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Original research

Predictive value of abnormally raised serum bilirubin in acute appendicitis: A cohort study

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HIGHLIGHTS

- Bilirubin should not be used as an independent biomarker of complicated (gangrenous/perforated) appendicitis.
- Statistical analysis showed overall serum bilirubin levels were minimally related to histological grade of inflammation.
- However analysis of bilirubin regarding clinical normalcy resulted in low predictive accuracy for complicated appendicitis.

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ABSTRACT

Appendicitis is a common clinical diagnosis aided by biochemical, haematological and radiological investigations. The role of some investigations, such as bilirubin, is controversial but could indicate complicated appendicitis. Accurate diagnosis enables prioritisation of patients on operating lists and a possible reduction in unnecessary investigations. **Methods**: This is a retrospective cohort study of 1347 patients who underwent appendicectomy. Statistical analysis of serum bilirubin levels was performed according to histological classification of appendicitis. **Results**: Mean serum bilirubin levels; perforated/gangrenous appendicitis 20.5 mg/L (SD 12.6), inflamed appendicitis mean 17.5 mg/L (SD CI 11.1), normal appendix mean 12.6 mg/L (7.0). Kruskal–Wallis indicated bilirubin levels were significantly different ($H = 128.87$, $df = 4$, $p < .001$) between histological groups, and a post hoc analysis with Bonferroni adjustment showed perforated/gangrenous to be significantly higher than all other groups ($p < .001$). Binary logistic regression combining White Cell Count (WCC) level, C-Reactive Protein (CRP) and Bilirubin levels gave a sensitivity and specificity of .69 with AUROC = .766 (std error .015) for gangrenous/perforated. Assessment according to clinical relevance showed only 30.4% of patients with an abnormally raised bilirubin had gangrenous/perforated appendicitis. **Conclusions**: Serum bilirubin does not independently predict perforation/gangrenous appendicitis. Statistical analysis showed differences in mean bilirubin between histological groups however this did not relate to clinical significance as bilirubin levels were still within normal clinical limits. Diagnosis of complicated appendicitis should be made on clinical grounds, with utilization of biochemical/haematological investigations, but there should not be independent reliance on investigations such as bilirubin.

1. Introduction

Appendicitis is a common presentation with the lifetime risk of appendicitis estimated at approximately 7% [1]. Currently preoperative diagnosis is a clinical diagnosis based on thorough history and clinical examination. The clinical assessment is supported by biochemical and haematological investigations such as White Cell Count (WCC) and C-Reactive Protein (CRP) and appropriate use of radiological investigations such as CT scanning and abdominal ultrasound.

Clearly accurate diagnosis is important, to not only prevent misdiagnosis and unnecessary surgery but also to differentiate simple acute appendicitis from a perforated or gangrenous appendix. Recent evidence from a large multicenter study [2] has suggested that patients with simple appendicitis can undergo short in-hospital waits prior to having their appendicectomy. However

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urgent surgery is still the treatment of choice for complicated (gangrenous/perforated) appendicitis due to the higher rate of co-morbidity and complications and the need to control the source of sepsis. It is therefore important to stratify patients into those with simple appendicitis who can undergo surgery at a safe opportunity and those with complicated appendicitis that require surgery more urgently.

There has been recent renewed interest in surgical literature regarding the use of biomarkers to predict clinical diagnosis and a number a studies including meta-analysis [3–14] have suggested that serum bilirubin levels may have a role in distinguishing simple acute appendicitis from a perforated or gangrenous appendix. If accurate, this would permit the prioritisation of patients with perforated appendicitis on operating lists. It may also reduce the number of unnecessary investigations, as patients would progress to theatre. The aim of this study is twofold, firstly to validate previous research with a large sample of UK based data and secondarily to assess if clinical normality of serum bilirubin has been taken into account when analyzing bilirubin samples and what this might mean for the predictive nature of serum bilirubin in complicated appendicitis.

2. Methods

2.1. Study design

This is a retrospective cohort study of all patients who underwent laparoscopic or open appendicectomy at the Great Western Hospital (GWH), Swindon over the period from January 2008 until September 2011.

