Medicine

HYPERBILIRUBINEMIA AS A PREDICTIVE FACTOR FOR APPENDICULAR PERFORATION

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ABSTRACT:
BACKGROUND: *SEARCHING FOR A RELIABLE PREOPERATIVE MARKER FOR SEVERITY OF ACUTE APPENDICITIS, RECENT STUDIES SUGGESTED THAT HYPERBILIRUBINEMIA COULD BE A USEFUL MARKER FOR APPENDICEAL PERFORATION. ITS RAPID DIAGNOSIS IS ESSENTIAL FOR IT LEADS TO FASTER TREATMENT, WITH IMPROVED OVERALL PROGNOSIS. THE AIM OF THIS RETROSPECTIVE STUDY WAS TO INVESTIGATE THE VALUE OF HYPERBILIRUBINEMIA AS A MARKER FOR APPENDICEAL PERFORATION IN PATIENTS WITH ACUTE APPENDICITIS.*
MATERIALS AND METHODS: *A RETROSPECTIVE STUDY OF PATIENTS ADMITTED TO THE 1ST SURGERY CLINIC OF THE UNIVERSITY EMERGENCY HOSPITAL OF BUCHAREST WITH THE DIAGNOSIS OF ACUTE APPENDICITIS AND WHO UNDERWENT APPENDECTOMY, CONFIRMING COMPLICATED ACUTE APPENDICITIS, BETWEEN 2005 AND 2012; THE DATA COLLECTED INCLUDED LABORATORY AND HISTOLOGICAL RESULTS, LENGTH OF STAY, ANTIBIOTIC TREATMENT AND COMPLICATIONS ASSOCIATED WITH APPENDECTOMY.*
RESULTS: *264 PATIENTS UNDERWENT APPENDECTOMY FOR COMPLICATED APPENDICITIS IN THE TIME INTERVAL OF THE STUDY. THE MEAN VALUE OF SERUM BILIRUBIN WAS 0.93 MG/DL FOR THE ENTIRE GROUP, WITH THE CONJUGATED BILIRUBIN MEAN VALUE OF 0.3 MG/DL. MEAN TOTAL BILIRUBIN LEVELS VARIED ACCORDING TO THE DIAGNOSIS AND HISTOLOGICAL RESULTS: IT WAS 0.75 MG/DL FOR THOSE DIAGNOSED WITH ACUTE APPENDICITIS WITHOUT PERFORATION AND 1.41 MG/DL FOR THOSE DIAGNOSED WITH APPENDICEAL PERFORATION (TEST SENSITIVITY 66.2%, SPECIFICITY 83.4%, POSITIVE AND NEGATIVE PREDICTIVE VALUES 59.5% AND 87.0%, OR 9.85, RR 4.54, p <0.005). THE RATIO OF CONJUGATED TO TOTAL SERUM BILIRUBIN LEVELS WAS ALSO HIGHER FOR THE PERFORATION GROUP: 0.43 VS. 0.23. THE SCORE COMPRISING THE VALUE OF SERUM BILIRUBIN AND THE RATIO OF CONJUGATED BILIRUBIN TO TOTAL SERUM BILIRUBIN IS CORRELATED TO THE RISK OF PERFORATION (PREVALENCE 26.9%, SENSITIVITY 85.9%, SPECIFICITY 76.2%, PPV 57.0%, NPV 93.6%, OR 19.5, RR 8.9, p <0.005).*
CONCLUSIONS: *PATIENTS WITH HYPERBILIRUBINEMIA AND/OR RATIO OF CONJUGATED TO TOTAL SERUM BILIRUBIN LEVELS ABOVE 0.3 AND CLINICAL SYMPTOMS OF APPENDICITIS SHOULD BE IDENTIFIED AS HAVING A HIGHER PROBABILITY OF APPENDICEAL PERFORATION THAN THOSE WITH NORMAL BILIRUBIN LEVELS.*

