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Original Research Article

DIAGNOSTIC VALUE OF BILIRUBIN AS A PREDICTIVE FACTOR FOR APPENDICULAR PERFORATION

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ABSTRACT

BACKGROUND

In order to distinguish individuals with a difficult perforated appendicitis from those with an acute appendicitis that is not too complicated, there is a growing need for quick and safe markers. That is why the current study was conducted to see if a higher-than-normal bilirubin level may be used as a predictor of an appendicular perforation diagnosis.

METHODS

Between October 2021 and October 2022, 100 patients who had been hospitalised at Government Vellore Medical College and Hospital for acute appendicitis and were undergoing emergency appendectomy participated in a prospective, non-randomized observational study. A Microsoft Excel spreadsheet was used to total and analyse the data that was gathered. The odds ratio, sensitivity, specificity, positive predictive value, and negative predictive value were computed using a 2 x 2 table.

RESULTS

Of the 100 patients, 36% had an appendicular perforation and 64% had a clinical diagnosis of acute appendicitis. Out of the 36 patients who received an appendix perforation diagnosis, 24 had high bilirubin levels and 12 had normal bilirubin levels. The age range of 21 to 30 years old was the one where appendicular perforations were most common. Compared to just 16.7% of individuals with values <=1, appendicular perforation was seen in 85.7% of patients with total bilirubin >1 mg/dl. There was a statistically significant difference

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($p<0.001$). Total bilirubin had 83.3% and 85.7%, respectively, of sensitivity and specificity in predicting the diagnosis of acute appendicitis and appendicular perforation. Total bilirubin had a 93.7% positive predictive value for both the diagnosis of appendicitis and appendicular perforation. 66.7% was the negative predictive value. 86.2% of patients with direct bilirubin >0.3 mg/dl developed appendicular perforation, whereas only 15.5% of patients with levels between 0.1 and 0.3 mg/dl experienced this condition.

CONCLUSION

In addition to or instead of other biochemical and radiographic markers, serum bilirubin has the specificity and sensitivity to predict appendicular perforation.

KEY WORDS

Appendicular Perforation, Bilirubin, Hyperbilirubinemia

INTRODUCTION

Clinically, acute uncomplicated appendicitis and perforated appendicitis can be difficult to differentiate, particularly in young children and the elderly. A potentially fatal disease can arise from appendiceal perforation. According to reports, the death rate for simple acute appendicitis is 0.3%; however, in cases where there is a perforation, the rate rises to 6%.[1] It's critical to diagnose appendiceal perforations as soon as possible to prevent the accompanying abdominal infection. Furthermore, while radiographic modalities like ultrasound and CT (Computed Tomography) scans are useful in assisting in the diagnosis of acute appendicitis, their sensitivity in identifying perforated appendicitis is lower. The creation of additional instruments beyond radiography and clinical evaluation may aid in early diagnosis. Bilirubin has been shown in numerous trials to be a helpful serological marker for anticipating appendicitis and appendiceal perforation.[2,3-5]

Adults have been reported to have a 17–20% risk of perforated appendicitis.[6] Early and long-term problems might arise from a perforated appendix. It is recognised as the primary factor in these patients' extended hospital stays and postoperative morbidity. After surgery, intestinal blockage, wound infection, bacterial peritonitis, intra-abdominal abscess formation, and prolonged ileus are among the morbidities associated with ruptured appendicitis. There is currently no one clinical or laboratory test that can accurately diagnose or treat acute appendicitis or perforation of the appendix. Moreover, no scoring system assesses the possibility of appendiceal perforation. Consequently, in order to diagnose acute appendicitis, predict the severity and extent of the condition, and choose the best course of treatment, a straightforward, affordable, and readily available test that is specific for acute appendicitis and its consequences is required, along with clinical findings.

