

# Role of Hyperbilirubinaemia as a Predictor of Complicated Appendicitis in Paediatric Population

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## Abstract

**Background:** Acute appendicitis is a common surgical emergency amongst the paediatric population. Available diagnostic tools are focussed to make a diagnosis of acute appendicitis. A definitive predictive factor for the diagnosis of complicated appendicitis is lacking. Thus, this aims to analyse hyperbilirubinaemia as a predictor of complicated appendicitis amongst the paediatric population. **Materials and Methods:** A prospective observational study was conducted in a tertiary hospital from November 2018 to October 2019. All children undergoing emergency appendectomy were included in the study. Preoperatively, patients were evaluated clinically, and routine investigations including total and direct serum bilirubin were sent. All patients were grouped as 'simple appendicitis' or 'complicated appendicitis' based on intra-operative and histological findings. Bilirubin level was compared between these groups and analysed. **Results:** A total of 52 children fulfilling the inclusion criteria were included. The mean age was  $13.2 \pm 4.2$  years, and the male: female ratio was 2.1:1. Thirty-four (65.4%) had simple appendicitis and 18 (34.6%) had complicated appendicitis. Total bilirubin was  $23.83 \pm 5.94$  mmol/L in the complicated appendicitis group and  $13.15 \pm 3.29$  mmol/L in the simple appendicitis group. Direct bilirubin was  $5.28 \pm 2.22$  mmol/L in complicated appendicitis and  $2.62 \pm 0.83$  mmol/L in simple one. Both total and direct bilirubin were significantly high in the complicated group ( $P < 0.001$ ) compared to the simple appendicitis group. On the Receiver operating curve (ROC), the best cutoff value for total and direct bilirubin was 21 and 5.5 mmol/L, respectively. The sensitivity and specificity of total and direct bilirubin were 72.2%, 100%, and 61.1%, and 85.3%, respectively. **Conclusion:** It is concluded that hyperbilirubinaemia is a good predictor for paediatric complicated appendicitis.

**Keywords:** Complicated Appendicitis, hyperbilirubinaemia, predictor

## INTRODUCTION

Acute appendicitis is a common abdominal surgical problem in the paediatric age group. Approximately 33% of children with appendicitis may present without typical features of abdominal pain or localised right lower quadrant pain with nausea and vomiting and along with delayed presentation predispose to complicated appendicitis, particularly amongst young children.<sup>[1-3]</sup> Complicated appendicitis encompasses perforated and gangrenous appendicitis secondary to infection of the appendix, all of which increases morbidity associated with this entity.<sup>[4,5]</sup> The risk of perforation increases with delayed diagnosis and often the delayed presentation in the setting of a developing country including Nepal is one of the major attributable causes. In a study by Rothrock and Pagane

amongst children of age group 5–12 years, the perforation rate was 7% if the diagnosis is made within 24 h and was 98% if delayed beyond 48 h.<sup>[6]</sup>

Different scoring systems are used to diagnose appendicitis. Modified Alvarado scoring for paediatrics and paediatric appendicitis score for appendicitis are specially designed for the paediatric age group.<sup>[7,8]</sup> These scoring systems consider symptoms and signs along with leucocytosis and have been proven useful to diagnose appendicitis. However, prediction of

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complicated appendicitis before surgery is yet to be discovered and no specific blood parameter to be reflective of complicated appendicitis.<sup>[5,9]</sup>

Secondary bacteraemia or endotoxaemia causing impaired excretion of bilirubin from the bile canaliculi in the setting of underlying overwhelming infection can be the possible mechanism explaining hyperbilirubinaemia in complicated appendicitis.<sup>[10]</sup> Estrada *et al.* hypothesised that hyperbilirubinaemia may be a specific marker for gangrenous or perforated appendicitis.<sup>[11]</sup> However, there are only a few studies in the literature that describe the finding of hyperbilirubinaemia in patients with complicated appendicitis. Therefore, considering hyperbilirubinaemia as one of the factors to detect complicated appendicitis in the paediatric group before surgical intervention, this study was conducted to analyse serum bilirubin as a predictor of complicated appendicitis in children.