KEY WORDS: HYPERBILIRUBINEMIA, APPENDICULAR PERFORATION, ACUTE APPENDICITIS, APPENDICULAR PERITONITIS

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INTRODUCTION

Acute appendicitis remains to this day the most common cause of acute abdomen and appendectomy is the most frequently performed emergency surgical intervention. Perforated appendicitis is the leading general surgical cause of death.[1,4,10]

The diagnosis of appendicitis is based on three elements – history of pain initially localized to the epigastrium or periumbilical, than localized to the right lower quadrant, nausea and anorexia; physical examination that reveals focal tenderness and/or voluntary guarding in the right lower quadrant; laboratory studies with white blood cell count elevated and neutrophilia more than 75%. [1,4,10]

The precise diagnosis of the evolutive form of appendicitis is difficult without a CT scan, which has few major drawbacks: it is expensive, it exposes the patient to risks for allergic contrast reaction and ionizing radiation, and it delays the initiation of treatment.

Searching for a fast, safe and cheap diagnostic tool, especially in the case of appendicular perforation, we found a few studies regarding the association between hyperbilirubinemia and perforated appendicitis or appendicular peritonitis.[2,5,6,8] Sand et al in a retrospective study of 538 patients with acute appendicitis concludes that hyperbilirubinemia has a specificity of 86% and sensitivity of 70% for caecal perforation, thus showing that patients with clinical symptoms of acute appendicitis and high bilirubin levels should be considered with high probability for cecal perforation. [8] Käser et al in a group of 725 patients with acute appendicitis of which perforation occurred in 155 cases, states that hyperbilirubinemia is a statistically significant marker for cecal perforation (38% for cecal perforation vs 22.3% for acute appendicitis without perforation). [6] Emmanuel et al in a group of 472 patients with acute appendicitis concluded that hyperbilirubinemia may be a marker for acute appendicitis and/or associated gangrenous appendicitis or cecal perforation - specificity of 70% for perforation. [5] Likewise, bilirubin increase is interpreted by Atahan et al as having value for the differential diagnosis of the evolutive form of acute appendicitis. [2]

The pathophysiology of the increase of the bilirubin level in perforated acute appendicitis might be represented by the action of E. coli endotoxin level on the hepatocyte bile flow by decreasing it. Research in this area has been undertaken 35 years ago in relation to the genesis of jaundice in sepsis, which occurs before the increase in blood level of liver enzymes by hepatocyte destruction caused by liver hypoperfusion. It was established that bile flow is affected by endotoxin infusion both directly, as well as through the release of inflammatory mediators (TNFα like mediators and interleukins) from immune cells under the action of endotoxin. The blockage is located at the hepatocyte membrane transport mechanisms. This prevents both the hepatocyte uptake of plasma products by blocking the transmembrane transport mechanisms in the basolateral membrane of hepatocytes, and at the canalicular excretion by blocking the transmembranary transporters in the apical membrane of hepatocytes, thus leading to higher total bilirubin blood level, mainly in the direct component. The maximum decrease of transmembranary transport is between 60% and 81% for the various compounds at 12 hours after endotoxin infusion, with subsequent functional recovery. [3,7,9,11]

MATERIALS AND METHODS

We conducted a retrospective analytical study of a homogenous group of 264 cases of acute appendicitis complicated by acute peritonitis in adults over 18 years of age, operated in the 1st Surgery Clinic of the University Emergency Hospital Bucharest, over a period of 8 years (Jan 2005-Dec 2012).

Data were collected from the file records of surgical interventions and from the patients' charts, the main selection criteria being the presence of acute peritonitis confirmed during surgical intervention.

