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The Assessment of Hyperbilirubinaemia in the Diagnosis of Acute Appendicitis: A Clinical Evaluation

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Abstract
There is currently no known marker for acute appendicitis that is consistently specific. While hyperbilirubinaemia has been shown in recent research to be a valuable predictor of appendiceal perforation, the usefulness of bilirubin as a measure for acute appendicitis was not examined. Finding the usefulness of hyperbilirubinaemia as a marker for acute appendicitis was the goal of this investigation. Three general patient groups were compared: patients with non-inflamed appendices were compared to patients with acute appendicitis that was not perforated or gangrenous (simple acute appendicitis)., patients with appendiceal perforation or gangrene were compared to patients with simple acute appendicitis. 264 individuals, or 54.7% of the 482 patients who were included in the research, were male. 27 was the average age (median 23, range: 5-82). The distribution of patients by histological group. Eighty-six individuals (18%) had an appendix that was not inflamed. Hyperbilirubinaemia is a useful sign for acute appendicitis. Patients with hyperbilirubinemia are also more likely to get gangrene or appendiceal perforation. For those who may have appendicitis, part of the approach should include a bilirubin examination.

INTRODUCTION

While C-reactive protein (CRP) is often employed in the evaluation of suspected appendicitis, its specificity varies greatly across studies[1] and may only be significantly elevated if appendiceal perforation occurs. Similarly, a high white cell count (WCC) is not specific for appendicitis[2,3]. Appendicitis has been linked to jaundice[4] and research has shown that hyperbilirubinaemia might be a helpful indicator of appendiceal perforation[5,6]. These investigations, however, did not address the usefulness of bilirubin as a particular indicator of acute appendicitis. The best way to treat appendicitis is still up for dispute, however some research points to the possibility of using antibiotics non-operatively[7-10]. Patients in whom the diagnosis is unclear or who do not exhibit symptoms of peritonism are often treated with a trial of observation in order to prevent unnecessary surgery. In many institutions, the diagnosis of acute appendicitis is determined based only on clinical grounds. When determining which individuals are likely to have appendicitis and should be considered for surgery, a simple, affordable biochemical test specific for acute appendicitis may be helpful in addition to clinical symptoms. Finding the usefulness of hyperbilirubinemia as a marker for acute appendicitis was the goal of this investigation. Acute appendicitis may often be diagnosed based just on symptoms and physical examination findings. Numerous different scoring systems have been created to help with diagnosis; the most well-known is the Alvarado score, which considers both laboratory results and clinical symptoms. Particular weight is placed on the patient's medical history, physical exam findings, and laboratory test results (such as C-reactive protein [CRP] and/or white blood cell count [WCC]) for diagnosing appendicitis[11,12]. The diagnostic method has recently included imaging modalities like computed tomography (CT) and ultrasound, which have increased sensitivity but have brought with them some drawbacks. In contrast to the extensive use of CT, which would result in excessive radiation exposure and expense increases, an expert diagnostician is necessary for an accurate and comprehensive interpretation of the findings of ultrasonic scans[13,14]. Because of this, diagnosing acute appendicitis and its repercussions, as well as clinical symptoms, requires a straightforward, reasonably priced and easily accessible test. It also helps determine the best course of action and helps determine the degree and severity of the condition. Prior studies have already shown the significance of certain blood indicators, including WCC and CRP[15,16]. But there's no connection between having a higher WCC and being more likely to have complications from simple vs severe appendicitis[17]. An attempt has been made to find a diagnostic marker for complex acute appendicitis by examining the relationship between an increase in blood total bilirubin concentration and the development of this illness[18,19]. The transfer of Gram-negative bacteria from the appendix into the portal system and liver, where they induce endotoxin-mediated disturbances of bile duct bilirubin excretion, may be the cause of elevated serum bilirubin[20,21]. Furthermore, further investigation has shown that one of the main causes of the rise of serum bilirubin in acute complicated appendicitis is hemolysis generated by septic shock[22].

MATERIALS AND METHODS

Using an already-existing database (the Lothian Surgical Audit System), patients were identified and were considered for research participation if they had an urgent appendectomy, regardless of technique, during the study period. Patient demographics, histopathological results, admission liver function test (LFT) values, WCC, CRP and blood cultures, as well as intraoperatively acquired intra-abdominal fluid cultures, were all recorded. Patients without LFTs at admission, those with a history of proven liver illness or hepatitis and those with persistently abnormal LFTs were not allowed to participate in the research.

