Elevated serum bilirubin levels may predict perforation of the appendix

Ann. Ital. Chir., 2019 90, 5: 427-431
pii: S0003469X19029841

Okan Murat Akturk, Doğan Yıldırım, Mikail Çakır, Yasar Murat Vardar

Department of Surgery, Haseki Training and Research Hospital, Istanbul, Turkey

Elevated serum bılirubin levels may predict perforation of the appendix

AIM: *Acute appendicitis is one of the most common pathology requiring emergency operations, and if perforated, can cause morbidity and mortality. The serum bilirubin levels were studied to see whether an elevation predicted perforation.*
MATERIAL AND METHODS: *In a retrospective cohort study the medical files of 221 patients who were operated for acute appendicitis were reviewed.*
RESULTS: *Total and indirect bilirubin levels were significantly higher in patients with a perforated appendicitis compared with patients with simple appendicitis. Elevated serum bilirubin had a sensitivity of 50.00 (95% CI 29.93 to 70.07) and a specificity of 80.73 (95% CI 74.43 to 86.05) when predicting a perforated appendicitis.*
CONCLUSIONS: *Appendiceal perforation may be accompanied with elevated serum bilirubin level. Assessment of bilirubin levels must be a part of the initial evaluation of a suspected appendicitis in the emergency room.*

KEY WORDS: Acute appendicitis, Gangrenous appendicitis, Perforated appendicitis, Serum bilirubin, Total Hyperbilirubinemia

Introduction

Appendicitis is one of the most common causes of emergency abdominal operations.iThe disease is more common in men than women and the lifetime risk of appendicitis is thought to be at 8.6% in men and 6.7% in women [1]. Despite this common presentation, correctly diagnosing acute appendicitis (AA) remains a challenge as clinical signs or positive blood results can be vague in up to 50% of the patients [2]. In Addition to that the diagnosis of appendicitis may still sometimes prove to be problematic, a delayed diagnosis may cause a simple appendicitis to progress to perforation which increases morbidity and mortality. To elude the complications of AA, a negative appendectomy (NA) has been deemed acceptable to a certain rate [3]. Identification and early intervention of perforated cases have crucial importance to potentially reduce the mordidity and mortality in a complicated appendicitis.

Acute appendicitis (AA) is defined as acute, gangrenous, or perforated forms: in acute or suppurative appendicitis, there is a neutrophilic infiltrate in the muscularis propria layer circumferentially, acute inflammation and ulceration of the mucosa but in gangrenous appendicitis there is transmural inflammation of the appendix with focal areas of mural necrosis, and defects in the appendiceal wall because of edema due to lymphatic and venous return impairment, thus, the condition leads to eventual perforation if untreated [4].

Hyperbilirubinemia results from imbalance between production and excretion of bilirubin in the liver. The gram negative bacteria which accumulate in the appendix secrete endotoxin that circulates and gets absorbed in portal circulation and cause hepatocellular discomfort that elevates the serum bilirubin levels [5]. Elevated levels

Pervenuto in Redazione Novembre 2018. Accettato per la pubblicazione Dicembre 2018
Correspondence to: Okan Murat Akturk, MD, Department of Surgery, Haseki Training and Research Hospital,Aksaray, Adnan Adıvar Caddesi, 34130 Fatih, İstanbul, Turkey (e-mail: omakturk@gmail.com)

of unconjugated hyperbilirubinemia associated with urinary tact infections have also been reported [6].
There have been some reports about the value of serum bilirubin levels in acute appendicitis both in diagnosis and prediction of perforation. In this study we aimed to see whether these parameters may be used as a predictor of perforated or gangrenous appendicitis and there is a correlation between the bilirubin levels and inflammation.

Material and Methods

The study was plotted as a retrospective cohort study. The medical reports of patients who were operated for a suspected appendicitis between April 2016 and April 2018 were reviewed. The preoperative diagnosis depended on a combination of physical examination, laboratory tests and radiological findings. The laboratory tests comprised of complete blood count, hepatic function, renal function tests. All patients went under a computerized tomography or ultrasound. In addition to this, the patients went under proper resuscitation and and fluid-electrolyte replacement before appendectomy.
The patients who went appendectomy for purposes other than appendicitis (normal appendix, parasitic appendicitis, intraoperative diagnosed Crohn disease, accompanying gynecological operations, appendiceal mucocele, carcinoid and plastrone) were excluded. Patients with a history of hepatotoxic drug intake, HBsAg positive and /or past history of jaundice, gallbladder thickness more than 3 mm in either computerized tomography or ultrasound scans in the preoperative imaging were excluded, as well.
The outcome variables are the elevated bilirubin levels and white blood cell count in gangrenous /necrotizing/perforated (GNP) appendicitis cases. The perforation, gangrenous and necrotizing (2 cases) condition was confirmed by the pathology report as a main output.

