Chirurgia (2013) 108: 829-834
No. 6, November - December
Copyright© Celsius

The Value of Serum Bilirubin Level and of White Blood Cell Count as Severity Markers for Acute Appendicitis

B. Socea[1,2], A. Carâp[1,2], M. Rac-Albu[2,3], V. Constantin[1,2]

[1]Surgery Department, "St. Pantelimon" Emergency Clinical Hospital, Bucharest, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]Medical Information Technology and Biostatistics Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Rezumat

Valoarea hiperbilirubinemiei și leucocitozei ca indicatori de severitate în apendicita acută

Sunt binecunoscute discuțiile privind corelațiile între leucocitoză și formele anatomoclinice ale apencicitei acute. Studii mai recente arată că hiperbilirubinemia serică s-ar putea impune ca indicator prognostic al formelor gangrenoase sau perforate. Pe o cazuistică numeroasă din clinica noastră, în decurs de un an, am studiat corelațiile între formele anatomopatologice de apendicită acută, numărul de leucocite și nivelul seric al bilirubinei totale și al fracțunii indirecte. Cu toate că se constată o corelație între formele severe de boală (gangrenoasă/perforată), leucocitoza și nivelul crescut al bilirubinei serice totale (cu predominanța fracțiunii indirecte), nici unul dintre indicatori nu s-a dovedit a fi patognomonic. Formele perforate cu peritonită localizată/generalizată se asociază mai frecvent cu hiperbilirubinemie.

Cuvinte cheie: apendicită acută, hiperbilirubinemie, perforație apendiculară, disfuncție hepatică în sepsis

Abstract

Discussions regarding the correlations between elevated white blood cell levels and clinical and pathological stages of acute appendicitis are well known. Recent studies show that a high level of serum bilirubin could emerge as a prognostic marker for gangrenous or perforated stages of acute appendicitis. We studied the correlations between anatomical and pathological stages of acute appendicitis and white blood cell count, serum total bilirubin, and indirect serum bilirubin on a large series of cases, in the course of one year, in our department. Although there being a correlation between severe forms of acute appendicitis (gangrenous, perforated), elevated white blood cell count, elevated serum bilirubin (mostly the indirect fraction), none of the indicators proved to have a definitive diagnostic value. Cases with perforation and localized/generalized peritonitis are more frequently associated with elevated bilirubin levels.

Key words: acute appendicitis, elevated bilirubin, perforated appendix, hepatic failure in sepsis

Introduction

A high white blood cell count has been considered a key element for diagnosing acute appendicitis for a long time. Recent years have seen studies emerge that showed that elevated serum bilirubin levels could indicate a severe/perforated case of acute appendicitis (1,2,3). An elevated Serum Total Bilirubin (STB), that is not explained by liver disease or biliary obstruction can be observed in many patients with acute

Corresponding author: Alexandra Carâp, MD
General Surgery Department
"St. Pantelimon" Emergency Clinical Hospital, Bucharest, Romania
Pantelimon street, no. 340-342, Bucharest
Romania
E-mail: alexandru_carap@hotmail.com

appendicitis. Cases of acute appendicitis without high white blood cell (WBC) count are also well known. The present study aims to analyse the correlations between the histological form of acute appendicitis and WBC levels, STB levels, trying to establish to what degree we can consider these findings in diagnosing the severity of the disease before surgery.

Material and Method

We analysed patients admitted and operated on in the Department of General Surgery of the "St. Pantelimon" Emergency Clinical Hospital from October the 1st 2012 to the 30th of September 2013 (one year). We excluded from the study patients with known liver disease (hepatitis, cirrhosis, Gilbert syndrome, Dubin-Johnson syndrome), patients with elevated serum levels of liver function enzymes (AST, ALT), known alcoholics, patients with known bile obstruction, hemolytic syndromes, conditions that could explain elevated STB levels. Our study is retrospective, observational. We collected the data from patient charts, laboratory results, supplemental imaging studies (abdominal ultrasound, CT), operative recordings, histological results.