## MATERIALS AND METHODS

This was a prospective, single-centre observational study conducted in the Pediatric Surgery Unit of Tribhuvan University Teaching Hospital, Kathmandu, Nepal, over a period of 1 year from November 2017 to October 2018. Ethical approval was taken from the ‘Institutional Review Board’ of the Institute of Medicine. Written informed consent was obtained from the parents of every paediatric patient.

All children diagnosed with acute appendicitis under the age of 16 were evaluated for eligibility in the study. Patients with an appendicular lump, appendicular abscess, diagnosed patients of liver disease, typhoid patients and patients on hepatotoxic drugs such as rifampicin, chlorpromazine and chemotherapeutic drugs were excluded. Diagnosis of acute appendicitis was made by a surgery on-duty doctor in an emergency. They were subjected to investigations to support the diagnosis. Investigations include complete blood count, liver function tests and renal function tests. Ultrasonography of the abdomen was performed in all patients diagnosed to have acute appendicitis. Open appendectomy was performed once the diagnosis was established.

Complicated appendicitis was defined as a gangrenous appendix or perforated appendix on gross finding or on histopathological examination. Others were termed as simple appendicitis. All patients were grouped as either ‘complicated appendicitis group’ or ‘simple appendicitis group’ based on the aforementioned criteria. Comparison of bilirubin level was done between complicated appendicitis and simple appendicitis groups to identify its predictive significance.

Statistical analysis was performed by SPSS for Windows, version 25 (IBM, Chicago, Illinois, USA). The continuous variable was presented as mean  $\pm$  standard deviation, and categorical variables are presented as absolute numbers and percentages. Student’s *t*-test was performed for continuous variables and a Chi-square test was performed for categorical

value to test the significance. Sensitivity, specificity, positive predictive value and negative predictive value of hyperbilirubinaemia were calculated. A receiver operating characteristic (ROC) was created to assess the overall performance bilirubin level for diagnosing complicated appendicitis. A *P* < 0.05 was considered statistically significant.

## RESULTS

During the study period, 54 children were diagnosed with acute appendicitis and operated on. Two patients were excluded from the study as one patient had associated liver abscess and the other was receiving antitubercular therapy. Finally, 52 patients were included in the final analysis. The result of this study revealed that the mean age was 13.2 years, and the majority was male (67.3%). Other demographic profiles of the patients are mentioned in Table 1.

Out of 52 patients, 34 (65.4%) had simple appendicitis and 18 (34.6%) had complicated appendicitis. The gangrenous appendix was found in 13 patients, and perforation was present in five patients of the complicated appendicitis group. Total bilirubin and direct bilirubin were significantly elevated in the complicated appendicitis group [Table 2].

Overall performance of total and direct bilirubin was calculated using the receiver operating curve as shown in Figure 1. The area under the curve was 0.876 for total bilirubin and 0.791 for direct bilirubin. At the cutoff level of 21 mmol/L of total bilirubin and 5.5 mmol/L of direct bilirubin, the diagnostic value was maximum. In 72.2% of complicated appendicitis, total bilirubin was more than 21 mmol/L and in 61.1% of complicated appendicitis, direct bilirubin was more than 5.5 mmol/L [Tables 3 and 4]. Sensitivity, specificity, positive predictive value and negative predictive values are shown in Table 5.

## DISCUSSION

Appendicitis often tends to have a severe form amongst children, and they are at higher risk of having complicated appendicitis.<sup>[12]</sup> On laparotomy, perforation could be present in as high as 30%–75% of children.<sup>[13]</sup> Thus, an accurate and early diagnosis of acute appendicitis is crucial to prevent

**Table 1: Demographic characteristics of the included patients**

Characteristics	Frequency
Age (years), SD	13.2
Sex (male:female)	67.3:32.7
Duration of symptoms (days), SD	2.1
Fever	72.6
Vomiting	66.8
Total leucocytes	13,200
Neutrophils (%)	83
Weight or any other variables	29.2

