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Hyperbilirubinemia is a Predictor of Gangrenous or Perforated Appendicitis

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Abstract **Original Research Article**

Introduction: Acute appendicitis is the most common acute abdominal condition that requires surgical intervention in childhood. Patients with complicated appendicitis (CA) were reported to have elevated serum bilirubin or reduced serum sodium levels in several studies. ***Aim of the study*:** The purpose of this study was to establish the role of hyperbilirubinemia as a predictive parameter for the prediction of either acute, or gangrenous/perforated appendicitis. ***Methods***: The present descriptive type observational study was accomplished in Department of Surgery, Faridpur Medical College Hospital, Bangladesh. Medical files of the patients, who underwent appendectomies between July 2015 and January 2016, were evaluated. Age, gender, preoperative white blood cell count (WBC), neutrophil count (NEU), neutrophil percentage (NEU %), C-reactive protein (CRP), total/ direct/indirect bilirubin levels, and preoperative presentation & severity, complication of disease, outcome and postoperative hospital stay findings were recorded. The Fisher's exact, Pearson's $\chi 2$, ANOVA, and Kreskas–Wallis tests while logistic regression for multivariate analysis was performed. P value < 0.05 was accepted as statistically significant\ for this study. ***Result*:** 50 patients of more than 15 years old participated in this study. Histopathological examinations revealed normal appendix in 11 (22%) patients, non-complicated acute appendicitis in 18 (36%), and appendiceal gangrene/perforation in 21 (42 %) patients. WBC, NEU, NEU%, and CRP levels were found significantly elevated in cases of acute and gangrenous/perforated appendicitis ($p < 0.01$). Total and direct bilirubin levels were also significantly higher in patients with acute and gangrenous/perforated appendicitis ($p < 0.01$). Multivariate analysis, higher levels of CRP were associated with 14 times, elevated total bilirubin levels were associated with five times, and elevated direct bilirubin levels were associated with 36 times greater risk for appendiceal gangrene/perforation ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively) were present among the study patients. ***Conclusion***: Hyperbilirubinemia, particularly with raised direct bilirubin levels, might be considered as a significant marker for the expectation of appendiceal gangrene/perforation.

Keywords: Hyperbilirubinemia, acute appendicitis, gangrene, perforation.

INTRODUCTION

An infected appendix is one of the most well-known reasons for abdominal pain requiring emergency surgery [1]. No reliably specific marker for the analysis of intense an acute appendicitis has been distinguished [2]. Sometimes, arriving at a legitimate diagnosis can be difficult. There may not be old style side effects and indications of an infected appendix, and different clinical states impersonate the determination, as there are a number of causes leading to pain in the right iliac fossa particularly in female patients [1]. These could defer a potential surgical intervention, and lead to appendiceal perforation with expanded morbidity and clinic stay [3]. The occurrence of perforated appendicitis in grown-ups has been accounted for to be 13-37 % or higher [4, 5]. Appendectomy for acute appendicitis is one of the most frequently performed surgical procedures in the United States [6]. A lot of studies are done on appendicitis since it was described by Fitz more than100 years ago [7], but the etiology and epidemiology of this disease remain poorly understood. Acute appendicitis has been and attributed to a variety of possible causes, including mechanical obstruction [8, 9], insufficient dietary fiber [10-13], familial susceptibility [14], factors related to improved socioeconomic conditions [15, 16], and bacterial, viral, and parasitic pathogens [17-21].

Elevated serum bilirubin levels, which are not explained by liver disease or biliary obstruction, can be observed in many patients with acute appendicitis [22]. This is one of the most commonly diagnosed surgical conditions, with Escherichia coli being one of the most frequent bacterial isolates in the disease. The relationship

of hyperbilirubinemia in patients with appendicitis is largely unknown. There are a couple of case reports in the researches that portray the finding of hyperbilirubinemia in patients with either serious postoperative contamination after appendectomy or with confounded an appendicitis [23].

This descriptive type observational study investigated the role of hyperbilirubinemia as a diagnostic parameter for the prediction of either acute, or gangrenous/ perforated appendicitis.

Objective of the Study

- ***General objective:*** The purpose of this study is to evaluate the investigating elevated serum bilirubin as a diagnostic marker for appendiceal perforation.
- ***Specific objective***: The current study aims to find the Outcome of appendicular perforation/ brust or gangrenous appendix after management.