Statistical Analysis

The variables age, white blood cell count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin and indirect bilirubin were tested for normality. All were found to be non-normally distributed except the white blood cell count. Thus, non-parametric analysis was employed to evaluate differences. Mann-Whitney U test, student's t test and χ^2 test were used to assess differences where appropriate.
We measured the diagnostic performance of the elevated serum bilirubin about the presence of a perforated appendicitis. We also made an analysis to see if serum bilirubin levels correlated with inflammation. All statistical tests were rendered with SPSS 22 (SPSS Inc, Chicago, Illinois). A value of P<0.05 was considered significant.

Results

A total of 218 patients out of 231 who went under appendectomy between 01/04/2016 and 01/04/2018 were included in the study, as they fulfilled the criteria. The median age was 29 IRQ(18-67). The male female ratio was 3,01 (174/57). In three cases the pathology specimen yielded normal appendix as the rate of negative appendectomy was 1.3% (3/231); one female patient had pelvic inflammatory disease, one male patient had Crohn disease, the other male patient had an appendiceal mucocele. In our study group there was 18 (7.5%) cases of perforation and 11 (4.5%) cases of gangrenous/necrotizing appendicitis cases. As considered for hyperbilirubinemia, 50 (23%) patients had a serum of total bilirubin level equal to or higher than 1,2 mg/dL. After the initial evaluation 218 (26 with gangrenous /necrotizing/perforated appendix) patients had total, direct and indirect bilirubin levels studied within 6 hours prior the operation (Table I).
In the binary regression analysis for the presence of a gangrenous/necrotizing/perforated (GNP) appendicitis, variables indirect bilirubin (p=0.019), total bilirubin (p=0.021) were found to be significant. White blood cell count (p=0.52), aspartate aminotrasferase (AST) p=0.906 and alanine aminotransferase (ALT) p=0.817 were found to be insignificant. We measured the diagnostic performance of the total and indirect bilirubin levels using receiver operating characteristic curves to identify patients

Table I - *Summary of the demographic and clinical characteristics of the study group.*

Perforated/ gangrenous/ necrotising appendicitis	N	Mean	Std. Deviation	
Direct bilirubin	yes	26	,2292	,17879
	no	192	,1864	,15258
Indirectbilirubin	yes	26	,8988	,58700
	no	192	,6878	,39486
Total bilirubin	1,00	26	1,1077	,72549
	,00	192	,8574	,47196
White blood cell	yes	26	15,3950	4,21177
	no	192	13,7720	3,85766
Age	yes	26	41,3462	15,87940
	no	192	30,9740	11,62253
AST	yes	26	23,7308	12,77046
	no	191	23,0576	13,09447
ALT	yes	26	22,9231	17,86824
	no	191	23,9267	21,25125

The serum levels and abbreviations of the parameters are as follows: Direct bilirubin as mg/dL, indirect bilirubin as mg/dL, total bilirubin as mg/dL, age in years, AST (aspartate aminotransferase) as U/L, ALT(alanine aminotransferase) as U/L, white blood cell as 10 ^3uL.