2.2. Outcome variables

Primary outcomes were preoperative serum bilirubin levels and histology. Histological reports were analysed from computerized hospital records by three investigators AC, SB and HD with *a priori* definitions of grade of appendicitis. The histological grade of the appendix was recorded as normal, fibrosis (implying previous inflammation), pinworm (*Enterobius vermicularis*) infestation, inflamed, or gangrenous/perforated and other. Histological diagnoses that were recorded as 'other' included carcinoid, endometriosis or appendix removed as part of another operation. Any inconsistency regarding the histological report was discussed with another member of the data collection team and agreement on diagnosis made to ensure reduction in bias.

Secondary data collected included Sex, Age, Length of Stay, admission Serum WCC, Serum Neutrophil count and Serum CRP. All serum investigations were analysed from a computerized hospital record.

2.3. Statistical analysis

Comparison between histological groups was performed using the non-parametric Kruskal–Wallis test coupled with a Bonferroni corrected post hoc pairwise application of the Mann Whitney test. Binary logistic regression was used to investigate the potential predictive value of the serum markers and gangrenous/perforated appendicitis. The utility of these regression models was assessed by using ROC curves.

A missing values analysis showed that missing data on serum markers (Serum WCC, Serum Neutrophil Count, Serum CRP and Serum bilirubin) occurred with a frequency of less than 7% and these missing data occurred without any discernible pattern in a substantial data set ($N = 1298$). On this basis, analyses have been conducted on an available case basis (pairwise deletion) and data imputation avoided.

To assess the clinical utility of such biomarkers cross-tabulations were performed taking into account the normality of each biomarker. In the GWH abnormality in each biomarker is predefined as Bilirubin <18 mg/L, CRP >5 mg/dL and WCC >11 $\times 10^9$/L.

This cohort study has been completed and reported according to the STROBE statement (www.strobe-statement.org).

3. Results

This work retrospectively analysed 1347 patients who underwent either laparoscopic or open appendicectomy. Appendixes removed as part of other operations were excluded from our analysis. There were 49 patients excluded from analysis due to either incomplete data sets or if the appendicectomy was performed for another reason (e.g. right hemicolectomy for malignancy). Therefore 1298 patients were analysed. 750 patients were female and 548 male. Mean age was 33 years (SD ± 17). Data was initially analysed according to gross numerical value and then according to clinical significance with normal value of bilirubin as ≤18 mg/L as per the Great Western Hospital's usual practice. The distribution of histological diagnoses is shown below (Fig. 1) with the totals for each diagnosis included, as can be seen the predominant histological finding was inflamed followed by normal appendix.

3.1. Descriptive analysis

Mean values and standard deviations for all markers are set out in Table 1. These descriptive statistics are based on a minimum sample size of $N = 317$ for Normal, $N = 41$ for Fibrosis, $N = 19$ for Pinworm, $N = 500$ for Inflamed and $N = 267$ for Gangrenous/Perforated. Each serum marker showed a degree of positive skewness.

Analysis using the Kruskal–Wallis test indicated that the distributions of serum bilirubin levels were not identical across all histology groups ($H = 128.87$, $df = 4$, $p < .001$). A pairwise post hoc application of the Mann Whitney test for bilirubin showed the median of inflamed to be significantly higher than histologically normal appendixes ($p < .001$), and median bilirubin for a gangrenous/perforated appendix was significantly higher than all others including the inflamed group ($p < .001$). A summary of the comparisons is given in Table 2.

3.2. Prediction of gangrenous/perforated appendicitis using binary logistic regression

Binary logistic regression was performed to measure the

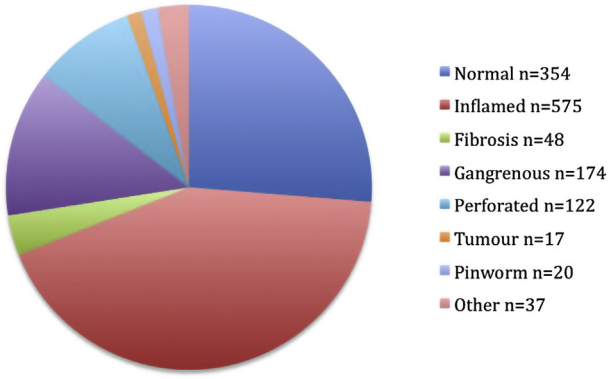

Fig. 1. Distribution of histological diagnoses of all resected appendixes.