METHODOLOGY & MATERIALS

A total of 50 consecutive patients aged more than 15 years old were selected for this study. The patients were selected after they are diagnosed clinically as acute appendicitis, appendicular perforation in surgery department of Faridpur medical college hospitals (both indoor & out door department) between July 2015 and January 2016 were evaluated retrospectively. The patients were divided into 3 groups after receiving their data. Group 1 included normal appendix (noninflamed appendix) patients, group 2 included acute appendicitis (non-complicated appendicitis) patients and group 3 included appendiceal gangrene/ perforation (complicated appendicitis) patients.

- ***Inclusive criteria:*** The patients who underwent appendectomies and signed the written consent form about the study and it purpose were included in this study.
- ***Exclusion criteria***: Any patients with any liver disease or biliary disorder, and cases with any histopathological findings other than non-inflamed, acute, or gangrenous/perforated appendicitis (i.e., mucocele, tumor, etc.) were excluded of this research.

Age, gender, preoperatively assessed white blood cell count (WBC, normal range 4000–10,000/mm3), neutrophil count (NEU, normal range 1400–6500/mm3), neutrophil percentage (NEU%, normal range 42.0–75.2 %), C-reactive protein (CRP, normal range 0.0–0.5 mg/dL), total bilirubin (normal range 0.0–1.2 mg/dL), direct bilirubin (normal range 0.0–0.2 mg/dL), indirect bilirubin (normal range 0.2– 1.0 mg/dL) levels, and the postoperative histopathological findings of the patients were recorded and evaluated. Statistical analyses were done by using the Fisher's exact, and Pearson's $\chi 2$ tests in addition to ANOVA and Kreskas–Wallis tests with Mann–Whitney *U*, Bonferroni, and Games-Howell post hoc tests for multiple comparisons, whereas logistic regression was performed for multivariate analysis. $P < 0.05$ value was considered statistically significant. Ethical clearance was taken from the Faridpur Medical College Hospital, Bangladesh ethics committees as required. Signed informed consent was obtained from patients or their guardians.

RESULT

The total study group of 50 patients consisted of 30 (60 %) men and 20 (40 %) women with a median age of 36. Histopathological examinations revealed findings of a normal appendix (negative appendectomy) in 11 (22%) patients, non-complicated acute appendicitis in 18 (36%) patients, and complicated appendicitis (perforated appendicitis) in 21 (42%) patients.

White blood cell count (WBC), neutrophil count (NEU), and neutrophil percentage (NEU %) were significantly higher in cases of acute appendicitis compared to cases of revealing normal appendiceal findings ($p < 0.001$). C-reactive protein (CRP) levels were significantly higher in the complicated appendicitis group when compared to the other two groups. Total bilirubin levels were in normal range in all negative appendectomy cases but elevated in the patients with acute appendicitis, and elevated significantly in patients with gangrenous/perforated appendicitis ($p < 0.001$). Direct bilirubin levels were slightly elevated in negative appendectomy cases, while this parameter was found to be elevated in patients with acute appendicitis, and in the patients with gangrenous/ perforated appendicitis revealing high diagnostic sensitivity and specifity ($p = 0.014$, and $p < 0.001$, respectively; $p < 0.01$). Though, the comparisons of indirect bilirubin levels between negative and positive appendectomy cases did not reveal statistical significance ($p = 0.08$; $p > 0.05$), this parameter was significantly higher in the gangrenous/ perforated appendicitis group when compared to the other two groups of patients ($p < 0.001$) [Table-1] (*Q1* First quartile, 25th percentile; *Q3* Third quartile, 75th percentile, [a] Welch ANOVA with Games-Howell post hoc test, mean ± standard deviation (SD) values are reported, [b] One-way ANOVA with Bonferroni correction post hoc test, mean ± standard deviation (SD) values are reported, [c] Kreskas–Wallis test with Mann Whitney *U* test as post hoc test, median (Q1, Q3) values are reported). According to multivariate statistical analysis, elevated CRP levels were associated with 14 times [$p = 0.003$, Odds Ratio (OR): 13.81, 95 % Confidence Interval (CI): 2.42– 78.92, Positive predictive value (PPV): 33.3 %, Negative predictive value (NPV): 95.6 %, Specifity: 35.5 %, Sensitivity: 95.1 %], elevated total bilirubin levels were associated with five times [$p = 0.044$, OR: 4.70, 95 % CI: 1.04–21.19, PPV: 70.6 %, NPV: 86.7 %, Specifity: 91.7 %, Sensitivity: 58.5 %], and increased direct bilirubin levels were associated with 36 times [$p = 0.001$, OR: 35.51, 95 % CI: 4.38–287.96,

