitis.
Methods: Preoperatively collected data of 100 cases of acute appendicitis (AA), proven histologically and operatively was assessed. The mean serological values of TLC, CRP and STB in cases of simple appendicitis SA, were compared with the mean value of these markers in cases of complicated appendicitis CA to establish the sensitivity, specificity, Positive predictive value and Negative predictive value of each for predicting complicated appendicitis.
Results: Of 100 cases studied, 26 were identified as complicated appendicitis (26%). Mean age was 25.34 and 29.12 respectively. Male to female ratio was slightly higher in CA, 1.8 vs 1.4. The mean TLC was significantly higher in CA vs SA (11.78+-2.19 vs 14.22+-3.23 (p=0.01) with sensitivity to identify CA 80.7%, a specificity of 35.1% PPV 30% and NPV of 84%. CRP levels were also significantly higher in CA (7.027+-2.6 vs 25.36+-7.11 <0.001) with sensitivity 88.5%, specificity 57%, PPV 42% NPV 93.3% for predicting CA.
Conclusion: We found that the values of TLC, CRP and STB are all significantly higher in cases of gangrenous and perforated appendicitis. While TLC and CRP are highly sensitive for identifying the presence of gangrene and perforation, STB has the highest specificity and, therefore, raised STB can more reliably predict the severity of Acute appendicitis.
Keywords: Total Leukocyte count, C-Reactive Protein, Serum Total Bilirubin, Clinico-pathological Severity,

INTRODUCTION

Acute appendicitis remains the commonest cause of acute surgical abdomen and the most frequently performed emergency abdominal operation. About 8.6% men and 6.7% women will have appendicitis during their lifetime[1]. The incidence in the UK is about 52 per 100,000 population. It is most prevalent among the young adults (10–30 year) but no age is immune. At extremes of age the complication rate tends to be higher, 50% in younger than 10 and older than 50, with reported perforation rate as high as 62.5% in children below weight[2,3,4]. Simple, uncomplicated appendicitis is cured effectively with appendectomy without a long recovery period. Gangrenous and perforated appendicitis, with abscess formation and varying degree of peritonitis, have been widely accepted as features of complicated appendicitis CA. In comparison to SA, CA can lead to significant postoperative morbidity and prolonged convalescence. As many as 30–50% cases of AA are known to have gangrene or perforation, necessitating prompt surgical intervention in the form of laparoscopic or open appendicectomy. Means to diagnose and investigate the severity are therefore warranted.

Acute Appendicitis is believed to be a clinical diagnosis. The clinical signs and symptoms are often enough to hint the diagnosis. A typical presentation involves vague peri-umbilical pain for several hours, later on shifting to the right iliac fossa (RIF), usually associated with anorexia and nausea. At best, only about 35–45% of patients present in a typical way and accurate diagnosis and evaluation of severity can prove elusive[4]. Surgeons frequently rely upon serological and radiological investigations to strengthen their diagnosis. Ultrasonography and Computed tomography (CT) have proved invaluable in confirming the diagnosis of acute appendicitis with sensitivity and specificity as high as 98% for CT and 71.2–83.3% for ultrasound. For establishing the presence of gangrene and perforation, the role of CT scan cannot be challenged[5]. These imaging techniques have been pivotal in reducing the number of unnecessary explorations in centres where they are routinely utilized. However, radiological

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evaluation can be costly as well as time-consuming and their routine use is not feasible everywhere. The radiation associated with the CT scan is another concern. Much interest exists, therefore, in finding simpler ways to diagnose AA and estimate its severity.
Several studies have elucidated usefulness of laboratory parameters for diagnosing appendicitis[6,7,8]. AA is an inflammatory condition caused by bacterial infection in the appendix. As a result of this inflammatory process the total leucocyte count TLC rises. Raised TLC has long been considered a fundamental element in diagnosing acute appendicitis. The reported overall sensitivity of TLC is about 65–85% and the specificity is about 32–82% Q.A Ahmed et al found Positive predictive value of TLC to be 93% and Negative predictive value 50% for diagnosing complicated appendicitis[8].