Three general patient groups were compared: patients with non-inflamed appendices were compared to patients with acute appendicitis that was not perforated or gangrenous (simple acute appendicitis)., patients with appendiceal perforation or gangrene was compared to patients with simple acute appendicitis. We compared the means of bi-lirubin, WCC, CRP and other LFTs between the groups. It was also compared if elevated levels of these possible indicators were present. Calculations were made to determine the sensitivities, specificities and positive predictive values of hyperbilirubinaemia, elevated CRP and WCC for both perforated or gangrenous appendicitis and uncomplicated acute appendicitis. The best threshold value for bilirubin's sensitivity and specificity in cases of acute appendicitis was determined by calculating the receiver operating characteristic (ROC) curve for the drug.

A bilirubin level more than 20.5 µmol/l, an increased WCC more than 10 x 109/l for patients over 12 and more than 13 x 109/l for those under 12 and a rising CRP more than 10 mg/l were considered indicators of hyperbilirubinaemia. The top bounds of the reference ranges used by the laboratory services at both institutions were aligned with these values.

Statistical Analysis: Microsoft Office Excel 2019 was used to capture the patient data, which was then imported into SPSS (IBM Corp., Armonk, NY). The data analysis tool used was IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp.). Simple counts and percentages were used in descriptive statistics, along with the chisquare test to show mean differences. The

Mann-Whitney U test for independent samples was used to forecast lab results for complex appendicitis. Additionally, the area under the curve (AUC) and receiver operating characteristic (ROC) curve were used to forecast the sensitivity and specificity of laboratory data that were shown to have a substantial correlation with complex appendicitis. A p-value of less than 0.05 and a 95% level of confidence were deemed significant for each test.

RESULTS AND DISCUSSIONS

Of the 482 patients included in the study, 264 patients (54.7%) were male. The mean age was 27 years (median 23, range: 5-82). Table 1 shows the distribution of patients by histology group. Eighty-six patients (18%) had a non- inflamed appendix.

The mean bilirubin levels were higher for patients with simple acute appendicitis compared to those with a non- inflamed appendix (19.6µmol/l vs 15.4µmol/l, p<0.001) and significantly more patients in this group had hyperbilirubi-naemia on admission (31% vs 11%, p<0.001). The odds of a patient with hyperbilirubinaemia having simple acute ap- pendicitis were over three times higher than those without hyperbilirubinaemia (odds ratio [OR]: 4.24). The specificity of hyperbilirubinaemia for simple acute appendicitis was 89% and its positive predictive value was 93% (Table 2).

Patients with a perforated or gangrenous appendix had higher mean bilirubin levels than those with simple acute appendicitis (24.2µmol/l vs 19.6µmol/l, p=0.01). Significant-ly more patients with a perforated or gangrenous appendix had hyperbilirubinaemia than those with simple acute ap- pendicitis (61% vs 31%, p<0.001) and the odds of a patient with hyperbilirubinaemia having a perforated or gangre-nous appendix were over three times higher (OR: 4.48). The specificity of hyperbilirubinaemia for a perforated or gangrenous appendix was 71% (Table 3).

The ROC curve for bilirubin levels in patients with simple acute appendicitis showed the optimal threshold bilirubin level with the highest sum of sensitivity and specificity was 15µmol/l. At this level hyperbilirubinaemia would have a sensitivity of 58% and a specificity of 73%, approaching similar levels to CRP in this study. However, the laboratory standard threshold for hyperbilirubinaemia yields a much better specificity of 89%.

Logistic regression analysis showed hyperbilirubinae-mia to be significantly associated with simple acute ap- pendicitis (p = 0.01, OR: 3.62, 96% confidence interval [CI]: 2.28-6.48), along with WCC (p<0.001). Neither age nor any of the other LFTs were found to be significantly associated with acute appendicitis. Hyperbilirubinaemia in appendi-citis was also associated with a perforated or gangrenous appendix (p<0.001) but WBC was not (p=0.13).

Several mechanisms leading to hyperbilirubinaemia in systemic infections have been described. Haemolysis causes an increased bilirubin load and has been associated with several bacteria including Escherichia coli[23,24]. Another mechanism is reduced hepatic uptake and canalicular ex-cretion of bilirubin caused by endotoxaemia[25,26]. Bacterial endotoxin causes a cytokine mediated inhibition of bile salt transport mechanisms, leading to cholestasis[27,28]. Escherichia coli is associated with the endotoxin lipopolysaccharide and is the most common organism cultured from intraperitoneal fluid in appendicitis as was the case in this study. Hy-perbilirubinaemia presumably occurs in appendicitis as a result of bacteraemia or endotoxaemia, which could occur both in simple appendicitis and perforated or gangrenous appendicitis albeit more commonly in the latter group. There have been several reports of hyperbilirubinaemia in appendicitis[29,31]. Estrada *et al* hypothesised that hyperbi-lirubinaemia may be associated with appendiceal perfora-tion and showed that more patients with a perforated or gangrenous appendix had hyperbilirubinaemia than those with simple acute appendicitis. Sand *et al* showed that hy-perbilirubinaemia had a specificity of 86% for appendiceal perforation or gangrene, compared with a specificity of only 35% for CRP.