Results

In the aforementioned period (October 1st 2012 - September 30th 2013), a number of 387 patients were operated for acute appendicitis (confirmed initially during surgery and then by histological examination) in the General Surgery Department of our emergency hospital. Most of them (379 - 97.9%) were admitted with the diagnosis of acute appendicitis. 2.1% of the patients were admitted with other diagnoses, as follows: acute abdomen, inflammatory pelvic disease, pyosalpinx, suspected tumor of the cecum, intestinal obstruction. Clinical course and further paraclinical studies deemed surgical intervention mandatory, intervention that confirmed the diagnosis of acute appendicitis and permitted their inclusion in the study. There were also 14 patients who were admitted with the diagnosis of acute appendicitis which was negated by further studies: the patient was either diagnosed with a non-surgical disease and was not operated (5 cases), or the intraoperative findings were not of acute appendicitis (pyosalpinx - 3 cases, ruptured ovarian cyst - 2 cases, ectopic pregnancy - 2 cases, perforated ulcer - 1 case, sigmoid volvulus 1 case). Preliminary data shows, once more, that there are still considerable errors in the diagnosis of acute appendicitis, false positive as well as false negative ones.

Regarding the data we analysed, preoperative blood cell count was present in all patients. Total and fractioned bilirubin was routinely assessed for most patients but not for all. In accordance, this data was available only for 70.8% of the cases with confirmed acute appendicitis (274 cases).

We considered all diseases, even if only by suspicion, other than peritonitis or sepsis, that could lead to elevated STB or of its fractions: known liver disease (hepatitis, cirrhosis, Gilbert and Dubin-Johnson syndromes, benign intrahepatic recurrent cholestasis), carriers of liver viruses or of HIV, parasitic diseases (hydatid disease), common bile duct stones, either previously known or diagnosed by ultrasound, patients with ALT levels three times the normal value (over 114 IU/L), patients with AST levels five times the normal value (over 170 IU/L), known alcoholics, hemolytic disorders.

Analysing these findings we set the following inclusion and exclusion criteria:

Inclusion criteria

- Patients admitted and operated during the aforementioned timeframe;
- The recording of preoperative WBC count, STB and of one of its fractions (direct DBR or indirect IBR);
- Age interval 18-80 years old;
- Macroscopic as well as microscopic confirmation of acute appendicitis.

Exclusion criteria

- Lack of preoperative STB or of its fractions;
- The presence of the aforementioned conditions, eventually responsible for STB elevation.

The number of patients that met these requirements was 210.

Preoperative imaging studies were present as follows:

- Abdominal ultrasound: 93 cases (44%);
- Computed-Tomography: 7 cases (3.3%);
- MRI: 2 cases (0.95%).

These made the diagnosis clear, clearly indicating appendix inflammation (thickening of the wall, presence of a fecalith, periappendicular fluid, fluid in the cul de sac Douglas) as follows: ultrasound - 39.8% (*Fig. 1, 2*), CT - 6 cases out of 7, MRI - one case out of 2.

Concerning histology the following categories were found in our study: catarrhal acute appendicitis (CAA), phlegmonous acute appendicitis (PAA), gangrenous acute appendicitis (GAA) and perforated acute appendicitis (PA) further subdivided in two categories: perforated acute appendicitis with localized peritonitis (PAAL) and with generalized peritonitis (PAAG); we defined two groups of acute appendicitis: non-severe (CAA, PAA) and severe acute appendicitis (GAA, PAAL, PAAG).

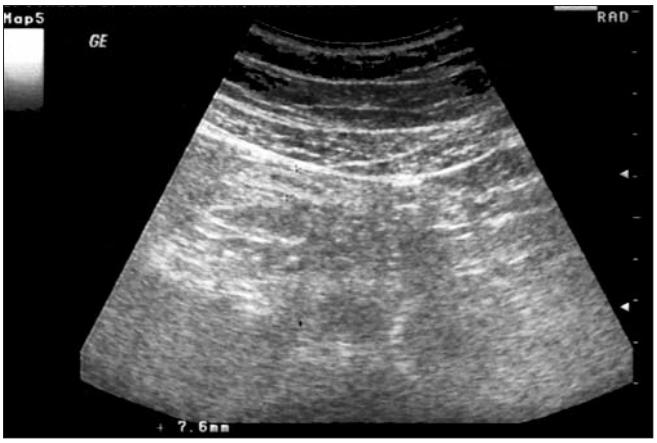

Figure 1. *Abdominal Ultrasound showing a thick-walled, non compressible appendix; intraoperative finding of phlegmonous acute appendicitis*