Recent research has revealed that patients may develop acute appendicitis based on their serum bilirubin levels. Additionally, some research has suggested a link between the severity and duration of appendicitis and hyperbilirubinemia.[7,8] The invasion of the appendix by gram-negative bacteria can be used to explain elevated blood bilirubin levels. This invasion can then cause the germs to migrate or invade the liver and portal system, interfering with the elimination of bilirubin through the bile ducts due to endotoxin action.

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Therefore, these markers can be employed in conjunction with clinical presentation to enhance preoperative diagnosis of acute appendicitis and to predict rupture as a novel measure of severity.

When appendiceal perforation and peritonitis coexist, prompt emergency surgery or percutaneous drainage is always required. Therefore, there is a growing need for quick and reliable markers that can distinguish between patients who have complex perforated appendicitis and those who have acute, simple appendicitis.

Therefore, the purpose of the current investigation was to determine whether a higher-than-normal bilirubin level might be used to predict the diagnosis of appendicular perforation.

MATERIAL & METHODS

Between October 2021 and October 2022, 100 patients who had been hospitalised at Government Vellore Medical College and Hospital for acute appendicitis and were undergoing emergency appendectomy participated in a prospective, non-randomized observational study. Participants older than 75 years or younger than 12 years and participants who had a history of biliary diseases (congenital or acquired), jaundice, cholilithiasis, liver disease, heavy drinking, hemolytic disease, or drug use that caused cholestasis were not allowed to take part in the study.

Levels of direct and total bilirubin were noted. For both total and direct bilirubin, the reference ranges were 0.3–1.0 mg/dl and 0.1–0.3 mg/dl, respectively. Based on the previously specified reference levels, the results were categorised as "raised" (hyperbilirubinemia) or "normal." A histological investigation was performed on these patients following surgery in order to confirm the clinical diagnosis both before and after the procedure. The final histological test was considered the gold standard for diagnosing and categorising patients as having a normal appendix, acute appendicitis, or acute appendicitis with perforation and/or gangrene. Based on the findings of a histological examination, patients were categorised as positive (acute appendicitis with perforation and/or gangrene) or negative (acute appendicitis without perforation or gangrene). A Microsoft Excel spreadsheet was used to total and analyse the data that was gathered. The odds ratio, sensitivity, specificity, positive predictive value, and negative predictive value were computed using a 2x2 table.

RESULTS

The current study was carried out from October 2021 to October 2022 at the Government Medical College, Vellore, in the Department of General Surgery. The study included 100 participants who had been clinically diagnosed with either appendicitis or appendicular perforation. Every patient had their LFTs and serum bilirubin levels documented.

Males (61%) outnumbered girls (39%) in this survey, with a mean age of 27 years across the board. The results showed that the direct bilirubin level was 0.29 mg/dL (0.1-1.5 mg/dL) and the mean total bilirubin was 0.85 (range, 0.20 – 2.50 mg/dL). Of the patients, 28% had normal bilirubin values, and 72% had hyperbilirubinemia, or elevated bilirubin levels. 60% of the 64 individuals who had acute appendicitis had normal bilirubin levels,

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compared to 4% who had elevated levels. Of the 36 patients with an appendicular perforation diagnosis, 24 percent had elevated bilirubin levels and the other 12 percent had normal levels.

Of the 100 patients, 36% had an appendicular perforation and 64% had a clinical diagnosis of acute appendicitis. According to the Alvarado scoring system, an appendicitis diagnosis with a score of 7-8 indicated 81% likelihood and a score of 9–10 indicated 19% certainty. Following surgery, 36% of patients had an appendicular perforation diagnosis, while 64% of patients had acute appendicitis.

