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ORIGINAL ARTICLE

Hyperbilirubinemia as a predictive factor in acute appendicitis

T. Eren[1] · E. Tombalak[1] · I. A. Ozemir[1] · M. Leblebici[1] · S. Ziyade[2] · O. Ekinci[1] · O. Alimoglu[1]

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Abstract
Purpose Our aim was to establish the role of hyperbilirubinemia as a predictive parameter for the prediction of either acute, or gangrenous/perforated appendicitis as well as to compare other parameters in a similar role.
Methods Medical files of the patients who underwent appendectomies between September 2013 and September 2014 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 the postoperative histopathological findings were recorded. The Fisher's exact, Pearson's χ^2, ANOVA, and Kruskal–Wallis tests while logistic regression for multivariate analysis was performed. $p < 0.05$ was accepted as statistically significant.
Results The study group of 162 patients consisted of 97 (60 %) men and 65 (40 %) women with a median age of 36 (18–90). Histopathological examinations revealed normal appendix in 21 (13 %) patients, non-complicated acute appendicitis in 100 (62 %), and appendiceal gangrene/perforation in 41 (25 %) patients. WBC, NEU, NEU%, and CRP levels were significantly higher in cases of acute and gangrenous/perforated appendicitis ($p < 0.01$). Total and direct bilirubin levels were also significantly elevated in patients with acute and gangrenous/perforated appendicitis ($p < 0.01$). According to multivariate analysis, elevated CRP levels 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).
Conclusions Hyperbilirubinemia, especially with elevated direct bilirubin levels, may be considered as an important marker for the prediction of appendiceal gangrene/perforation.

Keywords Hyperbilirubinemia · Acute appendicitis · Gangrene · Perforation

Introduction

Appendicitis is one of the most common causes of abdominal pain requiring emergency surgery [1]. No reliably specific marker for the diagnosis of acute appendicitis has been identified [2]. Sometimes it can be difficult to reach a proper diagnosis. There may not be classical symptoms and signs of appendicitis, and different clinical states mimic the diagnosis, as there are a number of causes leading to pain in the right iliac fossa particularly in female patients [1]. These might delay a possible surgical intervention, and lead to appendiceal perforation with increased morbidity and hospital stay [3]. The incidence of perforated appendicitis in adults has been reported to be 13–37 % or higher [4].

Elevated serum bilirubin levels, that are not explained by liver disease or biliary obstruction, can be observed in many patients with acute appendicitis [5]. Our aim was

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✉ T. Eren
drtunceren@gmail.com

[1] Department of General Surgery, School of Medicine, Goztepe Training and Research Hospital, Istanbul Medeniyet University, Dr. Erkin Street, Kadikoy, 34730 Istanbul, Turkey

[2] Department of Thoracic Surgery (Medical Statistics), School of Medicine, Bezmialem Vakif University, Istanbul, Turkey

to establish the role of hyperbilirubinemia as a diagnostic parameter for the prediction of either acute, or gangrenous/perforated appendicitis as well as to compare other parameters in a similar role.

Methods

The medical files of the patients operated on with the diagnosis of acute appendicitis in the Department of General Surgery between September 2013 and September 2014 were evaluated retrospectively. The study was approved by the Ethics Committee of our institution, and signed informed consent forms were obtained from all patients.

The patients who underwent appendectomies were included to the study group, whereas 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.

Age, gender, preoperatively assessed white blood cell count (WBC, normal range 4000–10,000/mm^3), neutrophil count (NEU, normal range 1400–6500/mm^3), 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 carried out with use of the Fisher's exact, and Pearson's χ^2 tests in addition to ANOVA and Kruskal–Wallis tests with Mann–Whitney *U*, Bonferroni, and Games-Howell post hoc tests for multiple comparisons, whereas logistic regression was performed for multivariate analysis. $p < 0.05$ was considered as statistically significant.