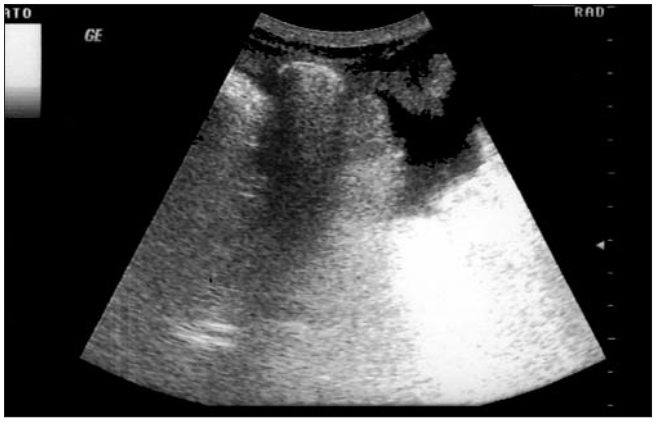

Figure 2. *Free fluid next to the appendix in the right iliac fossa*

Table 1. *Sex distribution and histological determination*

Histopathology form						
Sex	**CAA**	**PAA**	**GAA**	**PAAG**	**PAAL**	**TOTAL**
F	33	58	18	4	5	118
Row %	28.0	49.2	15.3	3.4	4.2	100.0
Col %	80.5	60.4	40.0	30.8	33.3	56.2
M	8	38	27	9	10	92
Row %	8.7	41.3	29.3	9.8	10.9	100.0
Col %	19.5	39.6	60.0	69.2	66.7	43.8
TOTAL	41	96	45	13	15	210
Row %	19.5	45.7	21.4	6.2	7.1	100.0
Col %	100.0	100.0	100.0	100.0	100.0	100.0

According to our local laboratory normal WBC count should be between 4400 and 11000/mm^3, STB 0-1 mg/dl, Indirect Serum Bilirubin - 1-0.7 mg/dl, AST 0-34 IU/L, ALT 0-38 IU/L.

Appendicular perforation is mainly influenced by pre-hospital time intervals, from the onset of symptoms to emergency room presentation, perforated cases being generally found to be present in 13 to37% of cases, and rarely beyond (4). Our study recorded a frequency of 13.3% perforated cases, and 34.7% cases of severe acute appendicitis (PA, GAA). The distribution of the study population based on histological results in the five categories (CAA, PAA, GAA, PAAL, PAAG) and the distribution according to sex of our 210 patients can be seen in *Table 1*. We can notice a significant difference in gender distribution for the various histological entities. For CAA 80.5% were female and 19.5% were male while for PAAG we recorded 30.8% female and 69.2% male (Chi-Square Test, p value=0.0002).

Statistical analysis was performed in order to evaluate and compare the various histological entities and their relation with STB, DBR, IBR, WBC count, starting with the unified severe and non-severe groups and concluding with the initial 5 histological aspects (CAA, PAA, GAA, PAAL, PAAG). Gender of the patients was taken into account for statistical analysis. Chi-Square, Mann-Whitney, Kruskal-Wallis and t-Student tests were performed. The Bonferroni correction was applied in some cases in order to eliminate errors that could result from the use of a large number of tests. Different results were obtained by group comparisons (p values can be seen in *Tables 2, 3, 4, 5*).