Another frequently used parameter is CRP. C-reactive protein (CRP) is an acute phase protein which increases in response to tissue injury and inflammation.[9] It is frequently found elevated in AA and high levels are particularly associated with gangrene and perforation, with reported sensitivity as high as 100%. Serum bilirubin levels have recently gained popularity as part of the work up for AA. Hyper-bilirubinemia[10] has often been noted not only in appendicitis but also in other infective conditions of the abdomen, suggesting a certain relationship could exist between bacteria and serum bilirubin.[11,13–16] Overwhelming sepsis due to intra-abdominal infections may result in dysfunction or damage to the hepatocytes.[17] This is reflected by raised serum bilirubin level. M. Jamaluddin *et al* found that elevated STB along with clinical signs and symptoms predicts complicated appendicitis with high accuracy[18].

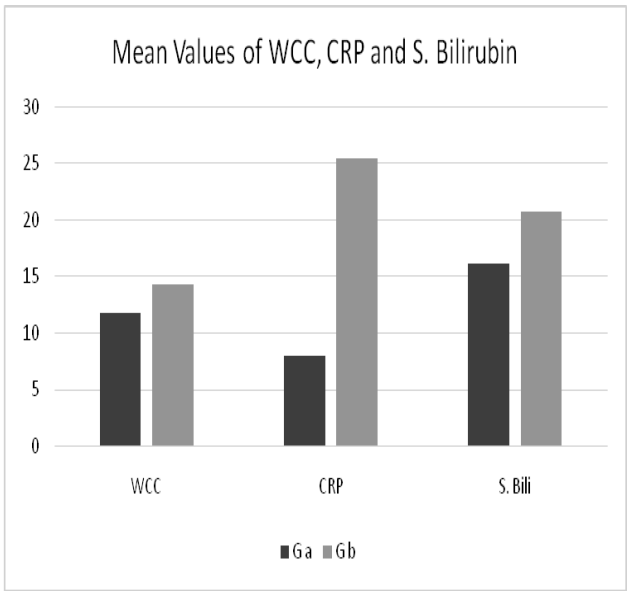
We set out to see if there is a significant difference in the levels of TLC, CRP, Serum Total Bilirubin in case of Simple appendicitis and complicated appendicitis and to find the irrespective accuracy in identifying the presence of complicated appendicitis.

MATERIAL AND METHODS

Data was prospectively collected for patients admitted with clinical suspicion of acute appendicitis having right iliac fossa pain for less than seven days and tenderness in RIF. Based on non-probability convenient sampling, 100 operated cases of Acute Appendicitis, later proven histologically, between July 2014 and December 2014 were assessed.[19] Children below 10 years were not included in the study for ease of statistical analysis. Those found to have normal histology were dropped from the study. Pre-operative TLC, CRP and Serum Bilirubin (SB) levels were recorded. Normal value of TLC CRP and STB was taken as 11,000/µL, 6 mg/ml and 17 µmol/L. All patients underwent open appendectomy through right iliac fosse incision. The operative findings were categorised as Simple Appendicitis or Complicated Appendicitis based on the presence of gangrene, perforation, abscess or peritonitis. Serological values for these selected variables were compared for both simple and complicated appendicitis to see if there was a significant difference between the two groups.