PPV: 49.4 %, NPV: 98.8 %, Specifity: 66.1 %, Sensitivity: 97.6 %] greater risk for appendiceal gangrene/perforation ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). However, in Table-2, no significant association could be determined between elevated indirect bilirubin levels and appendiceal gangrene/ perforation via multivariate analysis [$p = 0.392$, OR: 2.12, 95 % CI: 0.38–11.86, PPV: 77.3 %, NPV: 82.9 %, Specifity: 95.9 %, Sensitivity: 41.5 %] ($p > 0.05$) ([a] Pearson's $\chi 2$ test, [b] Pearson's $\chi 2$ and Fisher's exact test were used where appropriate).

Table 1: The comparison of the mean values of the preoperatively assessed blood test parameters among the three groups of patients according to their postoperative histopathological results

Preoperative parameters (normal range)	**Postoperative histopathological findings**			***P Value***	**Post-hoc (groups)**
	Group 1	**Group 2**	**Group 3**		
	Normal appendix (noninflamed appendix) *n*= 11 (22%)	**Acute appendicitis (noncomplicated appendicitis) *n*= 18 (36%)**	**Appendiceal gangrene/ perforation (complicated appendicitis) *n* = 21 (42%)**		
	Mean ± SD	**Mean ± SD**	**Mean ± SD**		
White blood cell count (4000–10,000/ mm3)	8576.19±2151.95	13,684.10±4038.21	14,902.44±4539.63	<0.001[a*]	1 < 2,3
Neutrophil count (1400–6500/mm3)	5553.33±1939.29	10,823.20±3710.54	12,212.29±4413.75	<0.001[a*]	1 < 2,3
Neutrophil % (42.0–75.2%)	63.70±8.94	77.48±8.57	80.66±8.04	<0.001[b*]	1 < 2,3
Median (Q1, Q3)		Median (Q1, Q3)	Median (Q1, Q3)		
C-reactive protein (0.0–0.5 mg/dL)	0.72 (0.33, 2.08)	1.15 (0.34, 5.06)	5.10 (2.22, 13.55)	<0.001[c*]	1,2 < 3
Total Bilirubin (0.0–1.2 mg/dL)	0.34 (0.23, 0.45)	0.57 (0.42, 0.85)	1.25 (0.89, 1.71)	<0.001[c*]	1 < 2 < 3
Direct Bilirubin (0.0–0.2 mg/dL)	0.12 (0.04, 0.19)	0.18 (0.12, 0.30)	0.42 (0.35, 0.64)	<0.001[c*]	1 < 2 < 3
In direct Bilirubin (0.2–1.0 mg/dL)	0.22 (0.16, 0.30)	0.43 (0.27, 0.60)	0.80 (0.56, 1.13)	<0.001[c*]	1 < 2 < 3

Table 2: The distribution of patients according to their preoperatively elevated blood test parameters among the three groups of patients in concern of their postoperative histopathological findings

Elevated preoperative parameters	**Postoperative histopathological findings**			***P Value***	**Post-hoc (groups)**
	Group 1	**Group 2**	**Group 3**		
	Normal appendix (noninflamed appendix) *n*= 11 (22%)	**Acute appendicitis (noncomplicated appendicitis) *n*= 18 (36%)**	**Appendiceal gangrene/ perforation (complicated appendicitis) *n* = 21 (42%)**		
White blood cell count >10000/mm3	3 (27.28%)	16 (88.89%)	18 (85.71%)	<0.001 [a,*]	1 < 2,3
Neutrophil count >6500/mm3	3 (27.28%)	16 (88.89%)	18 (85.71%)	<0.001 [a,*]	1 < 2,3
Neutrophil % >75.2%	1 (9.09%)	11 (61.11%)	15 (71.43%)	<0.001 [a,*]	1 < 2,3
C-reactive protein >0.5 mg/dL	5 (45.45%)	12 (66.67%)	20 (95.24%)	<0.001[a,*]	1,2 < 3
Total Bilirubin >1.2 mg/dL	0	2 (88.89%)	12(57.14%)	<0.001[a,*]	1,2 < 3
Direct Bilirubin >0.2 mg/dL	1 (9.09%)	7 (11.11%)	20 (95.24%)	<0.001[a,*]	1 < 2 < 3
Indirect Bilirubin >1.0 mg/dL	0	1 (5.56%)	9 (95.24%)	<0.001[a,*]	1,2 < 3