A synthesis of the results can show the following:

Table 2. *Statistical comparison between groups regarding parameter values, not considering sex*

***Mann-Whitney (**ANOVA) ***Kruskal-Wallis**		**DBR**	**IBR**	**STB**	**WBC count**
Reduced form	Severe	0.33 [0.24, 0.42]	0.76 [0.63, 1.05]	1.06 [0.92, 1.43]	12.78 [11.30, 18.40]
	Non-Severe	0.16 [0.10, 0.23]	0.38 [0.27, 0.52]	0.56 [0.40, 0.78]	10.20 [8.25, 12.70]
	p_value	0.0000*	0.0000*	0.0000*	0.0000*
Partially reduced form	Perforated AA	0.41 [0.28, 0.48]	0.98 [0.56, 1.38]	1.39 [0.90, 1.95]	16.92 [13.05, 20.35]
	GAA	0.27 [0.23, 0.37]	0.76 [0.66, 0.88]	1.04 [0.93, 1.13]	12.10 [10.80, 15.70]
	PAA	0.16 [0.11, 0.23]	0.41 [0.28, 0.54]	0.59 [0.43, 0.80]	10.98 [8.24, 13.65]
	CAA	0.12 [0.09, 0.19]	0.34 [0.24, 0.47]	0.46 [0.36, 0.66]	9.43 [8.29, 11.20]
	p_value	0.0000***	0.0000***	0.0000***	0.0000***
	Significant differences between groups (multiple comparison tests)	PAA and GAA (0.0000) PAA and PA (0.0000) GAA and CAA (0.0000) PA and CAA (0.0000)	PAA and GAA (0.0000) PAA and PA (0.0000) GAA and CAA (0.0000) PA and CAA (0.0000)	PAA and GAA (0.0000) PAA and PA (0.0000) GAA and CAA (0.0000) PA and CAA (0.0000)	PAA and PA (0.0000) GAA and PA (0.0160) GAA and CAA (0.0030) PA and CAA (0.0000)

Table 3. *Kruskal-Wallis, histological groups, not considering sex*

***Kruskal-Wallis	DBR	IBR	STB	WBC count
PAAG N=13	0.37 [0.29, 0.49]	0.63 [0.57, 1.31]	1.09 [0.91, 1.92]	16.30 [11.30, 20.40]
PAAL N=15	0.42 [0.27, 0.48]	1.05 [0.56, 1.50]	1.53 [0.90, 1.99]	17.55 [14.60, 18.90]
GAA N=45	0.27 [0.23, 0.37]	0.76 [0.66, 0.88]	1.04 [0.93, 1.13]	12.10 [10.80, 15.70]
PAA N=96	0.16 [0.11, 0.23]	0.41 [0.28, 0.54]	0.59 [0.43, 0.80]	10.98 [8.24, 13.65]
CAA N=41	0.12 [0.09, 0.19]	0.34 [0.24, 0.47]	0.46 [0.36, 0.66]	9.43 [8.29, 11.20]
p_value	0.0000***	0.0000***	0.0000***	0.0000***
Significant differences between groups (multiple comparison tests)	PAA and GAA (0.000000) PAA and PAAG (0.000001) PAAand PAAL (0.000009) GAA and CAA (0.000000) PAAG and CAA (0.000000) PAAL and CAA (0.000001)	AA and GAA P (0.000000) PAA and PAAG (0.000749) PAA and PAAL (0.000043) GAA and CAA (0.000000) PAAG and CAA (0.000022) PAAL and CAA (0.000001)	PAA and GAA (0.000000) PAA and PAAG (0.000013) PAA and PAAL (0.000010) GAA and CAA (0.000000) PAAG and CAA (0.000000) PAAL and CAA (0.000000)	PAA and PAAG (0.014063) PAA and PAAL (0.000044) GAA and PAAL (0.032943) GAA and CAA (0.005009) PAAG and CAA (0.000461) PAAL and CAA (0.000001)

Table 4. *Kruskal-Wallis test, considering histological results and sexes; Bonferroni correction (2 times multiplication of p values results in p values > 0.05, outside significant limits - strikethrough values)*