Results

The total study group of 162 patients consisted of 97 (60 %) men and 65 (40 %) women with a median age of 36 (range 18–90). Histopathological examinations revealed findings of a non-inflamed appendix (normal appendix–negative appendectomy) in 21 (13 %) patients, non-complicated acute appendicitis in 100 (62 %) patients, and findings of appendiceal gangrene/perforation (complicated appendicitis) in 41 (25 %) patients.

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

White blood cell count (WBC), neutrophil count (NEU), and neutrophil percentage (NEU%) were detected to be significantly higher in cases of acute appendicitis when compared with cases 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 revealing specifity for gangrenous/perforated appendicitis ($p < 0.001$). Total bilirubin levels were in normal range in all negative appendectomy cases whereas elevated in 10 % of the patients with acute appendicitis, and elevated significantly in 59 % of the cases with gangrenous/perforated appendicitis ($p < 0.001$). Direct bilirubin levels were slightly elevated in 10 % of negative appendectomy cases, while this parameter was found to be elevated in 39 % of patients with acute appendicitis, and in 98 % of the patients with gangrenous/perforated appendicitis revealing high diagnostic sensitivity and specifity ($p = 0.014$, and $p < 0.001$, respectively; $p < 0.01$). Although 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 ($p < 0.001$).

The distribution of patients according to their preoperative elevated blood test parameters among the three groups of patients in concern of their postoperative histopathological findings is summarized in Table 2.

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 elevated 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, 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 %] ($p > 0.05$).

Discussion

The incidence of acute appendicitis varies, but it is highly prevalent, occuring in 7–22 out of 10,000 people [6, 7]. Although non-perforated acute appendicitis can simply

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*	Post-hoc (groups)
	Group 1	Group 2	Group 3		
	Normal appendix (non-inflamed appendix) $n = 21$ (12.96 %)	Acute appendicitis (non-complicated appendicitis) $n = 100$ (61.73 %)	Appendiceal gangrene/perforation (complicated appendicitis) $n = 41$ (25.31 %)		
	Mean ± SD	Mean ± SD	Mean ± SD		
White blood cell count (4000–10,000/mm^3)	8576.19 ± 2151.95	13,684.10 ± 4038.21	14,902.44 ± 4539.63	<0.001[a,*]	1 < 2,3
Neutrophil count (1400–6500/mm^3)	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
Indirect 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

Q1 First quartile, 25th percentile; *Q3* Third quartile, 75th percentile

* $p < 0.01$

[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] Kruskal–Wallis test with Mann Whitney *U* test as post hoc test, median (Q1, Q3) values are reported

be treated via appendectomy, gangrenous, or perforated appendicitis can cause various complications that sometimes may result in life-threatening conditions including bacterial peritonitis, urinary disorders, small bowel obstruction, and intra-abdominal abscess formations [8, 9]. Despite the increased use of sophisticated imaging and non-invasive diagnostic modalities, such as ultrasonography, computed tomography scan, and laparoscopy, the rate of misdiagnosis of appendicitis has remained constant (15 %) as has the rate of appendiceal rupture [10]. No single clinical or laboratory test is able to reliably predict acute appendicitis or appendiceal perforation [11]. A combination of history, physical examination, laboratory tests, and radiological investigations is used for diagnosis. In cases with less typical symptoms & signs, an observation and re-evaluation period is applied by most physicians. However, this approach may sometimes result with prolonged hospital stay and delayed definitive treatment leading to perforation [12].

Several mechanisms leading to hyperbilirubinemia in systemic infections have been described including haemolysis, associated with bacteria, which causes an increased bilirubin load, and endotoxemia which results with reduced hepatic uptake and canalicular excretion of bilirubin [13, 14]. Bacterial endotoxin also causes a cytokine mediated inhibition of bile salt transport mechanisms, leading to cholestasis [15, 16].

Escherichia coli is associated with the endotoxin lipopolysaccharide and is the most common organism cultured from intraperitoneal fluid in appendicitis [17, 18]. The invasion of gram-negative bacteria (*E. coli*, etc.) into the muscularis propria of the appendix leads to direct invasion or translocation into the portal venous system and into the hepatic parenchyma interfering with the excretion of bilirubin into the bile canaliculi by a mechanism caused by the bacterial endotoxin [19]. Thus, hyperbilirubinemia takes place in either non-complicated, or perforated appendicitis as a result of bacteraemia or endotoxaemia [2].

