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Relation and association between bilirubin level and complicated appendicitis

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Abstract
Appendicitis (AP) is an inflammation of the appendix that occurs typically when the lumen gets obstructed. If the inflammation persists it will lead to complications such as perforation, collection, and phlegmon. on clinical examination typical acute appendicitis presented with fever, tenderness in the Right iliac fossa. laboratory investigations can aid in diagnosis usually it is presented with leukocytosis and elevated ESR and CRP in cases of complicated appendicitis. serum of bilirubin showed to be increased in some cases so hyperbilirubinemia can be a predictor of the severity of acute AP. In this article review, the aim is to know the association between complicated AP and elevated total and direct bilirubin.

Keywords: complicated appendicitis, bilirubin level, ESR and CRP

Introduction
AP is a common cause of acute abdominal pain, approximately 7% of the population will have AP in their lifetime [1]. It's caused by an obstruction of the lumen, which leads to inflammation of the appendiceal wall. There are many causes of the obstruction such as fecalith, lymphoid hyperplasia, foreign bodies. This inflammation leads to patients presenting most commonly with abdominal pain that classically begins in the periumbilical region and migrates to the right lower quadrant in 50% of patients, anorexia, nausea, vomiting [2]. There are common signs of acute AP such as the psoas sign, rovsing's sign, obturator sign [3]. On laboratory evaluation white blood cells (WBC) and C-reactive protein are elevated and considered highly sensitive [4]. Ultrasonography (US), and computed tomographic (CT) scan are considered helpful in the diagnosis of AP. Measurement of greater than 6 mm in diameter is considered a sign of inflamed appendix [5]. CT can show Appendiceal wall thickening and wall enhancement after infusion of contrast media. Also, it can reveal peri-appendiceal inflammatory changes such as fat stranding, phlegmon, free fluid, free air [6]. Appendectomy whether laparoscopic or open is considered the Standard management of acute AP [7]. Untreated AP may lead to appendiceal rupture which accounts for a majority of the complications. A peri-appendiceal abscess is considered another type of complication [8]. In this article, we are reviewing published papers written on the association between complicated AP and elevated direct and total bilirubin.

Material and methods
A search on PubMed of the published readily accessible, peer-reviewed, full articles written in English was conducted on perforation of AP and elevated direct bilirubin. Most articles include retrospective, observational, single, or multicenter studies. Full articles written in English were conducted (between 1990 to 2021), about the association between complicated AP and elevated total and direct bilirubin. The pediatric age group was excluded from the review.

Result and Discussion
It is assumed that elevated serum bilirubin occurs due to portal sepsis or empyema resulting in liver hepatocytes dysfunction or damage. This is thought to be caused by bacterial endotoxins or cytokines. Furthermore, studies have shown that the increased load of bacteria in appendicitis causes either direct invasion to the hepatic parenchyma which interferes with the excretion of bilirubin or translocation into the portal venous system. The mechanism is postulated to be biochemical instead of obstructive. elevated levels of circulating proinflammatory cytokines such as TNF and/or IL-6 are reflective of the hyper-dynamic state of sepsis [9].
An observational study was published in 2021, it was conducted on 110 subjects diagnosed with acute AP, 41 subjects (37.27%) had hyperbilirubinemia. 35 subjects out of 110 had complicated AP (gangrenes/perforated), 32 (91.42%) of which had mixed type hyperbilirubinemia. 75 subjects with uncomplicated AP, 09(12%) had mixed hyperbilirubinemia. The mean direct bilirubin for uncomplicated Ap subjects was 0.43 ± 0.10 ml/dl, on the other hand, it was 0.72 ±0.13 ml/dl for complicated AP, and they concluded that it was statistically significant [10].

A retrospective review to decide whether hyperbilirubinemia is to be considered a predictor for the perforation of acute AP was also conducted on 170 subjects, 157 of which are histologically confirmed AA. Hyperbilirubinemia was found in 59(38%) subjects.116 subjects (74%) had evidence of suppurative AP 36 (31%) of them had hyperbilirubinemia, while 41 (26%) had gangrenous/perforated AA and 23(56%) of which had hyperbilirubinemia. They also found that direct bilirubin findings were identical to that of total bilirubin. Which led them to the conclusion that the odds of appendiceal perforation are three times higher in patients with hyperbilirubinemia [11].

Another retrospective review on the relation of perforated appendicitis with a direct bilirubin of the files of 258 subjects who underwent appendectomies. they had 208 (81%) subjects with uncomplicated AA and 50 (19%) had perforated AA. Their study displayed that direct bilirubin level was high in 17(8.17%) and seven (14%) of non-complicated and perforated AA, respectively. So they concluded that DB has a higher diagnostic value than TB [12].

