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Original Research Article

Hyperbilirubinemia, C-reactive protein, total leucocyte counts and serum amylase as markers of gangrenous/perforated appendicitis

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ABSTRACT

Background: C-reactive protein, serum amylase, total leucocyte count, and total serum bilirubin have been used as adjuncts for the diagnosis of appendicitis. This study assessed the diagnostic value of these markers in patients with suspected acute appendicitis.
Methods: CRP, serum amylase, total leucocyte count, and total serum bilirubin values among the patients who presented with acute appendicitis were compared among patients who had perforated appendix and non-perforated appendix. The diagnostic value of CRP and TSB markers as a predictor for perforation were compared in terms of sensitivity, specificity, PPVs, and NPV, and the diagnostic accuracy was assessed by AUC using receiver operating characteristic (ROC) curve analysis.
Results: The values of TSB (mean 3.52, S.D 0.54, $p<0.001$), CRP (mean 9.84, S.D 1.30, $p<0.001$), amylase (mean 68.2, S.D 26.4, $p<0.001$) were found to be significantly correlated with complicated appendicitis.
Conclusions: This study concludes that estimation of pre-operative values of TSB, CRP, and serum amylase as a part of routinely done blood investigations in patients with suspected appendicitis, helps the surgeon in diagnosing complicated types of appendicitis at an earlier stage, though it cannot be generalized due to the small sample size, further studies are needed to establish the conclusion of the study.

Keywords: Appendicitis, C-reactive protein, Perforated appendicitis, Total serum bilirubin, Serum amylase

INTRODUCTION

The diagnosis of acute appendicitis can be made clinically by assessing the symptoms and physical findings and confirmed by laboratory tests and ultrasonography (USG). However, diagnosis is difficult sometimes even after all these tests, and in such doubtful cases either the diagnosis is missed or the patient's normal appendix is operated on, leading to an increase in mortality and morbidity, as there is no reliable specific marker for acute appendicitis has been identified till now and diagnosis of appendicitis remains a dilemma despite the advances in various laboratory and radiological investigations.[1,3] A new tool to help in the diagnosis of acute appendicitis would thus be welcome.

A raised white cell count is not specific for appendicitis and although C-reactive protein (CRP) is commonly used in the assessment of suspected appendicitis, its specificity varies markedly between studies and may only significantly raise once appendiceal perforation takes place however white cell count better detect early appendiceal inflammation and an elevated CRP level better detects perforated appendicitis and surgeon should decide on an appropriate operation time, select antibiotics and explain the prognosis to the patient.[1,9,10]

Some studies have noted raised serum amylase levels in patients first observed for pancreatitis but, later found to have acute appendicitis which became perforated and resulted in serious complications however, limited studies

are there to evaluate the diagnostic accuracy of serum amylase in the diagnosis of perforated appendicitis.[12]

Also, elevation of serum or urinary amylase or both was noted in 15 of 155 patients (10 percent) with appendicitis, of which six had perforated appendicitis, four with accompanying peri appendiceal abscesses. Although theories abound, the cause of amylase elevation in appendicitis remains conjectural.[12]

Hyperbilirubinemia, high CRP level, and fever may be useful predictors of the severity of acute appendicitis, with hyperbilirubinemia being especially useful among patients aged <65 years.[18,19] Acute appendicitis is the most common cause of "acute abdomen" in young adults, with patients at extremes of age are more likely to develop perforated appendicitis.[22,24]

The endotoxin of *E. coli* has been shown in vivo to affect physiological bile flow, which led to the theory that hyperbilirubinemia may possess inferential potential in the preoperative early diagnosis of appendicular perforation. Elevated serum bilirubin level will help in the early and accurate diagnosis of acute appendicitis and in predicting its serious complications, most importantly the perforation.[22]

Recently, the importance of hyperbilirubinemia or elevated serum bilirubin (serum bilirubin) and its association with acute appendicitis has been hypothesized that an association exists between hyperbilirubinemia and acute appendicitis and its complications such as appendicular perforation.[25]

Abruzzo et al noted elevation of amylase levels in 9 of 13 patients (70 percent) with peritonitis, secondary to appendicitis.[26]

It is hypothesized that an association exists between hyperbilirubinemia, CRP, and serum amylase in acute appendicitis and its complications such as appendicular perforation.