SD: Standard deviation

**Table 2: Total and direct bilirubin in simple and complicated appendicitis group**

Variable (in mmol/L)	Total patients (n=52)	Simple appendicitis group (n=34)	Complicated appendicitis group (n=18)	P
Total bilirubin	16.85±6.91	13.15±3.29	23.83±5.94	<0.001
Direct bilirubin	3.54±2.03	2.62±0.83	5.28±2.22	<0.001

**Table 3: Distribution of total bilirubin in simple and complicated appendicitis**

Bilirubin(mmol/L)	Simple appendicitis	Complicated appendicitis	Total
Total bilirubin (≥21)	0	13	13
Total bilirubin (<20)	34	5	39
Total	34	18	52

**Table 4: Distribution of direct bilirubin in simple and complicated appendicitis**

Bilirubin(mmol/L)	Simple appendicitis	Complicated appendicitis	Total
Direct bilirubin (≥4)	5	11	16
Direct bilirubin (<4)	29	7	36
Total	34	18	52

**Table 5: Sensitivity, specificity, positive and negative predictive value of bilirubin**

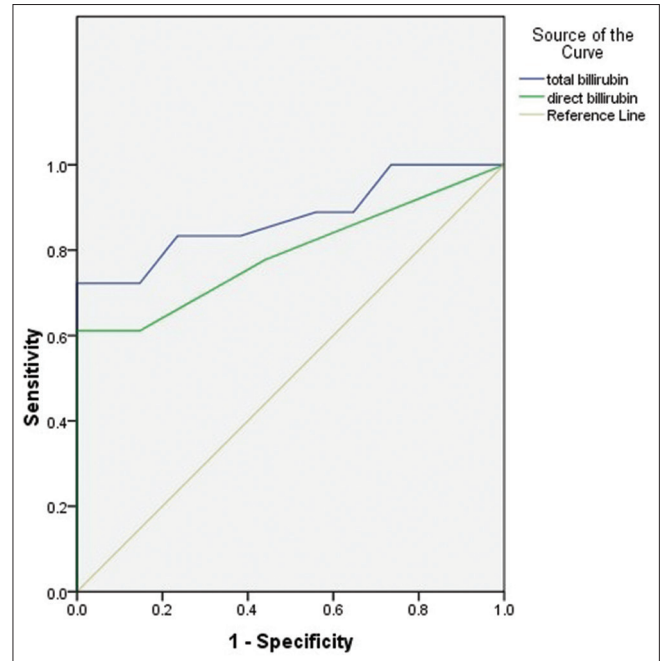
	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
Total	21	72.2	100	100	87.2	90.4
Direct	5.5	61.1	100	100	82.9	86.5

PPV: Positive predictive value, NPV: Negative predictive value

complications such as perforation and gangrene which increases morbidity and mortality. However, there is no single clinical or laboratory test that is able to reliably predict complicated appendicitis at an early stage. Surgeons may practice the 'wait and watch approach' for less typical symptoms which increases hospital stay and probably delay in treatment predisposing to causing more morbidity and mortality.

During appendicitis, the wall of the appendix becomes compromised and leads to the translocation of bacteria and endotoxins from the lumen into the portal system. Inflammatory cytokines may then travel to the liver, inducing intrahepatic cholestasis which forms the basis for hyperbilirubinaemia in appendicitis along with the probable mechanism mentioned previously.<sup>[14]</sup>

Leucocytosis and C-reactive protein (CRP) are widely used as markers for the early diagnosis of complicated appendicitis. The sensitivity and specificity of these markers are varied markedly in different studies.<sup>[14-16]</sup> CRP has been widely used as a marker for appendicitis and its complications. Although, CRP has higher sensitivity but lower specificity to appendicitis as compared to bilirubin.<sup>[14,17]</sup> This warrants a safe, economic, rapid, widely available, accurate diagnostic marker for complicated appendicitis that would be useful to

**Figure 1: Receiver operating curve of total and direct bilirubin in diagnosing complicated appendicitis**

detect and manage at an early stage and potentially decrease the morbidity burden. The estimation of serum bilirubin can fulfil many such criteria and is being increasingly considered.