RESULTS

Patients aged 12 to 71 years were included in the study. Mean age was 27.23. On the basis of operative findings, patients were divided into two groups. Group A comprised of patients with features of simple appendicitis and Group B comprised of patients having features of complicated appendicitis. 74 patients out of 100 had SA, and 26 patients had CA. In SA, male to female ratio M:F was 1.4:1, whereas in CA it was 1.8:1. Mean Total Leukocyte count in Group A (11.78+-2.19) was significantly less than that in CA 14.22+-3.23 p value 0.011 .Based on these figures, the sensitivity of raised TLC for identifying complicated appendicitis was 80.7% , specificity 35.2% ,positive predictive value PPV of 30% and negative predictive value NPV of 84%. Levels of CRP were found to be 7.027+_2.6 for SA versus 25.36+-7.11 for CA, (p<0.001). The sensitivity of CRP was quite high at 88.5% and specificity 57%, whereas PPV was 42% and negative predictive value was 93.3%. The level of serum total bilirubin was 16.11+-1.91 in Group A with SA and 20.69+-6.6 in Group B with CA. With levels up to 17 µmol/L as normal, the difference between the two groups was significant <0.001. The sensitivity of STB was 61.5% specificity 86% PPV 86.5% and NPV 80%.



Ga: Simple Appendicitis, Gb: Complicated Appendicitis

Table-1:

	SA (Mean±SD)	CA (Mean±SD)	P-Value
Age	25.34	29.12	NS
M:F	44:30	17:9	
WCC	11.78±2.19	14.22±3.23	0.011
CRP	7.027±2.6	25.36±7.11	<0.001
S. Total Bilirubin	16.11±1.91	20.69±6.6	<0.001

Table-2:

	Sensitivity	Specificity	PPV	NPV
WCC	80.7	35.1	30	84
CRP	88.5	57	42	93.3
S. Total Bilirubin	61.5	86.5	61.54	80

DISCUSSION

The outcome of appendicitis is closely related to the clinic-pathological severity[20]. G.C Grast et al found that morbidity in the form of long hospital stay, protracted use of parenteral antibiotics, surgical site infection, intra-abdominal collections as well as postdischarge SBO increases consistently with the extent of appendicitis[20]. There is also a significant mortality of 1–2% associated with complicated appendicitis especially in the developing countries[20]. Therefore, the importance of early diagnosis and prompt surgical intervention in cases with established severity cannot be emphasized enough. Also, recently, conservative treatment of acute appendicitis with antibiotics has shown promising results. The routine use of interval appendectomy after conservative treatment has also been challenged by many studies which indicate that in the absence of recurrent symptoms in the following 3–6 months, appendectomy may be avoided altogether[21]. However, many clinicians tend to treat only the cases of simple appendicitis conservatively, while most still place their faith in surgery as treatment of choice for cases with suspicion of gangrene and perforation. Preoperative reliable assessment of severity can be of great value in the decision making.

Appendicitis is relatively more common in males. According to the results of our study, a male preponderance was found, with male to female ratio in SA and CA 1.4:1 and 1.8:1 respectively, which matches various other studies. The rate of perforation and gangrene was 26% which is comparable to 32–34% in some studies. A much higher rate of complicated appendicitis is reported in patients more than 40 years old.[22] In our study, 16% of SA were older than 40, while 27% were older than 40 in CA. Late presentation to the hospital is a frequent cause of complication in Appendicitis. We found that the duration of symptoms at presentation was significantly higher in cases of gangrenous and perforated appendicitis (p<0.001).

Of the diverse panel of serological markers, we chose three common markers to assess their efficacy in diagnosing the severity of appendicitis. Total leukocyte count has been considered instrumental in the diagnosis of AA for ages. It has been a steady component of most clinical scoring systems devised for AA including Alvarado ,AIR, and RIPASA scores[23].Although commonly elevated in AA , raised TLC is not specific for AA and is elevated in most abdominal pathologies of inflammatory and infective origin. In a large scale study, W. Farooqi studied the role of various serological markers in assessing the severity of appendicitis. They found a sensitivity, specificity ,positive predictive value and negative predictive value of TLC for diagnosing perforation among cases of acute appendicitis to be 34%, 77%, 35% and 76%respectively[23]. They found that TLC was significantly higher in perforated vs non perforated appendicitis, 13.2 vs 13.85 p value <0.001. The results of our study are quite similar to theirs, with TLC raised in both simple and complicated appendicitis, but significantly higher in the latter group (11.78 vs 14.22). However, although the sensitivity of TLC for identifying CA was found comparatively higher 80.7%, the specificity was 35% which is considerably low. The PPV and NPV, however, were comparable 30% vs 35% and 84% vs 76%. There are a few studies which failed to demonstrate a relation of raised TLC with clinical severity of appendicitis[23]. Although sensitive for presence of complication, we found that Raised TLC is not highly accurate.