Another retrospective study that was published in 2015 in the European Journal of trauma and emergency surgery on the medical files of 162 subjects was also performed. The histopathological result on 21(13%) of them was found to have a normal appendix, 100(62%) were found to have AA and 41(25%) were found to have gangrenous/perforated appendix. The aim of this study as well as the other studies on this article review is to find whether there is a relationship between elevated levels of direct bilirubin and perforated AP. On their final result it appeared that there was an elevation in 39% of direct bilirubin in non-complicated AA patients, and in 98% of patients with gangrenous/perforated AA which eventually revealed high diagnostic sensitivity and specificity [13].

A different study was done on a period of 2 years on 351 patients to compare the factors that could distinguish between an acute AP and complicated AP. It included many factors such as age, gender, neutrophils, CRP, and serum bilirubin level which is the target of this article review. 240 (69%) patients were diagnosed with simple AA, 85 (24%) were complicated and 26 (7%) had normal appendix. In their study, there was a significant difference in serum bilirubin level between simple and complicated AP and their values were 0.95 ± 0.4 and 1.24 ± 0.7, respectively [14].

Between 2010 and 2017 a retrospective study was conducted on 318 patients to investigate the clinical significance of hyperbilirubinemia in patients with AP, the patients were divided into two groups, complicated AP like perforated AP in 37(11.6%) of the patients and gangrenous appendicitis in 148 (46.5%)of the patient's AP and simple AP (phlegmon or catarrhal appendicitis), preoperative clinical factors were compared between these two groups, the result data showed that complicated AP was significantly frequent in patients with hyperbilirubinemia ($P = 0.014$) [15].

Furthermore, a prospective study was published in 2013, it was conducted on 80 subjects, on the comparison of preoperative bilirubin levels between patients with perforated AP (40 subjects) and simple AP (40 subjects). Data analyzes showed that the mean total bilirubin level was higher in patients with perforated AA compared to those with simple non-perforated AA (1.04±05 mg/dl vs 0.7±0.1 mg/dl) [16].

On the other hand, a retrospective study was published in 2011, conducting 351 subjects to investigate the role of hyperbilirubinemia as a marker of appendix perforation, subjects were divided into 3 groups based on clinical and histological findings, group 1: 49 (14.0%), 257 (73.2%) in group 2, and 45 (12.8%) in group 3. Histological findings in Group 1and 2 results described as intact intestinal mucosa, were in Groupe 3 result finding was perforated acute AP. Total bilirubin levels were significantly higher in group 3 in comparison with 1 and 2 [17].

493 analyzed patients on another 2-year timeframe study to check the diagnostic accuracy of hyperbilirubinemia in foreseeing AP and its severity. 312(64%) had non-perforated AP, while 56(11%) had perforated. Their final result was a positive-negative likelihood ratio for elevated bilirubin was limited in discriminating between the non-perforated versus perforated AP groups (LR+ estimate 1.74 (95% CI 1.28 to 2.38) and LR- 0.72 (95% CI 0.55 to 0.93) [18].

Another 2 years study was retrospectively conducted on the files of 557 that were eligible to be included in the study. A histologically confirmed diagnosis of acute AP was found in 413(74.1%), 137of them were complicated acute AP, and 276 had a simple acute AP. And they discovered that serum bilirubin levels were higher when there was a diagnosis of perforated AP in comparison with non-perforated [Median (IQR) 13.0 μmol/L (9.00) vs. 11.0 μmol/L (9.00), respectively], but not statistically significant [11].

174 patients were enrolled in a study to evaluate the diagnostic value of total bilirubin in a suspected acute AP case. The patients were divided into different types of complications based on their historical pathological findings and there was a significant difference between these groups in total(p=0.044) and direct bilirubin (p=0.032) levels, which was demonstrated by the ROC curve as a sensitivity of 48% and specificity of 61% for the prediction of the severity of AA [19].

Conclusion

After reading and reviewing the relation between bilirubin and perforated AP, we found that only two articles concluded that although there was a slight elevation in bilirubin level in acute AP whether complicated or not, the relation between bilirubin and perforated appendicitis was not clinically significant. On the other hand, eleven articles stated that there is a high association between hyperbilirubinemia and perforated acute AP. However, their analytical data regarding sensitivity and specificity were slightly variable. We suggest that bilirubin levels are to be highly considered during the evaluation of any suspected acute AP. This early investigation though timeless could be preventable of any unexpected further complication.

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