In this study, the mean total bilirubin was  $16.85 \pm 6.91$  mmol/L and direct bilirubin was  $3.54 \pm 2.03$  mmol/L. Mean total bilirubin was  $23.83 \pm 5.94$  in complicated appendicitis as compared to  $13.15 \pm 3.29$  mmol/L in simple appendicitis. Similarly, direct bilirubin was  $5.28 \pm 2.22$  in complicated appendicitis as compared to  $2.62 \pm 0.83$  mmol/L in simple appendicitis. Both levels were raised significantly in complicated appendicitis. Complicated appendicitis comprised two groups: gangrenous without perforation and perforated appendix. *Post hoc* test confirms a significant difference with both forms of complicated appendicitis ( $P < 0.001$ ), but the difference was not statistically significant between these two gangrenous groups ( $P = 0.105$ ).

Chaudhary *et al.* conducted a study amongst fifty patients with appendicitis, in which total bilirubin was raised in 38 (76%) cases, whereas 12 (24%) cases had normal levels. Total bilirubin was significantly elevated in gangrenous and perforated appendices than those with simple appendicitis ( $P < 0.001$ ).<sup>[10]</sup> Although the rise in bilirubin in complicated appendicitis is also seen in adults, the result is insignificant and inconsistent among various studies. However, Käser *et al.* showed that bilirubin was not a superior predictor of complicated

appendicitis in adults.<sup>[18]</sup> Furthermore, with sensitivity and specificity of hyperbilirubinaemia being only around 50%, and CRP and TLC were a better predictor of perforated appendicitis in adults, according to Beltran *et al.*<sup>[19]</sup>

In this study, hyperbilirubinaemia had high sensitivity and specificity for complicated appendicitis. Total bilirubin was more sensitive (72.2% vs. 61.1%) as compared to direct bilirubin as a predictor of complicated appendicitis. Total bilirubin also has higher accuracy (90.4%) as compared to direct bilirubin (76.95%). Emmanuel *et al.* described hyperbilirubinaemia as total bilirubin more than 20.5 mmol/L and sensitivity of 30% and specificity of 80%.<sup>[17]</sup> Khan also showed that hyperbilirubinaemia has sensitivity of 86.6% in appendicitis.<sup>[20]</sup> A similar study of Nomura *et al.* showed gangrenous appendicitis was more common in the high preoperative total bilirubin group ( $P < 0.001$ ).<sup>[21]</sup> In a study by Sand, rise in serum bilirubin with perforated/gangrenous appendix had sensitivity and specificity of hyperbilirubinaemia was 70% and 86%, respectively.<sup>[14]</sup>

The predictive value of serum bilirubin has been demonstrated by many studies. There is variation of optimal threshold value. A receiver operating characteristics (ROC) curve was drawn for both total and direct bilirubin level to find the best cutoff level, in which 21 mmol/L for total and 5.5 mmol/L for direct bilirubin were the cutoff level. The sensitivity and specificity for elevated bilirubin are variable amongst different studies with variable threshold values. The sensitivity varied from 38% to 77% and the specificity from 70% to 87% in our study. These findings are almost similar to other reported studies.<sup>[11,20]</sup>

A raised total serum bilirubin level is a good indicator of complicated acute appendicitis, whether it is gangrenous or perforated appendicitis. It indicates a complication of acute appendicitis requiring early intervention to prevent peritonitis and septicaemia. Thus, patients with hyperbilirubinaemia combined with symptoms and signs consistent with severe acute appendicitis should be considered for early appendectomy. The generalisability of this study might be herald by the small sample size, and thus findings should be interpreted with caution. However, this can form the pilot study and can be a cornerstone for larger similar studies.

## CONCLUSION

Serum bilirubin estimation is a simple, cheap and easily available, reproducible investigation. Serum bilirubin is significantly raised in complicated appendicitis as compared to simple appendicitis and the total bilirubinaemia is more sensitive than direct bilirubinaemia in predicting a complicated appendicitis.

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## Conflicts of interest

There are no conflicts of interest.

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