Out of all the patients who were diagnosed with acute appendicitis, 4 had increased levels of bilirubin, whereas 60 had normal levels. Comparably, out of the 36 patients who were diagnosed with appendicular perforation, 24 had high bilirubin levels and 12 had normal bilirubin levels. (Table 1)

Characteristic	**N = 100**
Age	
Mean (SD)	27 (14)
Median (IQR)	24 (16, 32)
Range	11 , 75
Age Group	
11-20	41 (41%)
21-30	25 (25%)
31-40	18 (18%)
Above 40	16 (16%)
Sex	
Female	39 (39%)
Male	61 (61%)
Alvarado Score	
7	40 (40%)
8	41 (41%)
9	14 (14%)
10	5 (5.0%)
Total Bilirubin (mg/dL)	
Mean (SD)	0.85 (0.43)
Median (IQR)	0.80 (0.50, 1.10)
Range	0.20 , 2.50
Total Bilirubin Category	
>1	72 (72%)
<=1	28 (28%)
Direct Bilirubin (mg/dL)	
Mean (SD)	0.29 (0.22)
Median (IQR)	0.20 (0.10, 0.40)
Range	0.10 , 1.50

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Direct Bilirubin Category	
>0.3	71 (71%)
0.1-0.3	29 (29%)
Intra-Op Findings	
Acute appendicitis	64 (64%)
Appendicular perforation	36 (36%)
HPE	
Acute appendicitis	64 (64%)
Appendicular perforation	36 (36%)
Table 1	

Age Group	**Acute Appendicitis**	**Appendicular Perforation**
11-20	31 (48%)	10 (28%)
21-30	14 (22%)	11 (31%)
31-40	11 (17%)	7 (19%)
Above 40	8 (13%)	8 (22%)
Table 2: Intra-Op Findings** and **Age Group		

Table 2 depicts that appendicular perforation was more common in the 21–30 age range.

Total Bilirubin (mg/dL)	Intra-Op Findings		Total
	Acute Appendicitis	Appendicular Perforation	
<=1	60 (83.3%)	12 (16.7%)	72 (72%)
>1	4 (14.3%)	24 (85.7%)	28 (28%)
Total	64 (64%)	36 (36%)	100 (100%)
Table 3: Intra-Op Findings and Total Bilirubin			
Fisher's exact test P= <0.001 Significant			

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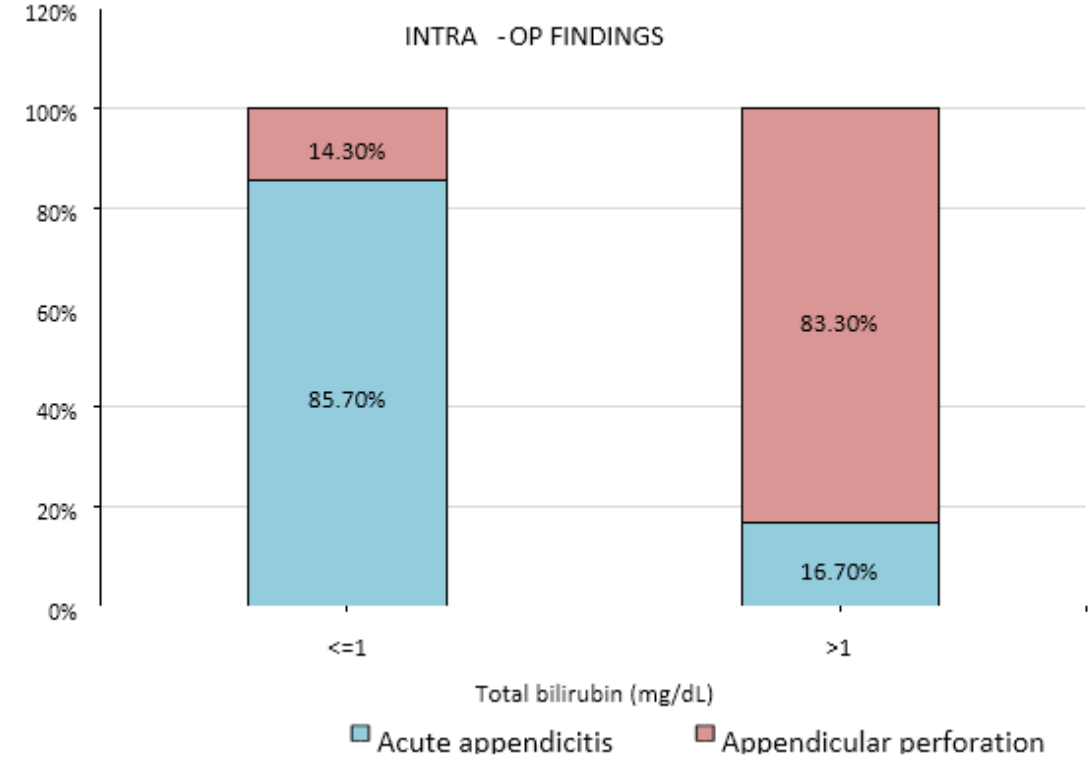