The second parameter we studied was CRP. It is an acute phase reactant. Its diagnostic value is based on its kinetic properties and as a marker for complicated/advanced appendicitis. CRP levels increase between 8–12 hours after the onset of inflammatory process and peak around 24 and 48 hours. Consequently, CRP may have less utility in the cases of simple appendicitis. However, with levels found to increase in tandem with the severity of the disease, it is a strong predictor of complicated appendicitis. S. Yokoyama et al established that CRP >5 mg/dl is an independent indication of surgery in AA, with a sensitivity of 84.3%, specificity of 75.8%, positive predictive value of 64.2% and NPV of 90.4%foridentifying complicated appendicitis . They found that the CRP levels were significantly higher (4.09±4.33 mg/dl vs 11.47±7.59 mg/dl, p<0.0001) in patients with perforated appendicitis ,needing early surgical intervention.[23] H.M. Moon found sensitivity of CRP for identifying complicated appendicitis was 57.6%; specificity, 98.3%, the positive predictive value 97.4%, and the negative predictive value was 68.5%[24] . These values in W. Farooqi's study were 54%, 79%, 49% and 82%. Studies have shown sensitivity of CRP as high as 98% for identifying perforation in

appendicitis15. In our study ,the level of CRP was found to be elevated in only 43% of simple AA with mean value of 7.027±2.6. However, the levels of CRP were significantly higher in CA with mean value 25.36±7.11. The sensitivity of CRP for CA was quite high at 88.5%, whereas the specificity was 57%, with PPV and NPV 42% and 93% respectively.

Of late, total serum bilirubin levels have been studied exhaustively to find a relation with acute appendicitis. The mechanisms behind sepsis-related hyperbilirubinemia may be explained by an imbalance between production and excretion of bilirubin by the liver[25]. It may be because of toxic hepatocellular damage, cholestasis or hemolysis caused by abdominal sepsis. Portal blood carries nutrients as well as noxious agents including bacteria and toxins absorbed from intestine. Reticuloendothelial system (RES) of liver acts as first line defence in clearing toxic substances, bacteria and its products. Escherichia coli endotoxin has been shown to impact physiological bile flow causing intrahepatic cholestasis and sinusoidal damage[25].

Andrew Emmanuel established hyperbilirubinaemia as a strong predictor of acute appendicitis[25], and found that it is more specific compared to TLC and CRP for identifying patients with perforation or gangrene, (respective specificity 70 19 36). However, Kaiser et al found hyperbilirubinemia inferior to CRP for detecting complicated appendicitis .Our study revealed the sensitivity of hyperbilirubinaemia for CA was 61.5%, which was considerably less than 80.7% and 88.5% for TLC and CRP. However, the specificity of STB for CA was 86.5% compared to 57% and 35% for CRP and TLC respectively, matched with high PPV 61.54%. Thus STB, when raised, is the most reliable marker of perforation and gangrene according to our results. Only one patient with high serum bilirubin was found among cases of simple appendicitis, while 62% in Ca had raised STB.

CONCLUSION

TLC, CRP and STB are all significantly raised in cases of complicated appendicitis with different predictive values. These markers can be of great value when combined with good history and clinical examination to predict the severity of AA. Of the three, raised STB is most reliable in predicting gangrenous or perforated appendicitis and presence of raised STB should prompt the surgeon to initiate aggressive management. Since radiological imaging was only obtained in the female population, we couldn't reliably compare the efficacy of laboratory findings to those of imaging.

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