In the context of the above discussion, the diagnosis of appendicitis can be difficult, occasionally taxing the skills of even the most experienced surgeon.[23] So there is a need for the study to conclude whether serum bilirubin, CRP, and serum amylase can be considered as new laboratory markers to aid in the diagnosis of complicated appendicitis and if so, do they have the predictive capacity to warn us about appendicular perforation. In this study, the levels of serum amylase, CRP, and TSB were evaluated as a potential marker for diagnosis of complicated appendicitis.

METHODS

Study design

It was a single institution-based prospective observational study.

Study place

The study was conducted at the department of general surgery, Shri Shankaracharya Institute of Medical Sciences, Bhilai, CG.

Study period

The duration of the study was from August 2022 to July 2023 (12 months).

Sample size

Sample size was 60.

Type of sampling

Simple random sampling was used.

Inclusion criteria

All patients diagnosed with acute appendicitis and its complications (gangrenous/perforation) were included.

Exclusion criteria

All patients with disease of the hepato-biliary system, with past h/o jaundice/liver disease, hemolytic disease, congenital or acquired biliary disease, appendicular lump, and patients undergoing interval appendicectomies or appendicectomies for other indications were excluded.

The following data was collected from the study population after taking informed consent from patients.

Demographic data

It included ame, age, sex, I.P number, duration of symptoms (history and examination).

Data related to the study criteria include blood investigations like complete blood count (CBC), C-reactive protein (CRP), liver function test (LFT) (TSB), serum amylase, kidney function test (KFT), and viral markers, and radiological imaging (USG/CT abdomen).

All the patients were subjected to the standard treatment with broad-spectrum antibiotics, surgical management, and other treatments as per the individual needs of the patient.

Statistical analysis

Results are presented within the style of tables.

Number, percentage, and appropriate statistical tests were applied and the p value was calculated based on which inference was drawn.

Ethical considerations

The study was approved by the institutional ethics committee before the commencement of the data collection. All the patients/legal guardians were explained about the study, the investigations, and operative procedures with their merits and demerits, expected results, and possible complications. If he/she agreed, then the patients were enrolled in the study.

RESULTS

Observations

The study was conducted from August 2022 to July 2023 for a period of 12 months. In this institutional-based prospective study, 60 patients were included and were categorized into two groups based upon the final histopathology report i.e., uncomplicated appendicitis group (n=37) and complicated appendicitis group (patients with gangrenous and perforated appendicitis; n=23).

Demographics

60 cases were included in the study as they met the inclusion criteria, with 35% belonging to 12-20 years age group (12 males, 9 females), 28.3% from 21-30 years age group (9 males, 8 females), 11.6% from 31-40 years age group (5 males, 2 females), 8.3% from 41-50 years age group (2 males, 3 females), 10% from 51-60 years age group (3 males, 3 females), and 6.6% from >60 age group (3 males, 1 female). Out of 60, 37 were categorized under Uncomplicated Appendicitis and the remaining 23 under complicated appendicitis. The mean age for complicated and uncomplicated was found to be 30.6±17.16, 33±14.7 respectively, with p=0.58 showing no significance difference in mean age between both groups.

Table 1 shows WBC values were insignificant as it was found to be raised in both uncomplicated as well as complicated appendicitis, with a p value of 0.37.

Tables 2-4 shows the mean value for TSB, CRP, and Amylase in uncomplicated appendicitis which was 1.56±0.30, 3.27±0.42, 28.6±11.3 respectively, and also in complicated appendicitis which was 3.52±0.54, 9.84±1.30, 68.2±26.4 respectively with p value <0.001, which suggest that there is significant difference between the TSB, CRP, and serum amylase values of both groups.

Table 1: TLC count distribution among study population.