Figure 1: Intra-Op Findings and Total Bilirubin

Compared to just 16.7% of individuals with values <=1, appendicular perforation was seen in 85.7% of patients with total bilirubin >1 mg/dl. There was a statistically significant difference (P <0.001). Figure 1 in Table 3.

Total bilirubin had a sensitivity of 83.3% and a specificity of 85.7% in predicting the diagnosis of acute appendicitis and appendicular perforation, respectively.

Total bilirubin had a 93.7% positive predictive value for both the diagnosis of appendicitis and appendicular perforation. 66.7% was the negative predictive value.

Direct Bilirubin (mg/dL)	**Intra-Op Findings**		**Total**
	Acute Appendicitis	**Appendicular Perforation**	
0.1-0.3	60 (84.5%)	11 (15.5%)	71 (71%)
>=0.3	4 (13.8%)	25 (86.2%)	29 (29%)
Total	64 (64%)	36 (36%)	100 (100%)
Table 4: Intra-Op Findings and Direct Bilirubin			
Fisher's exact test P= <0.001 Significant			

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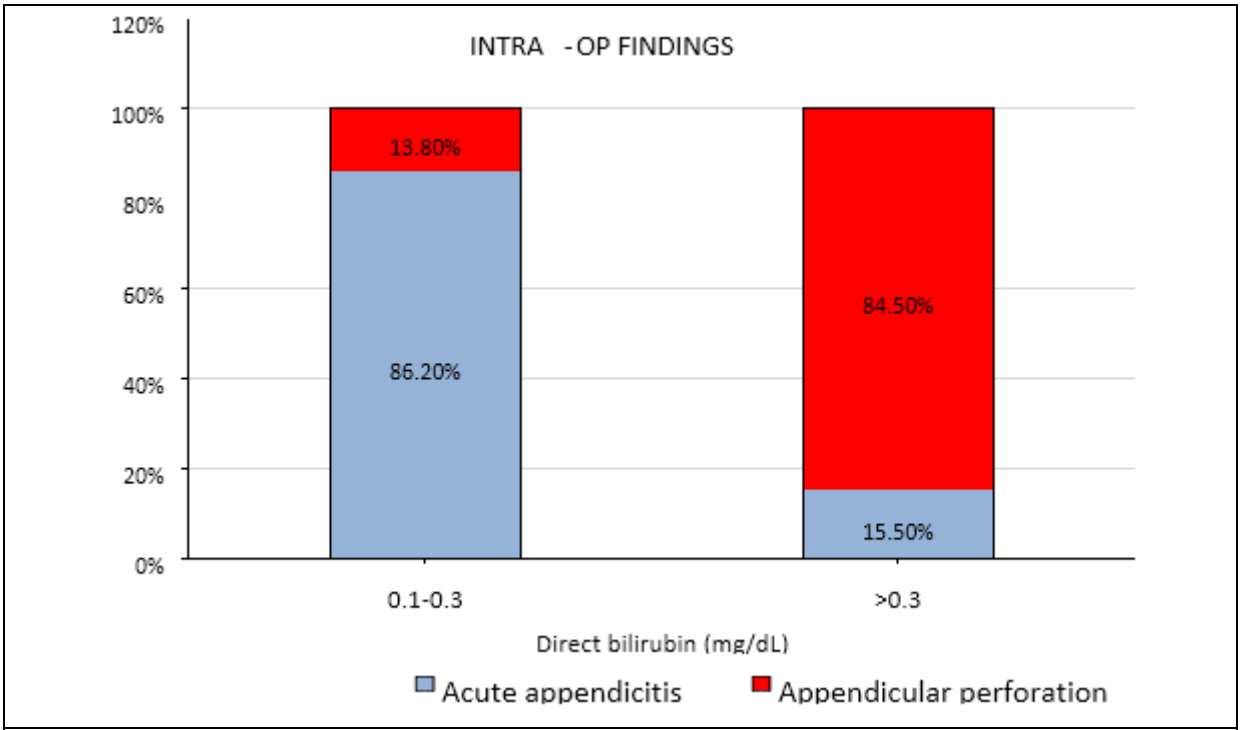