**Kruskal-Wallis		DBR	IBR	STB0	WBC count
Sex=F	PAAG	0.43 [0.32, 0.54]	0.55 [0.44, 0.85]	1.06 [0.87, 1.28]	10.37 [8.93, 15.80]
	PAAL	0.27 [0.17, 0.46]	0.70 [0.40, 1.41]	0.97 [0.57, 1.88]	15.90 [14.80, 16.10]
	GAA	0.31 [0.24, 0.37]	0.74 [0.66, 0.83]	1.04 [0.98, 1.13]	12.74 [11.50, 18.70]
	PAA	0.14 [0.09, 0.21]	0.37 [0.28, 0.57]	0.51 [0.39, 0.78]	9.60 [8.07, 11.90]
	CAA	0.11 [0.09, 0.18]	0.32 [0.24, 0.47]	0.44 [0.33, 0.65]	9.30 [8.29, 10.90]
	p_value	0.0000***	0.0000***	0.0000***	0.0000***
	Significant differences between groups (multiple comparison tests)	PAA and GAA (0.000042) PAA and PAAG (0.010540) GAA and CAA (0.000013) PAAG and CAA (0.004178)	PAA and GAA (0.000262) GAA and CAA (0.000002)	PAA and GAA (0.000016) GAA and CAA (0.000000) PAAG and CAA (0.013713)	PAA and GAA (0.016075) GAA and CAA (0.010261) PAAG and CAA (0.008133)
Sex=M	PAAG	0.37 [0.29, 0.47]	0.72 [0.63, 1.36]	1.09 [0.91, 1.99]	19.80 [15.50, 22.30]
	PAAL	0.42 [0.39, 0.49]	1.07 [0.94, 1.50]	1.55 [1.36, 1.99]	17.60 [14.60, 18.90]
	GAA	0.26 [0.22, 0.37]	0.76 [0.62, 0.88]	1.04 [0.91, 1.15]	11.70 [9.19, 13,78]
	PAA	0.21 [0.16, 0.26]	0.43 [0.33, 0.53]	0.68 [0.53, 0.80]	12.90 [9.54, 15.10]
	CAA	0.19 [0.16, 0.25]	0.39 [0.34, 0.46]	0.59 [0.49, 0.73]	10.90 [9.06, 11.55]
	p_value	0.0000***	0.0000***	0.0000***	0.0000***
	Significant differences between groups (multiple comparison tests)	PAA and PAAG (0.001818) PAA and PAAL (0.000067) ~~PAAG and CAA (0.034269)~~ PAAL and CAA (0.005684)	PAA and GAA (0.000001) PAA and PAAG (0.001020) PAA and PAAL (0.000033) GAA and CAA (0.000747) PAAG and CAA (0.005495) PAAL and CAA (0.000669)	PAA and GAA (0.000001) PAA and PAAG (0.000325) PAA and PAAL (0.000011) GAA and CAA (0.004453) PAAG and CAA (0.008814) PAAL and CAA (0.001404)	~~GAA and PAAG (0.025289)~~ ~~GAA and PAAL (0.026803)~~ PAAG and CAA (0.007494) PAAL and CAA (0.008211)

Table 5. *Mann-Whitney and T Student tests by histological groups; Bonferroni correction (5 times multiplication of p values renders some statistically insignificant).*

***Mann-Whitney** **Student T		DBR	IBR	STB	WBC count
PAAG	F (N=4)	0.4300±0.1395	0.6475±0.2956	1.0775±0.2896	12.3650±5.4233
N=13	M (N=9)	0.4056±0.1458	1.0622±0.6029	1.4678±0.7117	18.0922±5.1421
	p_value	0.7830**	0.2250**	0.3214**	0.0951**
PAAL	F (N=5)	0.2900±0.1733	0.8360±0.6477	1.1260±0.8199	16.3800±3.1618
N=15	M (N=10)	0.4330±0.1101	1.1200±0.4680	1.5530±0.5612	16.9660±3.7190
	p_value	0.0710**	0.3456**	0.2530**	0.7683**
GAA	F (N=18)	0.3022±0.0918	0.7478±0.2714	1.0500±0.3296	13.6472±4.0908
N=45	M (N=27)	0.2967±0.1255	0.8141±0.2904	1.1107±0.3895	12.1507±3.8922
	p_value	0.8728**	0.4457**	0.5893**	0.2224**
PAA	F (N=58)	0.1521±0.0824	0.4221±0.1800	0.5741±0.2227	9.60 [8.07, 11.90]
N=96	M (N=38)	0.2145±0.0790	0.4305±0.1508	0.6450±0.1935	12.90 [9.54, 15.10]
	p_value	0.0004**	0.8111**	0.1121**	0.0018*
CAA					
N=41	F (N=33)	0.1376±0.0808	0.3406±0.1627	0.4782±0.2034	9.5006±2.4086
M (N=8)	0.2263±0.1183	0.3975±0.0988	0.6238±0.1994	10.3788±1.8637	
	p_value	0.0153**	0.3517**	0.0761**	0.3428**