TLC count	Uncomplicated appendicitis (n=37) (%)		Complicated appendicitis (n=23) (%)	
<11000/cu.mm	12	32.43	5	23.80
>11000/cu.mm	25	67.56	18	78.26

P=0.37 NS (Chi-square test) i.e. no significant difference in the level of TLC count between both groups

Table 2: Serum bilirubin distribution among study population.

Bilirubin levels (mg/dl)	Diagnosis			
	Uncomplicated appendicitis (n=37) (%)		Complicated appendicitis (n=23) (%)	
Normal	17	45.94	4	17.39
Raised (>1)	20	54.05	19	82.60
Total bilirubin	1.56 (mean)	0.30 (SD)	3.52 (mean)	0.54 (SD)

P=0.02 S (Chi-square test) i.e. significant difference in bilirubin levels between both groups; for total bilirubin: p<0.001 HS (independent t-test) i.e. highly significant difference in mean bilirubin between both groups

Table 3: Distribution of C-reactive protein levels among study population.

CRPlevels (mg/dl)	Diagnosis			
	Uncomplicated appendicitis (n=37) (%)		Complicated appendicitis (n=23) (%)	
Normal	10	27.02	2	8.7
Raised	27	72.97	21	91.30
CRP mean	3.27 (mean)	0.42 (SD)	9.84 (mean)	1.30 (SD)

P=0.08 NS (no significant difference in CRP levels between both groups; for CRP mean: p<0.001 HS (independent t-test) i.e. highly significant difference in mean CRP between both groups

Table 4: Distribution of serum amylase levels among study population.

Serum amylase (mg/dl)	Diagnosis			
	Uncomplicated appendicitis (n=37) (%)		Complicated appendicitis (n=23) (%)	
Normal	21	56.75	7	30.43
Raised	16	43.24	16	69.56
Mean	28.6 (mean)	11.3 (SD)	68.2 (mean)	26.4 (SD)

P value 0.046 S (Chi-square test) i.e. significant difference in serum amylase levels between both groups; for mean: p<0.001, HS highly significant difference in mean serum amylase

DISCUSSION

The total number of patients included in the study was 60 and among them, 37 were categorized under uncomplicated appendicitis and the remaining 23 under complicated appendicitis with 74.9% of the study population under the age of 40 years, with male-female ratio 1.30:1 in the present study.

In the present study it was found that values of TSB, CRP, amylase were raised significantly in cases of complicated appendicitis, whereas WBC values were found to be insignificant as it was raised equally in both the groups.

Eric et al in their prospective study found that serum amylase was raised in both uncomplicated as well as complicated appendicitis.[8] Kim et al in a retrospective study found out that in uncomplicated appendicitis cases, CRP was raised with a mean value of 0.99 mg/dl (S.D±1.63) and WBC was also raised with a mean value of 12970 u/l (S.D±3730/ul) but in complicated cases, these values (8.10±6.90 mg/dl, 12850±5280/ul) were significantly raised respectively, with Moon et al also showing similar findings.[9,10]

Kar et al in their study found that the WBC was raised among patients with uncomplicated appendicitis as compared to complicated appendicitis whereas TSB was raised among patients with complicated appendicitis alone.[18]

Akai et al in their retrospective cohort study found that although CRP, WBC, and TSB were raised in both uncomplicated (3.04 mg/dl, 11,545/ul, 1.03 mg/dl) as well as complicated (9.87 mg/dl, 12661/ul, 1.18 mg/dl) appendicitis with significant raise in complicated cases.[19]

Zengin et al in their study found raised WBC with a mean value of 12500/ul in uncomplicated appendicitis, with normal TSB and CRP values, and raised WBC with a mean value of 13500/ul in complicated appendicitis, with normal TSB and CRP values.[20]

Bakshi et al found raised TSB values in uncomplicated and significantly raised values in complicated appendicitis with mean values of 0.79±0.16 mg/dl and 1.39±0.26 mg/dl respectively.[21]