Figure 2: Intra-Op Findings and Direct Bilirubin

86.2% of patients with direct bilirubin >0.3 mg/dl developed appendicular perforation, whereas only 15.5% of patients with levels between 0.1 and 0.3 mg/dl experienced this condition. There was a statistically significant difference ($p<0.001$). Figure 2 in Table 4.

In predicting the diagnosis of acute appendicitis and appendicular perforation, direct bilirubin's sensitivity and specificity were 84.5% and 86.2%, respectively.

The direct bilirubin test has a 93.7% positive predictive value for both the diagnosis of appendicitis and appendicular perforation. 69.4% was the negative predictive value.

DISCUSSION

Of the 100 patients in our study, acute appendicitis was diagnosed in 64 (64%) of them prior to surgery, and appendicular perforation was diagnosed in 36 (36%). After surgery, the diagnosis was confirmed using HPR (Histopathological Reports); any that did not match the preoperative diagnosis were excluded from the study. In patients with acute appendicitis without a perforation diagnosis (n = 64), bilirubin levels were normal (≤1.0 mg/dL) in 85.70% of cases, while they were elevated (>1.0 mg/dL) in 16.70% of cases. Of those who had an appendicular perforation (n = 36), only 14.30% had normal bilirubin levels (>1.0 mg/dL); in contrast, 83.30% had elevated levels. As a result, hyperbilirubinemia was seen in most individuals with acute appendicitis (16.70%) and appendicular perforation (83.30%).

According to a retrospective study by Sand M. et al.[1] 538 patients with histologically confirmed acute appendicitis who underwent laparoscopic or traditional appendicectomy had a mean bilirubin level of 0.9 mg/dl (0.6 SD mg). However, patients with appendicular perforation had significantly higher mean bilirubin levels (p 0.05) than those with non-perforated appendicitis. These levels were 1.5 mg/dl (0.9 SD mg/dl; range 0.4 to 4.3 mg/dl;

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median 1.4 mg/dl). In contrast to the white blood cell count, which showed a specificity of 0.55, C-reactive protein showed a specificity of 0.96 for appendicular perforation. According to the study's findings, those with hyperbilirubinemia should receive different care than people with normal bilirubin levels and appendicitis-related symptoms since they are more likely to experience an appendicular perforation.

Emmanuel A. et al. conducted a retrospective review of appendicectomies performed in two institutions (n = 472).[2] Histopathology and test findings were among the information gathered. Histology data was used to categorise the patients, and analyses were done for each group. They discovered that patients with appendicitis had mean bilirubin levels that were higher than those of patients with an uninflamed appendix (p 0.001). At admission, 30% of patients with appendicitis compared to 12% of patients without the condition had hyperbilirubinemia, and the likelihood of these patients getting appendicitis was more than three times higher (odds ratio: 3.25, p0.001). For acute appendicitis, hyperbilirubinemia had a 91% positive predictive value and 88% specificity. A burst or gangrenous appendix was associated with higher mean bilirubin levels (p=0.01) and a higher likelihood of hyperbilirubinemia (p=0.001) in patients with appendicitis. Thirty percent of patients with hyperbilirubinemia had a specific aetiology, such as gangrene or perforation. Not only were the white blood cell count and C-reactive protein levels lower for simple appendicitis (60% and 72%), but they were also lower for perforated or gangrenous appendicitis (19% and 36%). According to the authors, hyperbilirubinemia is a useful indicator of acute appendicitis. Patients with hyperbilirubinemia are also more likely to develop appendicitis or gangrene.

