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Comparative Study Between Diagnostic Accuracy of Serum Bilirubin Levels Versus C-Reactive Protein in Evaluation of Complicated Acute Appendicitis

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ABSTRACT

Objective: To compare the diagnostic accuracy of serum bilirubin levels versus C-Reactive Protein in evaluation of complicated acute appendicitis.
Study Design: Quasi-experimental study.
Place and Duration of Study: Department of General Surgery, Combined Military Hospital, Rawalpindi Pakistan, from Mar to Oct 2022.
Methodology: Using non-probability consecutive sampling technique, a total of 122 cases of acute appendicitis were enrolled in the study. Emergency appendectomy was performed, and cases were categorized as per operative findings into two groups: Group-A (uncomplicated) and Group-B (complicated) appendicitis. Pre-operative values of serum total bilirubin and C-Reactive Proteins were compared for both groups using IBM SPSS version 26.0.
Results: We analyzed the data for a total of 122 cases of acute appendicitis, among which 86(70.5%) were males and 36(29.5%) were females and 87(71.3%) patients had uncomplicated appendicitis while 35(28.7%) had complicated appendicitis. Sensitivity, specificity, Positive Predictive Value and Negative Predictive Value for serum total bilirubin were found to be 28.6%, 90.8%, 55.6%, and 75.9% respectively, while for C-Reactive Protein were 94.3%, 34.5%, 36.7%, and 93.7%, respectively. For complicated appendix, the most reliable indicator found in our study was, serum total bilirubin, which showed the highest specificity and Positive Predictive Value.

Conclusion: Serum total bilirubin levels, when raised in cases of acute appendicitis, are a strong indicator of the presence of complicated appendicitis, warranting aggressive resuscitation and management.

Keywords: Complicated Appendicitis, C-Reactive Protein, Serum Total Bilirubin.

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INTRODUCTION

The most commonly encountered cause of acute abdominal pain in all age groups is acute appendicitis, with lifetime risk of 8.6% in males and 6.7% in females.[1] Phlegmon, gangrene, abscess, perforation and varying degrees of peritonitis, differentiate complicated appendicitis from uncomplicated appendicitis[2] and the involvement of appendicular luminal obstruction due to lymphoid hyperplasia, fecolith, tumor or parasitic infection, can lead to localized inflammation of appendix, which, if untreated, can lead to perforation.[3,4] Acute appendicitis often presents with shifting pain in the periumbilical region along with fever, anorexia, nausea and vomiting, however, only 35-45% of patients present in the classical manner, thus, accurate diagnosis of disease severity can be difficult to determine [5] unless clinical, laboratory and radiological workup is performed concurrently. The clinical scoring system in use for excluding appendicitis is sensitive up to 99%, thereby decreasing the need for prolonged radiological imaging.[6] Alvarado score is another widely used scoring system with high degree of diagnostic accuracy, having sensitivity and specificity in literature of 94.9% and 72.7% respectively[7] while ultrasound remains the most widely used modality for ease of use with overall highest diagnostic accuracy.[8] Unfortunately, imaging techniques are costly, time-consuming and not easily available. Consequently, inflammatory markers, such as serum bilirubin and C-reactive proteins, can be used as markers of complicated appendicitis especially in the presence of fever, as the imbalance between hepatic and extra hepatic excretion of bilirubin leads to hyperbilirubinemia while the accumulation of gram-negative bacteria in the appendix leads to the

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secretion of bacterial endotoxins which get absorbed in portal circulation, causing hepatocellular damage and raising serum total bilirubin levels.[9,10] Thus, the rationale of our study was to compare the diagnostic accuracy of serum bilirubin levels with c-reactive protein, to determine the presence of complicated appendicitis.

