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Hyperbilirubinaemia in Predicting Perforated Appendices in Emergency Settings

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AM, MMA, MAA, NTA and AKD wrote the protocol, wrote the first draft of the manuscript, managed the analyses of the study and managed the literature searches. Authors MMA, MAA, NTA and AKD did the data collection, designed the study and performed the statistical analysis. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Introduction: Appendicitis is the most common abdominal emergency worldwide. Many standard laboratory tests are used to diagnose appendicitis, but there are no specific indicators. Some studies suggested that hyperbilirubinaemia correlates with appendiceal perforation. The objective of this study is to review the bilirubin level in patients with acute appendicitis (non-perforated appendix) and in those with a perforated appendix, to assess the efficacy of using the bilirubin level to predict if patients will have a perforated appendix.

Patients and Methods: This is a retrospective study of 269 patients who had undergone appendectomy from June 2008 to September 2016 in King Abdul Aziz University Hospital. These cases were classified histologically as acute non-perforated appendicitis and perforated or gangrenous appendicitis. The bilirubin levels of the two groups were compared in terms of the mean, sensitivity, and specificity.

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Results: Thirty-six out of 269 patients (13.4%) had perforated appendix; within this group, 23 patients (63.9%) had hyperbilirubinaemia with a mean of 21.38 µmol/l. The sensitivity and specificity of hyperbilirubinaemia in those with perforated appendicitis ere 63.88% and 81.1%, respectively.

Conclusions: Acute appendicitis is a clinical diagnosis, that must be supported by laboratory investigations. In addition to the clinical presentation and other laboratory investigations, the serum bilirubin level is an important indicator in predicting the presence of a perforated appendix.

Keywords: Non-perforated appendicitis; perforated; hyperbilirubinaemia.

1. INTRODUCTION

Acute appendicitis is the most common reason for performing abdominal surgery worldwide, and it most frequently occurs in the second or third decade of life [1]. The appendix lies in the right lower quadrant of the abdomen [2]. The pathophysiology of acute appendicitis begins as an obstruction with continuous secretion of mucus into the intraluminal space, that leads to distension and multiplication of gram-negative bacteria. This distension leads to mucosal ischaemia, with progression to gangrene and perforation [3]. Even with advances in diagnostic methods, the investigation of acute appendicitis remains challenging for surgeons [4]. The preoperative diagnosis is mainly clinical and based on a thorough evaluation of the patient's history, as well as a physical examination. The clinical assessment should be supported by laboratory tests such as the white blood cell count and C-reactive protein level, but there are no specific laboratory indices [5].

Recently it was proposed that a high bilirubin level is potentially associated with a perforated or gangrenous appendix. Bilirubin may be a helpful laboratory test for predicting if patients will have a complicated appendicitis preoperatively [6-8]. In this study, we reviewed the bilirubin level in patients with acute appendicitis (non-perforated appendix) and those with a perforated appendix to assess the efficacy of the bilirubin level in predicting patients with perforated appendix.

2. PATIENTS AND METHODS

2.1 Ethical Considerations

Our study was approved by the Ethical Committee of King Abdul Aziz Hospital, which is affiliated with medical school of King Abdul Aziz University, Jeddah.

2.2 Patients and Procedures

This is a retrospective study of all appendectomies that were performed at King Abdul Aziz University Hospital from June 2008 to September 2016. Patients were identified using an existing database (Phoenix by Al Anaiah). We included appendectomy patients who had documented preoperative liver function tests and complete blood count. The histology of the removed appendix and the type of surgical approach were also considered. Hyperbilirubinaemia was defined as a bilirubin level greater than 17 µmol/l. Data on patient demographics, hospital progress, laboratory results, and operations were collected. The patients' records were made anonymous prior to analysis.

A total of 906 patients underwent an appendectomy during the study period, but only 269 patients were included. Patients were excluded if they did not have a liver function test on admission, had missing histological data or had a history of a chronic liver disease, or children below the age of 13 years.

The patients were divided into two groups according to the histological findings of the removed appendix. Group 1 Included patients with acute, non-perforated appendicitis and group 2 included patients with perforated or gangrenous appendix.

2.3 Statistical Analyses

The statistical analysis was performed using SPSS version 22. Means and ranges were determined using an independent samples T test. The distribution of age was analysed with a histogram, and the risk factors are presented as an odds ratio which are calculated using logistic regression. The mean bilirubin levels were compared between the two groups. The one-way analysis of variance (ANOVA) was used to assess whether the means of two groups were statistically different from each other. The chi-square test was used to explore the existence of a statistically significant relationship between the categorical variables. The sensitivity, specificity, optimal cut off point for bilirubin, Area under the

curve (AUC), CI levels of AUC and positive, negative predictive values of hyperbilirubinaemiaa in each group were calculated by ROC (receiver operating characteristics analysis). A P-value of <0.05 was considered statistically significant.