Emergency appendectomy for uncomplicated acute appendicitis usually follows a short recovery period but same for the gangrenous or perforated appendicitis may be a life-threatening one. To avoid morbidities prompt diagnosis is the key factor.[21] Despite the increase in diagnostic modalities such as ultrasonography and computed tomography, the rates of appendicitis misdiagnosis and appendiceal rupture have remained constant.[19]

Estimation of serum total serum bilirubin (TSB), C-reactive protein (CRP), and serum amylase level is a simple, cheap, and easily available laboratory test, that can be added to the routine investigations in clinically suspected cases of appendicitis, which is usually not done as a marker of complicated appendicitis in an emergency setting.[21]

Comparison of various studies with a present study showing different values of CRP, TSB, and serum amylase in uncomplicated and complicated appendicitis in given in Tables 5-7.

Table 5: Comparison between present and different studies for values of CRP, WBC, TSB, and serum amylase in uncomplicated appendicitis.

Study	Age in years	CRP	WBC (10^3/ul)	Total serum bilirubin (mg/dl)	Amylase (U/l)
Kar et al[18]	21-40	-	>11×10^3	<1.1	-
Akai et al[19]	39.6	3.04	11,545	1.03	-
Kim et al[9]	38	0.99±1.63	12970±3730	-	-
Moon et al[10]	28.56±20.95	1.82±2.29	12,946±4316	-	-
Eric et al[8]	34 (12-67)	-	-	-	>140
Zengin et al[20]	30 (17-86)	-	12500 (3900-23000)	0.61 (0.19-2.33)	57 (14-174)
Bakshi et al[21]	23.5±13.5	-	-	0.79±0.16	-
Present study	33±14.7	3.27±0.42	>11×10^3	1.56±0.30	28.6±11.3

Table 6: Comparison between present and different studies for values of CRP, WBC, TSB, and serum amylase in complicated appendicitis.

Study	Age in years	CRP	WBC (10^3/ul)	Total serum bilirubin (mg/dl)	Amylase (U/l)
Kar et al[18]	21-30	-	<11×10^3	>1.1	-
Akai et al[19]	52.4	9.87	12661	1.18	-
Kim et al[9]	38	8.10±6.90	12850±5280	-	-
Moon et al[10]	47.19±22.94	10.10±10.05	13,337±4010	-	-
Eric et al[8]	34 (12-67)	-	-	-	>140
Zengin et al[20]	35 (18-85)	-	13500 (5400- 28200)	0.88 (0.24-3.73)	46 (22-117)
Bakshi et al.[21]	23.5±13.5	-	-	1.39±0.26	-
Present study	30.6±17.16	9.84±1.30	>11×10^3	3.52±0.54	68.2±26.4

Table 7: Mean values for WBC, TSB, CRP, and serum amylase with significant p values for TSB CRP, serum amylase, of present study.

Parame-ters	Uncomplica-ted appendi-citis (n=37)	Complicated appendicitis (n=23)	P value
WBC	>11000/cu.mm (25)	>11000/cu.mm (18)	0.37
TSB	1.56±0.30	3.52±0.54	<0.001
CRP	3.27±0.42	9.84±1.30	<0.001
Amylase	28.6±11.3	68.2± 26.4	<0.001

Limitations

Appendicitis and raised serum amylase levels may occur concurrently but, in this study, no relationship was found between higher amylase levels and acute complicated appendicitis, and require further large studies. Also the findings of this study cannot be generalized due to the small sample size, further studies are needed to establish the conclusion of the study.

CONCLUSION

In this institutional-based observational prospective study the data of the patients included in the study regarding the various markers i.e., TSB, CRP, serum amylase and WBC count were recorded and the following conclusion was made.

This small study can be used in the management of suspected complicated appendicitis by adding simple blood investigations. This study concludes that estimation of pre-operative values of TSB, CRP, and serum amylase can be used as a good markers and can be used as a part of routinely done blood investigations in patients with suspected appendicitis and helps the surgeon in diagnosing and managing the complicated type of appendicitis at an earlier stage which can prevent the morbidity and mortality arising from the same.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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