


**Research Article**

## Hyperbilirubinemia as a Predictor of Perforated Appendicitis

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### Abstract

Appendicitis is the most common cause of surgical abdomen. Delay in the diagnosis and appropriate management may lead to potentially life-threatening complications. Bilirubin is associated with the assessment of the severity of appendicitis. The objective of the study is to determine the role of hyperbilirubinemia in predicting appendiceal perforation. An online search was conducted in PubMed, Google Scholar, and PubMed Central to find relevant publications relating to hyperbilirubinemia in perforated appendicitis. Only studies conducted on humans were included. Out of the 1287 articles found, only seven were included in our final review. Of the seven articles included in the review, hyperbilirubinemia is confirmed as a useful predictor for perforated appendicitis or a marker of the severity of appendicitis. Preoperative bilirubin levels can be used as a diagnostic tool in perforated.

**Keywords:** Appendicitis; Hyperbilirubinemia; Perforated Appendicitis

### Introduction

Appendicitis is the inflammation of the appendix. Across the world, Acute appendicitis is the most common cause of acute abdomen in the world [1]. Luminal obstruction of the appendix progresses to suppurative inflammation and perforation, which in turn causes generalised peritonitis or an appendix mass/abscess. Due to the varying degree of presenting symptoms, the diagnosis of acute appendicitis is not easy [2]. The Alvarado scoring system is most commonly used to method, of differentiating between acute appendicitis and other causes of acute abdomen however, this method of scoring cannot differentiate between acute appendicitis and uncomplicated appendicitis, nor does take bilirubin levels into consideration [3,4]. There is no definite marker for impending appendiceal perforation. Many studies however have shown promising results when considering hyperbilirubinemia as a predictor of appendiceal perforation [5,6]. Hyperbilirubinemia is witnessed in septic patients, due to endotoxemia causing impaired drainage of bile into the bile canaliculi. This could occur in both- simple appendicitis and perforated or gangrenous appendicitis. Escherichia coli, also known as E.coli and Bacteroides are the most common isolates from the appendix [7]. It is hypothesised that bacterial endotoxin causes cytokine mediated inhibition of bile transport mechanisms, which leads to cholestasis [8]. In many health care facilities, acute appendicitis without any of the classic signs and symptoms- pain in the right lower abdominal quadrant, loss of appetite, nausea and vomiting, fever, inability to pass gas, and peritonism, is managed conservatively with antibiotics, and surgery is deferred. It is deferred which may later on progress to complicated appendicitis. Hence a simple investigation such as total bilirubin which comes under routine blood investigation panel

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may help the surgeon to decide if surgery is warranted for a case rather than to manage conservatively. The aim of the study the find the role of hyperbilirubinemia in predicting the appendiceal perforation

## Methods

PubMed, PubMed Central, and Google Scholar online databases were exclusively used for purposes of collecting corresponding data. Keywords such as ‘perforated appendicitis’ and ‘hyperbilirubinemia’ were used separately and in combination. In addition, MeSH search terms ‘perforated appendicitis’ and ‘hyperbilirubinemia’ were used to collect all relevant data. Study types in this review include retrospective studies, case-control and systematic review studies. No grey literature was included. Of the 1,287 scientific papers yielded, specific inclusion and exclusion criteria were applied, yielding 7 scientific papers which were included in our final review. Of those 7 papers, all met the quality specifications and were peer reviewed.

## Inclusion and exclusion criteria

All scientific papers were written in English and included data collected and reviewed from 2010 to 2020. The included scientific papers contain data collected from large sample sizes in a particular geographic area. Only studies conducted

on humans were included. And studies which compared hyperbilirubinemia between appendicitis and no appendicitis were not included. All the papers included patients admitted in the emergency ward who were clinically suspicious of appendicitis and, intraoperatively and histopathologically were confirmed to be appendicitis. And excluded all patients with liver disease, hepatitis, and haemolytic anaemia, abdominal trauma injury. The results of these studies were statistically analysed values with estimates of sensitivity, specificity, positive predictive value, negative predictive value or with univariate/multivariate analysis.

## Results

All the patients included in the study underwent appendectomy which was later on was confirmed with histopathological examination. In all the nine studies, hyperbilirubinemia is confirmed as a useful predictor for perforated appendicitis, or, as a marker of the severity of the appendicitis. In two studies, it is concluded that hyperbilirubinemia along with CRP levels, combined, is a better indicator of the severity of appendicitis than hyperbilirubinemia alone [9,10]. One systematic review by Burchart et al., points out that elevated serum bilirubin levels has a low sensitivity and a high specificity and hence therefore can be used as a supplemental indicator tool in

Table 1: Results of keyword searches

Key words	PubMed	PubMed central	Google scholar
Perforated appendicitis	2,480	1,524	57,500
hyperbilirubinemia	3,144	2,036	1,14,000
Perforated appendicitis and hyperbilirubinemia	22	5	1,260

Table 2: Organizes the studies used and their conclusion, which met the inclusion criteria.