In a series of 1008 patients, Farooqui et al. reported that, according to their statistical regression model, WBC count, bilirubin, and CRP levels as variables, had the highest negative predictive values when discriminating between perforated and non-perforated appendicitis [20]. D'Souza et al. concluded that hyperbilirubinemia was associated with complicated appendicitis, and that elevated bilirubin levels had a higher specifity (82 %) than both WBC (34 %) and CRP (21 %), but a lower sensitivity (70 %, 80 %, and 95 %, respectively) for perforated appendicitis versus simple appendicitis ($p < 0.01$) [21].

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^a							Post hoc (groups)[b]
	Group 1		Group 2		Group 3			
	Normal appendix (non-inflamed appendix) $n = 21$ (12.96 %)		Acute appendicitis (non-complicated appendicitis) $n = 100$ (61.73 %)		Appendiceal gangrene/perforation (complicated appendicitis) $n = 41$ (25.31 %)			
	n	%	*n*	%	*n*	%		
White blood cell count >10000/mm^3	6	28.57	87	87.00	36	87.81	<0.001[a,*]	1 < 2,3
Neutrophil count >6500/mm^3	6	28.57	91	91.00	35	85.37	<0.001[a,*]	1 < 2,3
Neutrophil % >75.2%	3	14.26	61	61.00	30	73.17	<0.001[a,*]	1 < 2,3
C-reactive protein >0.5 mg/dL	10	47.62	68	68.00	39	95.12	<0.001[a,*]	1,2 < 3
Total Bilirubin >1.2 mg/dL	0	0.00	10	10.00	24	58.54	<0.001[a,*]	1,2 < 3
Direct Bilirubin >0.2 mg/dL	2	9.52	39	39.00	40	97.56	<0.001[a,*]	1 < 2 < 3
Indirect Bilirubin >1.0 mg/dL	0	0.00	5	5.00	17	41.46	<0.001[a,*]	1,2 < 3

n number of patients

* $p < 0.01$

[a] Pearson's χ^2 test

[b] Pearson's χ^2 and Fisher's exact test were used where appropriate

In the present study, WBC count, NEU count, and NEU% were detected to be significantly higher in cases of acute appendicitis when compared to cases having undergone negative appendectomies revealing the diagnostic sensitivity of these parameters ($p < 0.01$). On the other hand, CRP levels were significantly higher in cases of complicated appendicitis revealing its specifity for gangrenous/perforated appendicitis ($p < 0.01$).

In their study of 157 patients, Estrada et al. reported the odds of appendiceal perforation to be three times higher for patients with hyperbilirubinemia compared to those with normal bilirubin levels, and concluded that elevated bilirubin levels had a predictive potential for the diagnosis of appendiceal perforation ($p < 0.05$, OR 2.96) [19]. In another study, Vaziri et al. stated that the mean bilirubin levels were significantly higher for patients with perforated acute appendicitis ($p < 0.01$) [12]. According to the series of Nomura et al., which evaluated data from 410 appendectomized patients, elevated serum total bilirubin levels increased the risk of gangrenous appendicitis approximately two folds ($p < 0.01$, OR 1.79) [22]. In our study, the odds ratio for elevated total bilirubin levels was calculated to be 4.7 referring to an approximately five fold likelihood for appendiceal gangrene/perforation ($p < 0.05$, OR: 4.70).

Chambers et al. stated that although bilirubin levels were significantly elevated in cases of complicated appendicitis, only 30 % of the patients with an abnormally raised bilirubin had gangrenous/perforated appendicitis [23]. We found the rate of abnormally raised total bilirubin levels to be 59 % in our gangrenous/perforated appendicitis group.