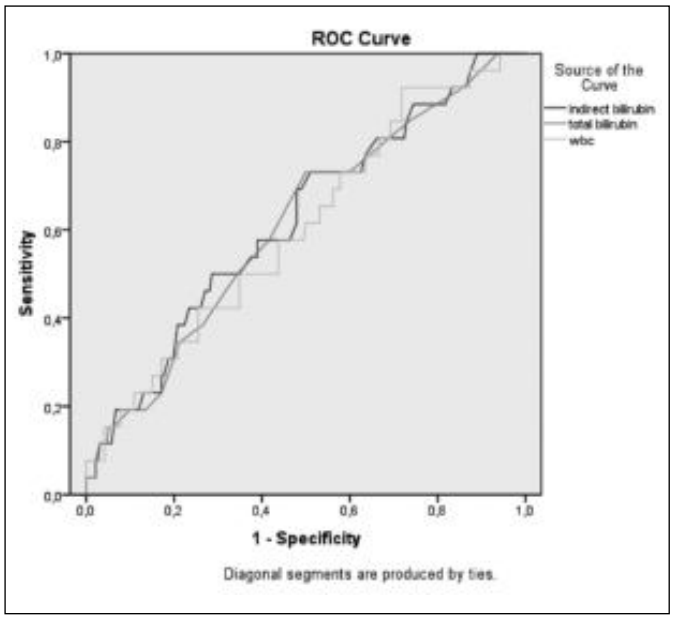

Fig. 1: Receiver operating characteristic curves of indirect bilirubin, total bilirubin and WBC count. Area under the curve (AUC) for indirect bilirubin, direct bilirubin and white blood cell count are 0,621, 0,614 and 0,604, respectively. Only AUC for indirect bilirubin level is significant, p=0,044.

with GNP. We also calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (–LR) for elevated serum values of total and direct bilirubin variables (Table II). Area under the curve (AUC) for indirect bilirubin, direct bilirubin and white blood cell count are 0.621, 0.614 and 0.604, respectively. Only AUC for indirect bilirubin level is significant, p=0.044 (Fig. 1).

In the non-parametric correlation analysis, the indirect and total bilirubin levels were found to be significantly correlated to white blood cell count, p=0.005 and p=0,009, respectively. The total bilirubin level correlated with indirect bilirubin level with a correlation coefficient (CC) of 0.967. The CC for total serum bilirubin and the serum indirect bilirubin levels correlated were 0.177 and 0.194, respectively. Indirect bilirubin correlated better with serum WBC levels.

Discussion

Acute appendicitis as a common abdominal emergency still represents to be problematic, for instead of remaining late and facing problems arising from perforation, a certain rate of negative appendectomies are considered acceptable by surgeons worldwide. This acceptable rate was even as high as up to 20-30% [7,8].

Computerized tomography or ultrasound imaging is now widely used as as tool to diagnose AA and moreover, to detect a complicated AA case. In a study the performance of the CT scan to find perforation was reported to have a sensitivity of 38%, the specificity was 96% [9]. Even so, the biochemical and hematological initial evaluation is an important part of the assessment in the emergency department. Besides, the evaluation of laboratory parameters are generally carried out before imaging studies. Any tool to improve the procedure of identifying a complicated appendectomy will both shorten the diagnostic process and potentially improve the outcomes avoiding any delay that may spring from a moderate time taken in the emergency room.

Estrada at al. reported elevated total bilirubin levels (>1 mg/dl) in 59 (38%) of 157 patients, On logistic regression they found significant relationship between the presence of appendiceal gangrene/perforation and the presence of hyperbilirubinemia [5]. The odds of appendiceal perforation are three times higher (odds ratio 2.96) for patients with hyperbilirubinemia compared to those with normal bilirubin levels. This finding is confirmed in our study as well. In addition to this, not only total bilirubin but also indirect bilirubin levels were found to be significant in the binary regression analysis for GNP appendicitis, (p=0.021) and (p=0.019), respectively. We calculated the odds ratio for the total bilirubin group as 4.1892 95 % CI (1.7936itoi9.7847). However, in our study group an elevated total bilirubin level was accepted as any value above or equal to 1,2 mg/dL.

In a study by Saxena et al, they discovered that an elevated level of serum bilirubin (≥4 mg/dl) was present in patients with a perforated appendix (87.7%) (30/35) in a study group of 215 patients. Overall, they found that out of 213 patients, raised serum bilirubin ≥1.2 mg/dl was present in 195 (91.5%) patients, out of which 194

TABLE II - *Sensitivity, Specificity, +LR and –LR, Positive Predictive Value, of total and indirect bilirubin levels for prediction of perforation at elevated serum levels taken as cut-off.*

	Sensitivity (95% CI)	Specifity (95% CI)	+LR (95% CI)	–LR, (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value(95% CI)
Indirectbilirubin	50 (29,93 70,07)	71.35 (64.4 to 77.63)	1.75 1.12 to 2.72	0.70 0.47 to 1.04	19.12 (13.16 26.94)	91.33 (87.66 to 93.99)
Total bilirubin	50.00 (29.93 to 70.07)	80.73 (74.43 to 86.05)	2.59 (1.60 to 4.20)	0.62 (0.42 to 0.92)	26.00 (17.84 to 36.24)	92.26 (88.97 to 94.63)

(+LR) positive likelihood ratio, (–LR) negative likelihood ratio, elevated total bilirubin ≥ 1,2 mg/dL, elevated indirect bilirubin ≥ 0,8 mg/dL

(99.4%) patients had inflamed appendix [10]. However, in our study only one patient had a total bilirubin level higher than 3 mg/dL and no patient had higher than 4 mg/dL. When considering the higher levels of total bilirubin, in our study group only 50/218 (23%) patiets had serum bilirubin levels ≥ 1,2 mg/dL.