Study	Location	Study period	Samples	Conclusion
Khan et al. [14]	India	2012-2014	100 samples of appendicitis, of which 44 were perforated appendicitis	Serum bilirubin appears to a new promising laboratory marker for perforation
Kumar et al. [9]	India	2013-2016	200 samples of appendicitis of which 92 were perforated appendicitis	CRP and Hyperbilirubinemia can be used to predict the appendicular perforation preoperatively and that their roles are comparable and there is no advantage one over the other
Akai et al. [10]	Japan	2010-2017	318 samples of appendicitis of which 134 were complicated appendicitis	Hyperbilirubinemia, high CRP levels and fever may be useful predictors of severity of acute appendicitis
Burcharth, et al. (systematic review) [11]	Denmark		2,243 patients from 5 studies	Serum bilirubin can be used as a supplemental diagnostic tool in perforated appendicitis
Vaziri, et al. [15]	Iran	2010-2012	80 patients of which 40 were perforated appendicitis	Hyperbilirubinemia in patients with appendicitis indicates a higher likelihood of a perforated appendix
Zejnnullahu et al. [12]	Kosovo	2016-2018	201 patients of which 136 were complicated appendicitis	Combination of total and direct bilirubin can improve clinical diagnosis and classify patients with acute need for surgery
Hong et al. [13]	South Korea	2009-2010	1,195 samples of appendicitis of which 197 were perforated appendicitis	Hyperbilirubinemia is useful in deciding to operate and in diagnosing the severity of the disease.

the diagnostic process [11]. Two other studies conducted in South Korea and Kosovo, concluded that elevated serum bilirubin levels can help to classify patients on the basis of severity of appendicitis, and help in the decision to operate on the affected patient or manage this patient conservatively.

## Discussion

Acute appendicitis can be treated by either appendicectomy or by conservative management. Complicated appendicitis, whether perforated or gangrenous, may lead to complications such as bacterial peritonitis, urinary disorders, or intra-abdominal abscess formation, which can lead to life threatening conditions [16]. Thus, earlier the diagnosis of a perforated appendix, better is the outcome, and hence makes the surgeon to take a decision to operate early and prevent complications. Even after the advent and use of ultrasonography and computed tomography, the rate of misdiagnosis of appendicitis and appendiceal perforation has remained the same [17]. In addition, the radiological investigations have a lot of disadvantages which includes high cost, exposure to radiation, operator dependency, availability, allergy to contrast and also delays the time to intervene surgically. Also, WBC and C- reactive protein have been found out to be sensitive blood investigation, but with low specificity [18,19]. As shown by Kalliakmanis et al, reliable diagnosis of appendicitis can be made with just physical examination and laboratory testing, without the use of sophisticated investigations [20]. Appendicitis presents with varied presentations and those with mild signs and symptoms are usually placed on conservative protocol or under observation by many practitioners. However, this method delays the appropriate management and therefore extends the hospital stay. There are many studies on hyperbilirubinemia in appendicitis [3-13], which are listed on the table above. Among which, the largest study is the study by Burchart et al, a systematic review and includes around 2,243 patients of appendicitis collected from five papers, which concluded that hyperbilirubinemia can be used a supplemental diagnostic tool in the diagnosis of perforated appendicitis. Inflammation associated with appendicitis leads to mucosal ulceration and infiltration by bacteria found native to the appendix [21]. *Escherichia coli*, also known as *E.coli* and *Bacteroides* are the most common isolates from the appendix along with the aid of their endotoxins reach the liver after ulceration causing bacteraemia/sepsis which might occur in both appendicitis and perforated appendicitis but more common in the latter [7]. The development of jaundice in sepsis is known to be caused by various different bacteria, the most common being gram-negative bacteria [22]. Various different mechanisms have been described in the development of hyperbilirubinemia in sepsis [23]. Haemolysis of red blood cells causes an increased bilirubin production which is associated with several bacteria, including *E.coli*. Endotoxemia causes

reduced hepatic uptake and canalicular excretion of bilirubin. Endotoxemia is also associated with cytokine mediated inhibition of bile salt transport mechanisms, which in turn leads to cholestasis. In all the seven studies selected for this review, hyperbilirubinemia appears to be a useful predictor of a appendiceal perforation. In a study conducted by Hong et al., in a South Korean study comprised of a sample size of 1,195 in addition to the presence of hyperbilirubinemia, SIRS score also proved to be a useful predictor of appendiceal perforation [13].

## Conclusion

In conclusion pre-operative bilirubin levels can be used as a diagnostic tool in perforated appendicitis cases. Hyperbilirubinemia along with clinical signs, symptoms and other routine bloodwork can help aid surgeons in making better decisions in management and the need for surgery. Further studies are needed to develop a scoring system in order to incorporate bilirubin levels along with CRP and WBC levels in the assessment of the severity of the appendicitis, which would be useful in resource limited hospital settings.

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