DISCUSSION

In the present study, WBC count, NEU count, and NEU% were detected to be significantly higher in the group of acute appendicitis (noncomplicated) in comparison with the group undergone negative appendectomies revealing the diagnostic sensitivity of these parameters ($p < 0.01$). However, CRP levels were significantly higher in the group of complicated appendicitis revealing its specifity for gangrenous/ perforated appendicitis ($p < 0.01$).

The differential diagnosis of appendicitis includes a long list of common gastrointestinal and genitourinal disorders. Before the popularity of imaging, the accuracy of clinical diagnosis of appendicitis was around 80% and the traditional teaching that a rate of up to 20% for pathologically normal appendices at appendectomy (‘‘negative appendectomy’’). It also was noted that the rate of negative appendectomy was inversely proportional to the rate of perforation [24].

A study commented on the use of 2 simple and easily applied scoring systems (Ohmann and Eskelinen scores) in a primary care setting. Another research carried out in Chile, with the diagnostic punctuation appendicitis scoring system, based on 9 predictive factors that were applied by nonphysician health care professionals. The decisions made by these nonphysician professionals were compared with the diagnostic orientation made by an expert surgeon, and a very high level of agreement was found [25]. A study carried out of 50 patients, the level of serum bilirubin was higher than 3 mg/dL in cases of gangrenous/perforated appendicitis while in cases with acute appendicitis it was lower than 3 mg/dL ($P<0.05$). The study said that it was predominantly isolated hyperbilirubinemia in the majority of cases [26]. An imaging base research established that, the physical findings of acute appendicitis were well established, but it is still not clear which ones predict advanced pathology. Abdominal CT scan may become the main diagnostic tool for patients with acute appendicitis with a high sensitivity and specificity [27].

M. Sand *et al*., (2009) establish in a study that, hyperbilirubinemia, an excessive amount of bilirubin in the blood, either because of increased bilirubin production or alteration of bilirubin clearance, has not been well recognized as a potential laboratory marker for aiding preoperative diagnosis of a perforated appendix. Both mechanisms, increased production and alteration of bilirubin clearance, lead to an accumulation of bilirubin and might play a role in the observed hyperbilirubinemia of patients with appendiceal perforation [28]. On the other hand, a study found CT as a better solution. According to Pediatr Radiol (2009), the false-positive rate of clinical and laboratory diagnostic test results, however, has not changed over the last 20 years, CT is able to diagnose an alternative condition, such as inflammatory bowel disease, intussusception, infectious enteritis or colitis, pancreatitis, Meckel’s diverticulum, hydronephrosis, pyelonephritis, and abdominal neoplasms in up to 50% of child and adult patients with clinically suspected appendicitis who undergo CT [29]. Where, Y.H. Jo *et al*., commented that the clinical diagnosis and the surgeon's decision to operate may be altered by the CT scan, but we did not compare the treatment decisions before and after CT imaging in the current study. It is possible that routine use of CT may delay time to operation thereby increasing the perforation rate [30].

A study found that, that hyperbilirubinaemia is a significant marker for simple acute appendicitis and not only appendiceal perforation. Patients with hyperbilirubinaemia were significantly more likely to have simple acute appendicitis than those with a normal bilirubin. They found that hyperbilirubinaemia had a high specificity of 88% and positive predictive value of 91% for simple acute appendicitis. Although only a limited number of patients had CRP levels measured in the study, the specificity of hyperbilirubinaemia for simple acute appendicitis was higher than that of CRP, which was only 71% [31].

Limitations of the Study: This study has limitation of study population. This single center study may not express a proper conclusion.

CONCLUSION AND RECOMMENDATIONS

The research indicates that Hyperbilirubinemia, elevated direct bilirubin levels, may be considered as an important marker for the prediction of appendiceal gangrene/perforation. For the assessment of patients with suspected acute appendicitis, bilirubin levels may be routinely included. Still, with the development of pathological system, more studies may help to find accurate result.

Declaration of the Patients’ Consent: Written consent was collected from the patients.

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Conflicts of Interest: N/A

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