In a prospective study by Chaudry et al, of 50 patients, hyperbilirubinemia was found in 30 of 42 patients with acute suppurative appendicitis and in all 8 patients with gangrenous/perforated appendicitis. They found a mixed hyperbilirubinemia (both conjugated and unconjugated) in most of the patients with at the no or minimal elevation (<100 U/L) in ALT and AST in most of the cases. They were also able to define a level of SB was higher than 3 mg/dL in cases of gangrenous/perforated appendicitis as in acute appendicitis this value was lower than 3 mg/dL (P<0.05) [11]. Again, in our study group only one patient had a total bilirubin level higher than 3 mg/dL, but in our study we observed a mixed hyperbilirubinemia, as well.

In another study it was again confirmed that patients with appendiceal perforation have a mean bilirubin level of which was significantly higher than those with a nonperforated appendicitis with a mean of i1.5 mg/dL and a spesifity of 86 for appendiceal perforation [12]. This serum level is closer to our result of total serum bilirubin which is 1,107±0,73 with a specificity of 0,81.

In a review by Burcarth et al, they found out that bilirubin was significantly higher in patients with appendiceal perforation compared with patients with appendicitis without perforation. Elevated serum bilirubin for determining the risk of perforation in appendicitis has low sensitivity but higher specificity, with a range of sensitivity from 0.38 to 0.77 and a specificity ranging from 0.70 to 0.87 in predicting appendiceal perforation. They thought that this would be a supplement in the diagnostic procedure of the disease [13]. Our results are in agreement with their findings, as our specificity is 0,5 while sensitivity is 0,81, thus, we infer that our reults confirm their conclusion.

In a study by Khan et al, they investigated the sensitivity, specificity, positive predictive value, negative predictive value of the elevated total serum bilirubin in AA and its complications and identified the positive predictivity of total bilirubin for perforated appendicitis as 86.96 % (95% CI: 73.73 % to 95.03 %) [14]. In their study TSB was elevated in 87(82.07%) cases a mean of 2.26mg/dL, (range 1.2-11.5mg/dL), which is both more frequent and higher than our study (mean serum level of TSB was 1,107±0,7 mg/dL and 20,8% of patients had elevated serum TSB levels).

The underlying mechanism about this finding might be that liver dysfunction due to bacteremia has long been observed. Although the mechanism is not clear bacterial toxins and fever can cause jaundice [15,16]. In addition to this, it has been shown that intraportally injected Streptococci induce acute hepatitis and then vanish [17]. Endotoxins that are found in the peripheral blood stream impair the liver's mechanism for the bilirubin uptake and excretion [18]. Endotoxins may cause cholestasis by lowering the biliary salt transport via cytokins like tumor necrosis factor [19]. Sepsis was found to be an important factor in rise of the bilirubin levels in an study made on critically ill patients (> 2 mg/dL or 34 μmol/L) [20]. In the early paheses of appendicitis mucosal ulceration takes place which helps the bacterial translocation of into the portal system where endotoxin and direct bacterial damage my cause hyperbilirubinemia [21].

Conclusion

A perforated appendicitis may have serious complications causing elongated hospital stay and morbidity. Patients with an elevated serum bilirubin level are more likely to have their appendix perforated and at risk for complications. These patients need a prompt action to lower the potential complications. Serum bilirubin levels must be kept in mind as a useful tool in the evaluation of acute appendicitis in the emergency room.

Riassunto

L'appendicite acuta è una delle patologie addominali di emergenza più comuni, e se perforata può essere causa di morbilità e mortalità. Abbiamo studiato per verificare se i livelli sierici di bilirubina sono in grado se elevati di far prevedere la perforazione.

Sono stati esaminati retrospettivamente sulle cartelle cliniche 221 pazienti sottoposti a appendicite acuta.