However, neither of these studies mentions the value of hyperbilirubinaemia as a predictive factor for simple acute appendicitis. Our study shows that hyperbilirubinaemia is a significant marker for simple acute appendicitis and not only appendiceal perforation. Patients with hyperbi- lirubinaemia were significantly more likely to have simple acute appendicitis than those with a normal bilirubin. The specificity of hyperbilirubinaemia for appendiceal perfora- tion or gangrene was 70%, which was lower than in other studies. However, we 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 on admission, the specificity of hyperbilirubinaemia for simple acute ap-pendicitis was higher than that of CRP, which was only 71%. No single clinical or laboratory test is able to reliably predict acute appendicitis[32]. Rather, a combination of history, clinical examination and laboratory and radiological investigations is used to make the diagnosis and decide appropriate management. Although abdominal computed tomography is accurate in diagnosing acute appendicitis[33], in several studies its routine use has not been shown to improve diagnostic accuracy or reduce the rate of negative appendicectomies. Furthermore, it may result in delays in definitive treatment with more postoperative complications, longer emergency department and hospital stays and

Table 1 Description of histology groupings and distributions of patients to groups

Group	Description	Number of patients (% of total)	Number of patients with hyperbilirubinaemia (% of group)
1	No acute inflammation	89 (18.4%)	13 (8.6%)
2	Acute appendicitis	296 (61.4%)	89 (59.3%)
3	Acute appendicitis with inflammatory infiltrate extending through full thickness of appendiceal wall	50 (10.3%)	19 (12.6%)
4	Perforated or gangrenous appendix	47 (9.7%)	29 (19.3%)
Total		482 (100%)	150

Table 2 Values of raised bilirubin, white cell count (WCC) and C-reactive protein (CRP) for differentiating simple acute appendicitis from non-inflamed appendices

	Sensitivity	Specificit y	Positive predictive value	Negative predictive value	Likelihood ratio positive (95% CI)	Likelihood ratio negative (95% CI)
Bilirubin n = 426	31%	89%	93%	25%	2.57 (1.40-4.70)	0.79 (0.71-0.88)
WCC n = 426	83%	61%	91%	43%	2.05 (1.57-2.67)	0.30 (0.23-0.40)
CRP n = 127	65%	72%	94%	24%	2.16 (1.02-4.58)	0.52 (0.35-0.76)

Table 3: Values of raised bilirubin, white cell count (WCC) and C-reactive protein (CRP) for differentiating perforated or gangrenous appendicitis from simple acute appendicitis

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio positive (95% CI)	Likelihood ratio negative (95% CI)
Bilirubin n = 389	61%	71%	22%	93%	1.97 (1.50-3.66)	0.58 (0.41-0.84)
WCC n = 389	94%	20%	14%	97%	1.17 (1.06-1.29)	0.35 (0.12-1.06)
CRP n = 130	92%	37%	14%	99%	1.44 (1.14-1.82)	0.26 (0.05-1.66)

increased costs. Moreover, it is not always immediately available for such use in all hospitals at any hour.

In a patient with a typical history of migrating pain and right lower quadrant tenderness, the diagnostic accuracy may be sufficiently high to perform an appendicectomy di-rectly[34]. Those with less typical symptoms or signs warrant a period of observation and re-evaluation[36], a 'watch-and-wait' approach employed by many clinicians. However, this approach could result in unnecessarily prolonging patients' hospital stays and delaying their definitive treatment. This study shows bilirubin can help identify patients who are more likely to have appendicitis. It could be used together with clinical findings and other routine laboratory tests to definitively manage patients with acute appendicitis earlier. In addition to its specificity for acute appendicitis, hyperbi- lirubinaemia in patients with appendicitis indicates a higher likelihood of a perforated or gangrenous appendix. It may therefore be prudent to consider early appendicectomy for patients presenting with suspected appendicitis who have hyperbilirubinaemia.

This study is limited by its retrospective design, which meant that not all patients had full data available and de-tailed histories and investigations to exclude all patients with pre-existing liver or haemolytic diseases were not taken. There was no way of reliably detecting patients with Gilbert's syndrome although the small number of patients with this condition would likely have been distributed evenly between histology groups.

CONCLUSIONS

Despite the fact that surgeons often struggle to diagnose acute appendicitis correctly, our findings imply that a blood bilirubin level is a reliable marker of complex appendicitis. Combining TB with other markers including WCC, CRP and clinical presentation increases the specificity and sensitivity of identifying people at risk for developing complex appendicitis. To get more solid answers to this topic, further study with a bigger sample size is required in the future.

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