Estrada J. et al. examined the relationship between hyperbilirubinemia and appendicitis in a retrospective analysis.[4] The study comprised patients whose liver function tests were abnormal upon arrival and who had pathologically diagnosed appendicitis. A logistic regression analysis was performed to determine the factors influencing the likelihood of appendicular gangrene or perforation. The independent variables were the patient's age, the length of time they had been experiencing symptoms, temperature, white blood cell counts, the systemic inflammatory response score, and bilirubin levels. Compared to patients with acute suppurative appendicitis, patients with gangrene or perforation had a significantly higher prevalence of hyperbilirubinemia (p=0.004). As for the other factors, there were no statistically significant differences. Hyperbilirubinemia was the sole predictor that significantly impacted the presence of appendicular gangrene or perforation, according to logistic regression analysis (p=0.031, 95% confidence interval, 1.11–7.6). The researchers came to the conclusion that high bilirubin levels can be used to tell if an appendix is perforated because people with hyperbilirubinemia had a 3.96 times higher chance of having an appendix perforate compared to people with normal bilirubin levels.

Serum bilirubin levels in patients with perforated appendicitis were significantly greater than in patients with acute appendicitis without a rupture, per J. Burcharth et al.[9] The average serum bilirubin levels of patients with perforated appendicitis varied from 23 to 26 μmol/L. Depending on the individual threshold values, the specificity was often high. Furthermore, in situations where blood bilirubin levels were elevated, NPV was significant, whereas PPV was usually low.

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Serum bilirubin levels rise in perforated appendicitis due to hepatic dysfunction during sepsis, just like in sepsis of any other origin. It has been proposed that bilirubin be taken into consideration when evaluating these patients because of this. Serum total bilirubin levels (p=0.044) and direct bilirubin (p=0.032) showed a significant difference between the various diseased groups in the study by Mohammad Reza Motie et al.[10] The total bilirubin ROC curve showed a sensitivity of 48% and a specificity of 61% in predicting the severity of acute appendicitis. Total blood bilirubin greater than 0.85 mg/dl was the cut-off value with the best performance when predicting the chance of a ruptured appendix. Total blood bilirubin, including direct and indirect forms, was found to be considerably elevated in cases of acute suppurative appendicitis and significantly greater in cases of gangrenous or perforated appendicitis in the study by Chaudhary et al.[1]

Sand et al.[1] showed that while CRP had a specificity of only 35%, hyperbilirubinaemia had an 86% specificity for appendiceal perforation or gangrene. For perforated acute appendicitis, STB has an 88% specificity and a 91% positive predictive value, according to Emmanuel et al.[2] In fact, Khan et al. have demonstrated 80% sensitivity and 100% specificity for TSB.[11] Estrada et al.[4] also showed that bilirubin levels of more than 1 mg/dl have a threefold risk of perforated appendicitis. Nevertheless, some research has revealed that bilirubin has no diagnostic relevance in predicting perforated appendicitis.[12,13]

A meta-analysis conducted by S. Giordano et al.[8] showed a pooled sensitivity of 0.49, a pooled specificity of 0.82, a positive likelihood ratio of 2.51 and a negative likelihood ratio of 0.58. A positive likelihood ratio >5 or a negative likelihood ratio of 0.2 indicates strong diagnostic evidence. This study presented a cumulative analysis of almost 5000 patients from studies in different settings and demonstrated the value of hyperbilirubinemia as a predictor of appendiceal perforation.