3. RESULTS

This study on 269 patients showed that, the peak of acute Appendicitis was between the age of 15 and 30 years, the age was ranging between 13 and 72 years; the mean age was 26.1 years (Fig. 1).

One hundred sixty-nine out of 269 patients (62.8%) were male, while 100 patients (37.2%) were female (Table 1).

Sixty-seven patients (approximately ¼) of the total sample size had high bilirubin level, while 202 patients had normal level.

Among the 36 patients with a perforated appendix, 23 (63.9%) had high bilirubin level, with a range of 18-88 µmol/l and a mean of 21.38 µmol/l (p<0.0001). Among the 233 patients with acute, non-perforated appendicitis, 44 (18.9%) had a high bilirubin level, with a range of 18-45 µmol/l and a mean of 12.50 µmol/l (p<0.0001) (Table 3).

Regarding other liver enzymes there wear no significant difference between the acute perforated appendicitis and acute, non-perforated appendix (Table 4).

The odds of a patient with hyperbilirubinaemia in perforated appendicitis was over 7.5 times higher than that of those with normal bilirubin (odds ratio [OR]: 7.59 P. Value : 0.002). The sensitivity of hyperbilirubinaemia in those with appendicitis was 63.88% and the specificity was 81.11% (Table 5).

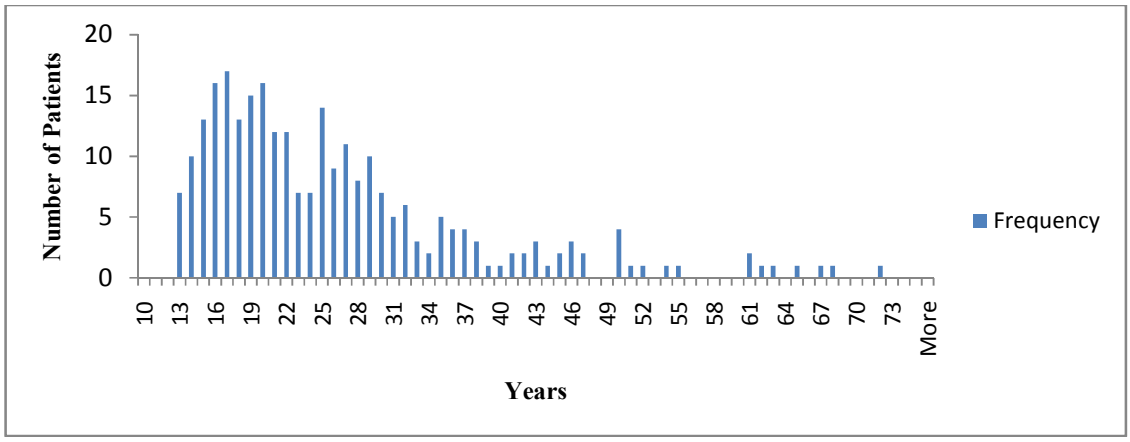

Fig. 1. Age distribution of both patients with a perforated appendix and acute non-perforated appendecitis

Table 1. Gender distribution of patients with a perforated Appendix and those with an acute, non-perforated appendix

	Perforated appendix	Acute appendix	Total	P. value
Male	31	138	169 (62.8%)	0.002
Female	5	95	100 (37.2%)	
Total	36 (13.4%)	233 (86.6%)	269 (100%)	

Table 2. Shows the appendiceal histology of the patients

	Number of patients	%
Perforated appendix	36	13.4
Acute, non-perforated appendix	233	86.6
Total	269	100

Table 3. The bilirubin level in patients with a perforated appendix and acute, non-perforated appendix

	Acute, Perforated appendix		Acute, non-perforated appendix		P. value
	Number of patients	%	Number of patients	%	
Normal bilirubin	13	36.1	189	81.1	<0.001
High bilirubin	23	63.9	44	18.9	
Total	36	100	233	100	

Table 4. The mean of the liver enzymes excluding bilirubin

	Acute, perforated appendix	Acute, non-perforated appendix	Overall	P. value
ALT	44.35	35.54	36.69	0.019
AST	26.45	21.58	22.22	0.041
ALP	108.38	115.58	114.60	0.559

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase

Table 5. The sensitivity and specificity of hyperbilirubinaemia in patients with perforated appendicitis

Sensitivity	63.88%	
Specificity	81.11%	P. value
Positive predictive value	34.32%	(<0.001)
Negative predictive value	93.56%	
Optimal Cut off point	17.5	
Area Under the Curve (AUC)	0.784	
Area Under the Curve CI	LB	UB
	0.717	0.852

CI: Confidence interval; LB: Lower Bound; UB: Upper Bound

One hundred sixty-four patients underwent open appendectomy (61%), while 105 (39%) patients underwent laparoscopic surgery.

4. DISCUSSION

Appendicitis is inflammation of the vermiform appendix, which is a wormlike structure delineated during the fifth month of gestation [9]. The base of the appendix is located at the posteromedial wall of the caecum, where the taeniae coli converge [10]. It is lined by the colonic epithelium [3].