The criteria used are summarized in the following table (1):

Table 1: Study group selection criteria

Inclusion criteria	-Phlegmonous acute appendicitis -Gangrenous acute appendicitis -Perforated acute appendicitis	Complicated by	-Serous peritoneal reaction -Localized acute peritonitis -Generalized acute peritonitis -Appendiceal abscess
	That underwent appendectomy, confirming diagnosis during surgery		
Exclusion criteria	-Phlegmonous acute appendicitis -Gangrenous acute appendicitis -Other appendicular pathology -Pelviperitonitis -Colonic neoplasms -Ileitis -etc	Without acute peritonitis	
	-Refusal of surgical intervention or conservatory treatment -Infirmation of acute peritonitis during surgery – visually or by microbiology testing		

For the selected cases we collected the following data:

- identification and time frame data: name, gender, age, date of admission and discharge, date of surgical intervention
- diagnosis: admission diagnosis, discharge diagnosis, complications, particular forms of acute appendicitis or peritonitis
- clinical data: history, physical exam, other symptoms
- laboratory findings and imagistic studies: white blood cell count, value of total and direct bilirubinemia, abdominal ultrasound or CT-scan (if done), histology results and microbiological studies of peritoneal fluid
- treatment and clinical evolution: type of antibiotic used and interval of administration, clinical evolution of patient – locally and generally, complications.

Collected data were analyzed using Microsoft Office Excel 2000 9.0 (Microsoft Corporation) and Epi Info 7.1.1.14 (Centers for Disease Control and Prevention). Confidentiality index (CI) was set at 95%.

RESULTS

The main features and data of the studied group are shown in table (2):

Table 2: Main characteristics of the study group

Total number= 264 **Characteristic**		**n***	**% ****	**95 % CI*****
Gender	Male	161	61.0	54.8 – 66.9
	Female	103	39.0	33.1 – 45.2
Age interval	under 20 years of age	17	6.44	3.80 – 10.11
	20 – 29 years of age	76	28.79	23.40 – 34.66
	30 - 39 years of age	73	27.65	22.34 – 33.47
	40 - 49 years of age	28	10.61	7.16 – 14.96
	50 - 59 years of age	35	13.26	9.41 – 17.95
	60 - 69 years of age	22	8.33	9.41 – 17.95
	70 - 79 years of age	9	3.41	1.57 – 6.37
	over 80 years of age	4	1.52	0.41 – 3.83

White blood cell count	< 3.99	4	1.5	0.4 – 3.8
	4.0 – 8.9	14	5.3	2.9 – 8.7
	9.0 – 10.9	26	9.9	6.2 – 15.8
	11.0 – 14.9	85	32.2	24.1 – 39.9
	≥ 15.0	135	51.1	44.9 – 57.3
Associated pathology	Yes	52	19.7	15.1 – 25.0
	No	212	80.3	75.0 – 84.9
Postoperative diagnosis	Phlegmonous acute appendicitis	48	18.2	13.7 – 23.4
	Gangrenous acute appendicitis	145	54.9	48.7 – 61.0
	Perforated acute appendicitis	71	26.9	21.6 – 32.7
Postoperative peritonitis - type	Localized	154	58.3	52.1 – 64.3
	Generalized	54	20.5	15.8 – 25.8
	Appendiceal abscess	41	15.5	11.4 – 20.5
	Retroperitoneal appendiceal abscess	15	5.7	3.2 – 9.2

*number of cases
**percentage
***Confidentiality Index of 95%

We evaluated the value of total bilirubin (TB) as well as its direct compound (DB) for the patients with acute complicated appendicitis in the study group. The normal range for the laboratory analyzer used is 0.3 mg/dL – 1.2 mg/dL for total bilirubin and 0 mg/dL – 0.5mg/dL for direct bilirubin.

The mean value of total bilirubinemia for the study group was 0.93 mg/dL with a minimum of 0.1mg/dL and a maximum of 2.8 mg/dL. The mean value of direct bilirubinemia was 0.3 mg/dL, with a minimum of 0.01mg/dL and a maximum of 2.2 mg/dL.