Analysing values for STB and IBR results in clear differences between patients with severe and non-severe forms of the disease. Regarding the subgroups of these forms, similar values were obtained for CAA and PAA that are not statistically significant. In a similar fashion, we obtained very close results, that provide no statistical significant differences between subgroups of severe forms (GAA, PAAL, PAAG). Median value for STB for severe forms was 1.06 mg/dl [0.92, 1.43], while for non-severe forms it was 0.56 [0.40, 0.78]. Median value of STB for perforated forms was calculated to be 1.39 mg/dl [0.90, 1.95], value that does not differ significantly from the value for GAA - see *Table 2*. Values are presented as follows: Median [first quartile = 25th percentile, third quartile = 75th percentile].

Regarding WBC count, median values grow steadily with the severity of the inflammation from the catarrhal to the perforated forms. We can again find two interiorly homogenous groups and statistically different from one another - but the component is different: the group of perforated appendicitis is differentiated from the group of non-perforated (CAA, PAA, GAA). Only the median value for perforated appendicitis - 16920/mm^3 [13050, 20350] differs from the rest.

Discussions

Several serum markers have been analyzed in order to predict the severity of acute appendicitis including IL-6 and lipopolysaccharide binding protein (5) The presence of jaundice in sepsis is well documented, especially associated with Gram-negative pathogens (6,7,8). Several mechanisms have been described explaining STB elevations in systemic infections. The hemolysis produced by certain bacteria (including E. coli), produces an increase in indirect and total serum bilirubin (7,9). Also, some endotoxins released in the peripheral blood stream are responsible for impeding the liver's mechanism for bilirubin uptake and canalicular excretion (10,11). Endotoxins produce cholestasis by damaging biliary salt transport through cytokine mediated mechanisms (12,13). E. coli is the most frequently isolated bacteria from peritoneal fluid in acute appendicitis (14,15), and its presence is associated with the lipopolysaccharidic endotoxin. Elevated STB in acute appendicitis can either appear as a result of bacteremia, or of endotoxinemia, both possible in the catarrhal and phlegmonous forms as well as in the gangrenous or perforated ones (16).

There are studies that report the presence of elevated STB in acute appendicitis (17,18,19). Estrada et al. have formulated the hypothesis that jaundice can be associated with perforation of the appendix, serving as a severity marker (20). They explain the elevated STB by the invasion of the Gram-negative bacteria through the muscularis propria of the appendix, leading to direct invasion or translocation of the germs in the portal system and the liver, interfering with bilirubin excretion through bile ducts by endotoxin action. Emmanuel et al. find that STB has a specificity of 88% and a positive predictive value of 91% for perforated acute appendicitis (16), while Sand et al find an 86% specificity for gangrenous or perforated forms, compared with only a 35% specificity of the C reactive protein (21). Hong, on a large series of 1195 patients, also finds as significant the value of STB in the identification of perforation (22). In this setting we aimed to find out what our series shows. ROC curves helped set the cut-off value of STB at 0.865, lower than the standard of 1. The sensitivity

Table 6. *Significance calculation for 0.865 cut-off value of STB*

Cut-off	Severe	Non-severe	TOTAL
STB > 0.865 (+)	63	10	73
STB < =0.865 (-)	10	127	137
TOTAL	73	137	210

Table 7. *Significance calculation for STB value of over 1 mg/dl*

Cut-off	Severe	Non-severe	TOTAL
STB > 1 (+)	45	1	46
STB < =1 (-)	28	136	164
TOTAL	73	137	210

of the test is 86.30% and the specificity is 92.70%. The positive predictive value (PPV) is 86.30% and the negative predictive value (NPV) is 92.7% (*Table 6*).