In a series of 472 patients having undergone appendectomies, Emmanuel et al. stated that hyperbilirubinemia had a specifity of 88 % and a positive predictive value (PPV) of 91 % for acute appendicitis, and a specifity of 70 % for gangrenous/perforated appendicitis, also revealing that bilirubin levels were higher in the latter group ($p < 0.01$) [2]. Sand et al. determined that hyperbilirubinemia had a specifity of 86 % for appendiceal perforation or gangrene, compared with a specifity of only 35 % for CRP [24]. Adams et al. evaluated 557 patients having undergone emergency appendectomies, and reported that despite being within normal serum range, bilirubin levels were significantly higher in the appendicitis group. Additionally, although bilirubin was higher in patients with a perforated appendicitis, they found no statistically significant difference

between perforated and non-perforated appendicitis cases ($p > 0.05$). However, according to their results, the specifity of hyperbilirubinemia for perforated appendicitis was 93 %, sensitivity 9 %, PPV 24 %, and NPV 82 %. Although they concluded that hyperbilirubinemia was highly specific with regard to perforation, possibly because of few perforated cases in their study, they could not definitely recommend hyperbilirubinemia to be used to predict perforation [25].

In the present study, median values for total bilirubin were determined as 0.34 mg/dL in the normal appendix group, and 0.57 mg/dL in the acute appendicitis group, and despite being elevated in the acute appendicitis group, both values were in normal serum range reflecting no significant differences ($p > 0.05$). Although the comparisons of CRP, and total bilirubin levels between negative and positive appendectomy cases did not reveal statistical significance ($p > 0.05$), these parameters were significantly higher in the gangrenous/perforated appendicitis group than the other two groups of patients ($p < 0.01$, and $p < 0.01$, respectively). 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 %], and 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 %] greater risk for appendiceal gangrene/perforation ($p < 0.01$, and $p < 0.05$, respectively).

Despite numerous studies evaluating the predictive role of total bilirubin levels for acute appendicitis cases [19–25], no studies investigating the significance of direct and indirect bilirubin levels for this subject have been detected in the literature so far. The assessment of direct bilirubin levels, which is considered to represent the novelty of our study, revealed significantly elevated values in patients with either acute non-complicated, or gangrenous/perforated appendicitis ($p < 0.01$). According to multivariate statistical analysis, elevated direct bilirubin levels were associated with 36 times greater risk for appendiceal gangrene/perforation [$p = 0.001$, OR: 35.51, 95 % CI: 4.38–287.96, PPV: 49.4 %, NPV: 98.8 %, Specifity: 66.1 %, Sensitivity: 97.6 %] ($p < 0.01$). However, 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 %] ($p > 0.05$).

The utilization of clinical examination, radiological evaluations, and laboratory tests including white blood cell count, C-reactive protein levels, and bilirubin levels can assist in the diagnosis of acute appendicitis [2, 9]. Serum total/direct bilirubin estimation, which is a simple, cheap, and easily available test in every laboratory, can be added to the routine investigation list of clinically suspected cases of acute appendicitis for the prediction of possible appendiceal gangrene or perforation.

Conclusions

Hyperbilirubinemia, especially with elevated direct bilirubin levels, may be considered as an important marker for the prediction of appendiceal gangrene/perforation. Bilirubin levels may be routinely included in the assessment of patients with suspected acute appendicitis.

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Compliance with ethical standards

Conflict of interest Tunc Eren, MD; Ercument Tombalak, MD; Ibrahim Ali Ozemir, MD; Metin Leblebici, MD; Sedat Ziyade, MD, Associate Professor of Thoracic Surgery; Ozgur Ekinci, MD; Orhan Alimoglu, MD, Professor of General Surgery declare that they have no conflict of interest. Additionally, all authors declare that no source of funding exists, and that they have no direct or indirect commercial financial incentive associated with publishing this article.

Ethical approval Approval for this study was obtained from the Ethics Committee of Istanbul Medeniyet University School of Medicine, and signed informed consent forms were obtained from all patients. Each author hereby acknowledges that the final state of this manuscript is prepared and sent with his approval having been taken.

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