I livelli di bilirubina totale e indiretta sono risultati significativamente più alti nei pazienti con appendicite perforata rispetto ai pazienti con appendicite semplice. L'iperbilirubinemia sierica ha dimostrato una sensibilità di 50,00 (IC 95% 29,93 a 70,07) e una specificità di 80,73 (95% CI 74,43 a 86,05) nel prevedere una perforazione appendicolare.

Dunque la perforazione appendicolare può essere accompagnata da un elevato livello di bilirubina sierica. La valutazione dei livelli di bilirubina deve essere una parte della valutazione iniziale di una sospetta appendicite nel pronto soccorso.

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV: *The epidemiology of appendicitis and appendectomy in the United States*. Am Journ Epidemiol, 1990; 132(5):910-25.

2. Ansari P: *Appendicitis. Merck Manual*. NJ. U.S.A: Whitehouse Station, 2017.

3. Jones K, Peña AA, Dunn EL, Nadalo L, Mangram AJ: *Are neg-*

ative appendectomies still acceptable? Am Journ Surg, 2004; 188(6), 748-54.

4. Carr NJ: *The pathology of acute appendicitis.* Annals of Diagnostic Pathology, 2000; 4(1):46-58.

5. Estrada JJ, Petrosyan M, Barnhart J, Tao M, Sohn H, Towfigh S, Mason RJ: *Hyperbilirubinemia in Appendicitis: A New Predictor of Perforation*. Journal of Gastrointestinal Surgery, 2007; 11:714-18.

6. Shahian M, Rashtian P, Kalani M: *Unexplained neonatal jaundice as an early diagnostic sign of urinary tract infection*. Internat Journ Infect Dis, 2012; 16:e487-e490.

7. Lee SL, Walsh AJ, Ho HS: *Computed tomography and ultrasonography do not improve and may delay the diagnosis and treatment of acute appendicitis*. Arch Surg, 2001; 136(5):556-62. doi:10.1001 /archsurg.136.5.556.

8. Anonymous: *A sound approach to the diagnosis of acute appendicitis* (editorial). Lancet, 1987; 1:198-200.

9. Verma R, Grechushkin V, Carter D, Barish M, Pryor A, Telem D: *Use and accuracy of omputed tomography scan in diagnosing perforated appendicitis*. Am Surg, 2015; 81(4):404-07.

10. Saxena D, Tandon M, Shah Y, Gedam BS: *Hyperbilirubinemia as a diagnostic tool for the prediction of appendicular perforation: A prospective study*. Euroasian J Hepatogastroentero, 2016; 5(2):87-89.

11. Chaudhary P, Kumar A, Saxena N, Biswal, UC: *Hyperbilirubinemia as a predictor of gangrenous/perforated appendicitis: A prospective study*. Annals of gastroenterology, 2013; 26(4), 325-31.

12. 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):193-98.

13. Burcharth J, Rosenberg CH, Gögenur JI: *Hyperbilirubinemia as a predictor for appendiceal perforation: a systematic review.* Scand Journ Surg, 2013; 102(2), 55-60.

14. Khan S: *Elevated serum Bilirubin in Acute Appendicitis: A new diagnostic tool.* Kathmandu University Medical Journal, 2008; 6 (2): 161-5.

15. Morgan HR: *Pathologic changes produced in rabbits by a toxic somatic antigen derived from Eberthella Typhosa.* Am J Pathol, 1943; 19:135-45.

16. Harris BR: *Alterations in liver function as an index of toxemia in pneumococcus lobar pneumonia*. J Clin Invest, 1927; 4:211-24.

17. McMahon HE, Mallory FB: *Steptococcus hepatitis*. Am J Pathol, 1931; 7:299-325.

18. Roelofsen H, Vander Veere CN: *Decreased bilirubin transport in the perfused liver of endotoxemic rats.* Gastroenterology, 1994; 107(4):1075-84.

19. Whiting JF, Green RM: *TNF-alfa decrease hepatocyte bile salt uptake and mediated endotoxin induced cholestasis*. Hepatology, 1995; 22(pt 1):1273-278.

20. Kramer L, Jordan B, Druml W, Bauer P, Metnitz PG: *Incidence and prognosis of early hepatic dysfunction in critically ill patients. A prospective multicenter study. Austrian epidemiologic study on intensive care, ASDI study group.* Crit Care Med, 2007; 35(4):1099-10.

21. Sisson RG, Ahlvin RC, Harlow MC: *Superficial mucosal ulceration and the pathogenesis of acute appendicitis*. Am J Surg 1971; 122:378-80.