We correlated the value of total bilirubin with the time elapsed from the onset of symptoms to the examination: bilirubinemia was higher as the time interval was longer: the mean value of total bilirubin level was 0.79 mg/dL at 12 hours from the onset of symptoms, 0.90 mg/dL at 24 hours from onset, 1.08 mg/dL at 72 hours from onset, as shown in chart (1):

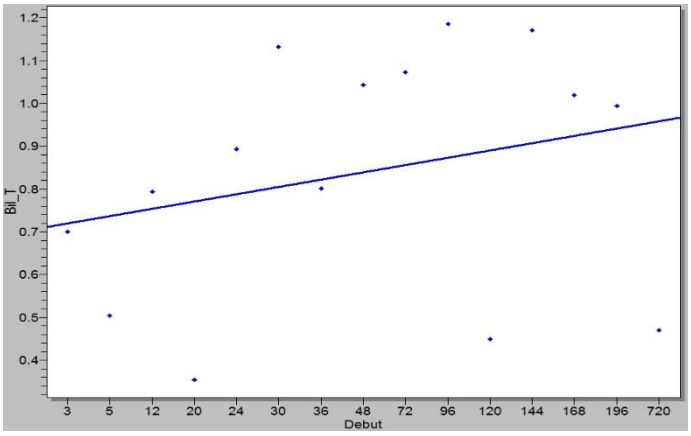

Chart 1: The mean value of TB in relation to the time from onset of symptoms

The value of direct bilirubinemia is as well correlated with the time from onset: mean value for 12 hours from onset was 0.22 mg/dL, mean value for 24 hours from onset was 0.28 mg/dL and mean value for 72 hours from onset was 0.47 mg/dL, as shown below (chart 2):

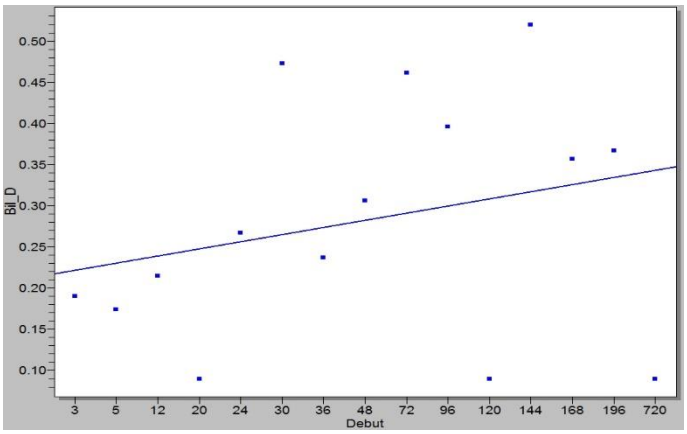

Chart 2: The mean value of DB in relation to the time from onset of symptoms

We also compared the values of TB and DB in relation to the postoperative diagnosis, which resulted in the conclusion that the mean value of these is higher in the order: phlegmonous acute appendicitis (PhAA)-gangrenous acute appendicitis (GAA)-perforated acute appendicitis (PAA).

For the cases diagnosed with phlegmonous appendicitis the mean value of TB was 0.61 mg/dL, the mean value for gangrenous appendicitis was 0.80 mg/dL and for perforated appendicitis the mean value was as high as 1.41 mg/dL.

The elevated value of TB was based mainly on the elevation of the value of DB for the case of perforation especially, as follows: mean value of DB for phlegmonous appendicitis was 0.15 mg/dL, mean value for gangrenous appendicitis was 0.19 mg/dL and mean value for perforated appendicitis was 0.64 mg/dL.