Bilirubin is considered one of the indices to predict a perforated appendix, [11,12]. Bilirubin is produced by destruction of the haem products.

The incidence of Acute appendicitis is approximately 233/100,000 people and the highest is in patients aged 10 to 19 years, that occurs more frequently in the second and third decades of life than at other time points. In our study we found that the peak age of appendicitis was between 15 to 30 years. It was also higher among men than in women 1.69:1, that is a nearly similar to the published ratio (male to female ratio: 1.4:1) [13].

Acute, uncomplicated appendix is difficult to distinguish clinically from a perforated appendix, especially in elderly people and children. Perforation usually occurs due to a delayed diagnosis [14-16].

The most frequent cause of inflammation of appendicitis is obstruction of the lumen of the appendix by a fecolith in adults and lymphoid hyperplasia in children [17]. The lumen distal to the obstruction, develops increased intraluminal pressure. When it exceeds the venous pressure, the small venules and capillaries become thrombosed, leading to engorgement and congestion of the appendix. When the inflammatory process reaches the serosa of the appendix and the parietal peritoneum in this region produces the classical right iliac fossa pain. Therefore, when the small arterioles get thrombosed, the appendix becomes ischaemic, infarcted, and then gets perforated [18], bacteria leak through the necrosed walls, and pus forms within and around the appendix.

Bacteraemia and endotoxemia result in hyperbilirubinaemia, which could occur both in patients with acute, non-perforated appendicitis

and in those with perforated or gangrenous appendix. This occurs more frequently in the latter group, as seen in our study which showed that more patients with a perforated appendix had hyperbilirubinaemia (63.9%) than did those with acute, non-perforated appendicitis. Different studies have described the mechanisms that may explain hyperbilirubinaemia. *Escherichia coli*, which is considered the most common organism cultured from intraperitoneal fluid in those with appendicitis, is associated with endotoxin lipopolysaccharides [19,20]. Endotoxaemia causes decreased hepatic uptake and which result in increasing canalicular excretion of bilirubin, according to Roelofsen et al. and Bolder et al. [21,22]. Bacterial endotoxins produce cytokine-mediated inhibition of bile salt transport mechanisms, resulting in cholestasis [23,24],that both lead to hyperbilirubinaemia.

Classically, acute appendicitis is a migratory periumbilical pain to right iliac fossa. Patients with a perforated appendix may present with high fever and rectal fullness [25]. In addition to signs and symptoms of peritonitis, as reduced appetite, fever, nausea, thirst, vomiting, and chills [26].

The clinical picture of acute appendicitis can be straight forward but in most of cases, they come with vague signs and symptoms which fit a long list of differential diagnosis and the decision of surgery cannot depend only on clinical picture and should be supported by laboratory and imaging studies.

Many laboratory investigations are available to determine the inflammatory condition of the appendix , but there is no single, specific laboratory indicator to determine if the appendix is perforated or not [27]. Individually, these tests are weak and nonspecific discriminators, but have a high discriminatory power when they are combined with each other [27,28]. The white blood cell count and C-reactive protein level are usually used to evaluate suspected appendicitis, but their specificity differs among studies and may be only sufficiently elevated once appendiceal perforation occurs [29-31].

Studies had shown that hyperbilirubinaemia is a useful predictor of appendiceal perforation; their analysis ranged from sensitivity (60% to 77%), Specificity 70% to 87%), positive predictive value (21% to 45%) negative predictive value (92% to 96%) and cut off value (15 to 18 umol/l) [32-34]. Our study exhibited similar results; Sensitivity (63.88%) , Specificity (81.11%) and others are shown in Table 5. however, Beltran et al. did not find that hyperbilirubinaemia is a better predictor of perforation than C-reactive protein in their prospective study [35].

Diagnostic imaging has also been applied widely to diagnose acute appendicitis. Ultrasound is less expensive than other methods and saves time [36]. Multi-detector computed tomography is considered as a gold standard imaging method to diagnose suspected appendicitis because of its high sensitivity and specificity [37,38]. Magnetic resonance imaging has valuable diagnostic accuracy in the evaluation of acute appendicitis in children and pregnant patients [37,38]. The classical approved treatment of acute appendicitis is appendectomy either conventional or laparoscopically [39-41].

5. STRENGTHS AND LIMITATIONS

The limitation of our study is its nature as a retrospective and single-centre study, therefore, even with these limitations; we think these results can help to differentiate between patients with acute non-perforated appendicitis and those with a perforated appendix. We do recommend adding bilirubin level to the preoperative investigation list, we also recommend further prospective multi-centre studies on the efficacy of bilirubin level in predicting appendiceal perforation.

6. CONCLUSION

Appendicitis is a challenging surgical problem, that needs emergent surgical intervention. There is no specific laboratory work that could define perforated appendix, thus our study refers to high Bilirubin level combined with clinical signs of appendicitis may be an indicator of perforated appendix.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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