When a patient arrives at the emergency room with acute appendicitis, they undergo a primary evaluation that includes a clinical examination, blood tests, and possibly imaging studies.

A decision is made regarding observation, which may or may not involve antimicrobial treatment, planned surgery within the next 12 to 24 hours, or an emergency operation. If symptoms and signs suggest a perforated appendicitis serum bilirubin measurement is one additional tool in the primary evaluation. Hyperbilirubinemia alone is not a strong enough predictor but might be more useful when integrated into a scoring system. In this regard, further studies would be useful, especially in resource-poor settings with limited availability of a CT or other imaging studies.

CONCLUSION

In addition to or instead of other biochemical and radiographic markers, serum bilirubin has the specificity and sensitivity to predict appendicular perforation.

REFERENCES

[1] Sand M, Bechara FG, Holland-Letz T, Sand D, Mehnert G, Mann B. Diagnostic value of hyperbilirubinemia as a predictive factor for appendiceal perforation in acute appendicitis. Am J Surg 2009;198(2):193-8.

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[2] Emmanuel A, Murchan P, Wilson I, Balfe P. The value of hyperbili-rubinaemia in the diagnosis of acute appendicitis. Ann R Coll Surg Engl 2011;93(3):213-7.
[3] Atahan K, Üreyen O, Aslan E, Deniz M, Çökmez A, Gür S, et al. Preoperative diagnostic role of hyperbilirubinaemia as a marker of appendix perforation. J Int Med Res 2011;39(2):609-18.
[4] Estrada JJ, Petrosyan M, Barnhart J, Tao M, Sohn H, Towfigh S, et al. Hyperbilirubinemia in appendicitis: A new predictor of perforation. J Gastrointest Surg 2007;11:714-8.
[5] Käser SA, Fankhauser G, Willi N, Maurer CA. C-reactive protein is superior to bilirubin for anticipation of perforation in acute appendicitis. Scand J Gastroenterol 2010;45(7-8):885-92.
[6] Flum DR, Morris A, Koepsell T, Dellinger EP. Has misdiagnosis of appendicitis decreased over time? A population-based analysis. JAMA 2001;286(14):1748-53.
[7] Nomura S, Watanabe M, Komine O, Shioya T, Toyoda T, Bou H, et al. Serum total bilirubin elevation is a predictor of the clinicopathological severity of acute appendicitis. Surg Today 2014;44(6):1104-8.
[8] Giordano S, Pääkkönen M, Salminen P, Grönroos JM. Elevated serum bilirubin in assessing the likelihood of perforation in acute appendicitis: a diagnostic meta-analysis. Int J Surg 2013;11(9):795-800.
[9] Burcharth J, Pommergaard HC, Rosenberg J, Gögenur I. Hyperbilirubinemia as a predictor for appendiceal perforation: a systematic review. Scand J Surg 2013;102(2):55-60.
[10] Motie MR, Nik MM, Gharaee M. Evaluation of the diagnostic value of serum level of total bilirubin in patients with suspected acute appendicitis. Electronic Physician 2017;9(4):4048-54.
[11] Khan S. The diagnostic value of hyperbilirubinemia and total leukocyte count in the evaluation of acute appendicitis. J Clin Diagn Res 2009;3(4):1647-52.
[12] Beltran MA, Mendez PE, Barrera RE, Contreras MA, Wilson CS, Cortes VJ, et al. Is hyperbilirubinaemia in appendicitis a better predictor of perforation than C-reactive protein? A prospective study. Indian J Surg 2009;71(5):265-72.
[13] Panagiotopoulou I, Parashar D, Lin R, Antonowicz S, Wells AD, Bajwa FM, et al. The diagnostic value of white cell count, C-reactive protein and bilirubin in acute appendicitis and its complications. Ann R Coll Surg Engl 2013;95(3):215-21.