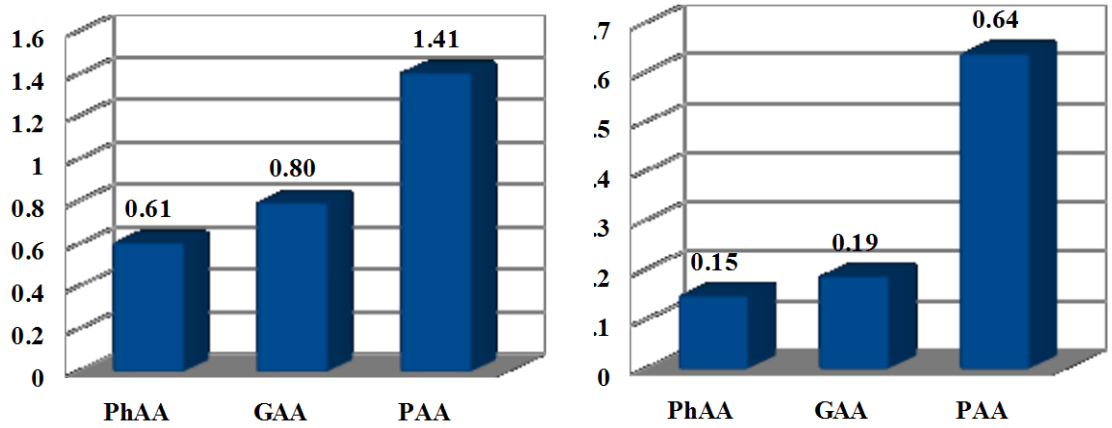

Chart 3 and 4: The mean value of TB (mg/dL) and the mean value of DB (mg/dL) in relation to the postoperative diagnosis

Taking into consideration the normal value of TB (up to 1.2 mg/dL for the laboratory analyzer we used) and the values obtained for the study group, we established the following categories for the cases in the study group:

- patients with value of TB within normal ranges – TB less than 1.2 mg/dL;
- patients with mild rise of TB: TB between 1.2 to 1.5 mg/dL;
- patients with severe rise of TB: TB over 1.5 mg/dL.

The distribution of cases according to this classification is shown in the table (3).

Table 3: Distribution of cases according to value of TB

Phlegmonous acute appendicitis				
	Frequency	Percent	Cumulative percent	CI 95%
TB < 1.2 (mg/dL)	43	89.60%	89.60%	77.3 – 96.5 %
TB = 1.2 – 1.49 (mg/dL)	5	10.40%	100.00%	3.5 – 22.7 %
TB ≥ 1.5 (mg/dL)	0	0.00%	100.00%	0.0 – 7.4 %
Total	48	100.00%		
Gangrenous acute appendicitis				
	Frequency	Percent	Cumulative percent	CI 95%
TB < 1.2 (mg/dL)	118	81.40%	81.40%	74.1 – 87.4%
TB = 1.2 – 1.49 (mg/dL)	24	16.60%	98.00%	10.9 – 23.6 %
TB ≥ 1.5 (mg/dL)	3	2.10%	100.00%	0.4 – 5.9 %
Total	145	100.00%		
Perforated acute appendicitis				
	Frequency	Percent	Cumulative percent	CI 95%
TB < 1.2 (mg/dL)	19	27.50%	27.50%	23.0 – 46.0 %
TB = 1.2 – 1.49 (mg/dL)	24	33.80%	61.30%	16.9 – 38.6 %
TB ≥ 1.5 (mg/dL)	28	39.40%	100.00%	28.0 – 51.7
Total	71	100.00%		

It can be observed that the distribution of the values of TB is correlated with the postoperative diagnosis, as for PhAA most cases have TB within normal ranges, with only 10.4% of cases with mild rise of TB, as well as GAA for which almost 20% have values of TB higher than normal; for PAA in exchange the cases with values of TB higher than normal is significantly higher than those with values within normal ranges, as approximately 73% of cases have TB more than 1.2 mg/dL, with 40% of cases with TB higher than 1.5 mg/dL.

As for other clinical data recorded, the rise of TB is correlated with the extension of voluntary guarding – for voluntary guarding limited to the inferior right quadrant the mean TB level was 0.98 mg/dL, and for voluntary guarding extended to the entire abdomen the mean value of TB was 1.79 mg/dL.