METHODOLOGY

This quasi-experimental study was conducted at Combined Military Hospital (CMH), Rawalpindi Pakistan, from March to October 2022, after taking approval from the Ethical Research Committee (ERC) of the institute via certificate ERC no. 301, dated 22 Feb 2022. The minimum sample size calculated for the study was 45, as the hypothesized diagnostic accuracy of consolidated factors, c-reactive protein, and serum bilirubin was 97%, with a 95% confidence level and 5% error of the mean as described in literature.[11,14] We enrolled 122 patients after taking informed, written consent, using non-probability consecutive sampling.

Inclusion Criteria: Patients belonging to either gender, aged more than 12 years, who reported to Accident and Emergency Department, with complaints of pain in right iliac fossa (RIF) lasting less than 7 days, with subsequent referral to surgical team and confirmed diagnosis as acute appendicitis, with confirmatory investigations including complete blood counts, serum total bilirubin, c-reactive protein, urine routine examination and abdominal ultrasound were included.

Exclusion Criteria: Patients having pregnancy, positive hepatitis B and C tests, choledocholithiasis, documented history of hemolytic disorder, chronic liver disease, jaundice or biliary disease were excluded from our study.

C-reactive protein and serum total bilirubin levels were noted preoperatively and documented on a data collection form. Patients diagnosed as acute appendicitis were prepared for emergency appendectomy after taking informed written consent. Patients were given pain relief and fluid-electrolyte replacement along with prophylactic antibiotic at the time of induction of anesthesia. Emergency appendectomies were performed, and findings were documented with specimens sent for histopathological examination. Phlegmon, gangrene, perforation, and abscess were categorized as complicated appendicitis while absence of these findings was labelled as uncomplicated appendicitis. Laboratory values for CRP and serum total bilirubin were compared for both uncomplicated and complicated appendicitis using IBM Statistical Package for the Social Sciences (SPSS) version 26.0. Chi-square test was applied to all categorical variables while the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for serum total bilirubin levels and CRP levels were also calculated with a *p*-value of ≤0.05 considered as statistically significant.

RESULTS

We enrolled 122 cases of acute appendicitis, of which 86(70.5%) were males while 36(29.5%) were females. Patients ranged in age from 12-70 years. Uncomplicated appendicitis (Group-A) was noted in 87(71.3%) patients while 35(28.7%) had complicated appendicitis (Group-B). In Group-B (n=35), serum total bilirubin was raised in 10 patients, while CRP was raised in 33 patients, as shown in Table-I. In Group-A, the female to male ratio was 1:1.9 while in Group-B, it was 1: 4. Mean value of serum total bilirubin in Group-A was 10.54+5.1µmol/L, which was significantly less than that in Group-B of 16.3+10.1µmol/L, with *p*-value of 0.007. Mean value of CRP in Group-A was 25.5±20.3mg/ml, which was significantly less than that of Group-B with 91.1±60.2mg/ml, (*p*-value<0.001), as shown in Table-II. In Group B, serum total bilirubin showed low sensitivity, high specificity and high PPV, while CRP showed high sensitivity, low specificity and low PPV, as illustrated in Table-III.

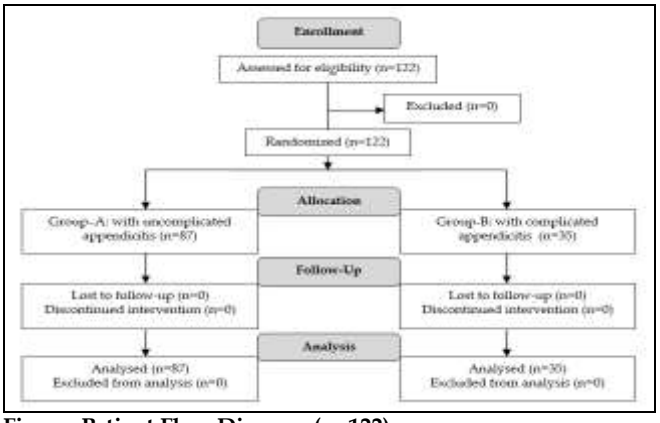

Figure: Patient Flow Diagram (n=122)