For a value of 1 STB, the sensitivity of the test is 61.64% and the specificity is 99.27%. PPV is 97.83% and NPV is 82.93% (*Table 7*).

Conclusions

Although a correlation between the severe forms of the disease (gangrenous, perforated) and the values of WBC, TSB and of its fractions, none of the investigated markers proved to be diagnostic. Perforated forms associated with localized peritonitis are more frequently associated with the elevation of STB and the indirect fraction, than the other forms (catarrhal and phlegmonous). Elevated STB (over 1 mg/dl), in the clinical setting of acute appendicitis, can differentiate severe forms with high specificity (99.2%). Even normal levels of STB, but over 0.86, can constitute an alarm signal.

The value of WBC sees a linear elevation that parallels the severity of the disease with a significant jump in the moment of perforation. A value over 16920 WBC/mm^3 was shown by half of the cases with a perforated appendicitis.

References

1. 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. 2013 Jul 24. [Epub ahead of print]
2. 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.
3. Hong YR, Chung CW, Kim JW, Kwon CI, Ahn DH, Kwon SW, et al. Hyperbilirubinemia is a significant indicator for the severity of acute appendicitis. J Korean Soc Coloproctol. 2012; 28(5):247-52.
4. 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.
5. Brănescu C, Serban D, Dascălu AM, Oprescu SM, Savlovschi C. Interleukin 6 and lipopolysaccharide binding protein - markers of inflammation in acute appendicitis. Chirurgia (Bucur). 2013;108(2):206-14.
6. Whitehead MW, Hainsworth I, Kingham JG. The causes of obvious jaundice in South West Wales: perceptions versus reality. Gut. 2001;48(3):409-13.
7. Chand N, Sanyal AJ. Sepsis-induced cholestasis. Hepatology. 2007;45(1):230-41.
8. Orban C. Diagnostic criteria for sepsis in burn patients. Chirurgia (Bucur). 2012;107(6):697-700.
9. Shander A. Anemia in the critically ill. Crit Care Clin. 2004; 20(2):159-78.
10. Roelofsen H, van der Veere CN, Ottenhoff R, Schoemaker B, Jansen PL, Oude Elferink RP. Decreased bilirubin transport in the perfused liver of endotoxemic rats. Gastroenterology. 1994; 107(4):1075-84.
11. Bolder U, Ton-Nu HT, Schteingart CD, Frick E, Hofmann AF. Hepatocyte transport of bile acids and organic anions in endotoxemic rats: impaired uptake and secretion. Gastroenterology. 1997;112(1):214-25.
12. Green RM, Beier D, Gollan JL. Regulation of hepatocyte bile salt transporters by endotoxin and inflammatory cytokines in rodents. Gastroenterology. 1996;111(1):193-8.
13. Whiting JF, Green RM, Rosenbluth AB, Gollan JL. Tumor necrosis factor-alpha decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis. Hepatology. 1995;22(4 Pt 1):1273-8.
14. Brook I. Bacterial studies of peritoneal cavity and postoperative surgical wound drainage following perforated appendix in children. Ann Surg. 1980;192(2):208-12.
15. Baron EJ, Bennion R, Thompson J, Strong C, Summanen P, McTeague M, et al. A microbial comparison between acute and complicated appendicitis. Clin Infect Dis. 1992;14(1):227-31.
16. Emmanuel A, Murchan P, Wilson I, Balfe P. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. Ann R Coll Surg Engl. 2011;93(3):213-7.
17. Agrez MV, House AK, Quinlan MF. Jaundice may herald an appendiceal abscess. Aust N Z J Surg. 1986;56(6):511-3.
18. Ogilvie TA. Acholuric jaundice and appendicitis. Br J Surg. 1951;38(152):529-30.
19. Dawes T, Burrows C. Abdominal pain and jaundice: appendiceal perforation an important differential. Emerg Med Australas. 2007;19(3):276-8.
20. 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(6):714-8.
21. 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.
22. Hong YR, Chung C-W, Kim JW, Kwon CI, Ahn DH, Kwon SW, Kim SK. Hyperbilirubinemia is a significant indicator for the severity of acute appendicitis. J Korean Soc Coloproctol. 2012;28(5):247-52.