Table-I: Laboratory Values of Inflammatory Markers (n=122)

Marker	Group A 87(71.3%)	Group B 35(28.7%)
Bilirubin >17 µmol/L	8(9.2%)	10(28.6%)
Bilirubin <17 µmol/L	79(90.8%)	25(71.4%)
C-reactive protein >10 mg/ml	57(65.5%)	33(94.2%)
Negative c-reactive protein mg/ml	30(34.4%)	2(5.7%)

Table-II: Mean Values of Markers for Both Groups (n=122)

	Group A (Mean+SD)	Group B (Mean+SD)	*p*-value (≤0.05)
Age (years)	30.39+11.2	37.43+18.2	
Serum total bilirubin (µmol/L)	10.54+5.1	16.3+10.1	0.007
C-reactive protein (mg/ml)	25.5+20.3	91.1+60.2	<0.001

Table-III: Diagnostic Accuracy of Serum Bilirubin Levels and C-Reactive Protein (n=122)

Parameter	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Positive Likelihood Ratio	Negative Likelihood Ratio
Serum Total Bilirubin >17 µmol/L	28.6%	90.8%	55.6%	75.9%	3.11%	0.8%
CRP >10 mg/ml	94.3%	34.5%	36.7%	93.7%	1.44	0.17

DISCUSSION

Among patients having complicated appendicitis, morbidity is significantly increased by longer length of hospital stay due to intra-abdominal abscess formation, thus, early diagnosis followed by surgical intervention can prevent drastic complications, for which c-reactive protein can serve as a potentially valuable marker of acute disease[15,17] as, when compared with uncomplicated appendicitis, higher levels of CRP were observed in complicated appendicitis cases, while literature reported sensitivity of CRP to be 73.6% and specificity 73.9%, with PPV and NPV being 58.1% and 85.1%, respectively.[18-20] As the imbalance between hepatic production and extra hepatic excretion of bilirubin leads to hyper-bilirubinemia, the accumulation of gram negative bacteria in the appendix, leads to inflammation and secretion of bacterial endotoxins, that circulate and get absorbed in portal circulation, leading to hepatocellular damage, raising the serum total bilirubin levels[9] which one study reported as a predictor of complicated appendicitis.[17] Another researcher identified risk factors for complicated appendicitis to be fever, raised CRP levels and raised serum total bilirubin levels[10] while another study similarly pointed out low sensitivity and high specificity of elevated serum bilirubin levels in diagnosis of complicated appendicitis[11] with one author reporting significant correlation of severity of appendicitis with serum total bilirubin levels,[12] similar to our findings. In another study, raised levels of serum total bilirubin and CRP were important inflammatory markers in patients aged above 65 years, predicting the increased severity of the disease.[13] The results of our study were supported by another author, showing significant results for serum total bilirubin levels and CRP levels when they were employed in assessing the clinic-pathological severity of acute appendicitis.[18] In this study, we compared the diagnostic accuracy of CRP versus serum total bilirubin levels, to aid in evaluation of complicated acute appendicitis and we affirmed the greater specificity and PPV of serum total bilirubin, confirming it to be a reliable indicator for prediction of complicated appendicitis.

LIMITATIONS OF STUDY

This study has several notable limitations. The single-center design may limit generalizability to other populations and healthcare settings. The non-probability consecutive sampling method could introduce selection bias. Our study did not account for potential confounding factors such as timing of blood sample collection relative to symptoms. Additionally, there was no control for inter-observer reliability for the surgical findings or histopathological examinations, which could affect the consistency of categorizing cases as complicated versus uncomplicated appendicitis.

CONCLUSION

We found serum total bilirubin to have the greatest specificity and PPV in our study, thus it can be used as a strong indicator of the presence of complicated appendicitis, warranting aggressive management by the surgeon.

Conflict of Interest: None.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MIR & SMK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SRQN & AAK: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

HAM & UMR: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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