Another correlation observed was that between the rise of mean TB and DB levels and the presence of other pathologies – TB of 0.87mg/dL for previously healthy patients compared to 1.17 mg/dL for the other group and DB of 0.26 mg/dL for previously healthy patients compared to 0.50 mg/dL for the other group; this observation might have practical importance as patients with previous serious pathologies might not have a clinical presentation concordant with the diagnosis or severity of acute appendicitis.

Observing the rise of bilirubinemia mainly based on its direct component, we decided to calculate the ratio of DB and TB as a separate test and we came to the conclusion that this ratio is higher for cases of perforated acute appendicitis than for cases with other forms of complicated appendicitis – 0.43 to 0.23.

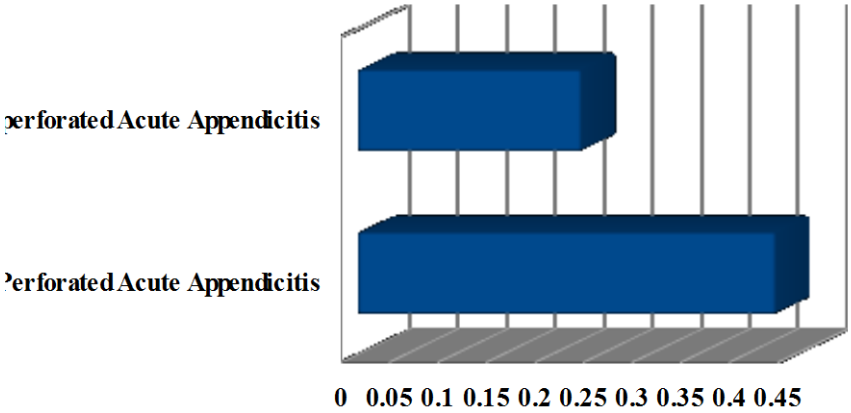

Chart 5: The DB/TB ratio in relation to perforation of the appendix

We formulated the hypothesis of a statistical correlation between the value of TB, the ratio DB/TB and the presence of perforation of the appendix and its subsequent lesions of the peritoneum. Based on this hypothesis, we ran the statistical analysis to determine the prediction value of bilirubinemia for appendicular perforation.

Analyzing the values of TB in the study group it can be easily observed that in the case of perforated acute appendicitis most of the cases had a value of TB higher than normal – 73.2% of which 33.8% with mild rise of TB and 39.4% with severe rise of TB level.

Introducing the data to the 2x2 contingency table, we obtained the following data for the predictive value of the total bilirubinemia level for appendiceal perforation:

- sensitivity of the test (Se) 66.2%
- specificity of the test (Sp) 83.4%
- PPV=59.5% and NPV=87%
- OR = 9.85
- RR = 4.54
- $p<0.005$,

Which validates the hypothesis.

As for the predictive value of both TB and DB for appendiceal perforation we established a scoring system comprising of 1 point for values of TB higher than 1.2 mg/dL and 1 point for value of DB/TB ratio higher than 0.3.

Table 4: Score system for bilirubinemia rise

Variables	**Points**
Total bilirubinemia ≥ 1.2 mg/dL	1
Direct bilirubinemia/Total bilirubinemia ratio ≥ 0.3	1
TOTAL (maximum)	2

Appling the score to the study group we obtained the following data (table 5):

Table 5: Bilirubinemia score for the different postoperative diagnosis

DIAGNOSIS	**Score**						**TOTAL**
	0		**1**		**2**		
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**	
PhAA	40	83.30%	7	14.60%	1	2.10%	**48**
GAA	107	73.80%	36	24.80%	2	1.40%	**145**
PAA	10	14.10%	33	46.50%	28	39.40%	**71**
TOTAL	**157**	**59.50%**	**76**	**28.80%**	**31**	**11.70%**	**264**

Considering the risk for appendiceal perforation present for patients with bilirubinemia score ≥ 1 (at least one of TB or DB/TB ratio positive), it can be observed the predominance of score value 0 for 59.5% of cases, signifying the probability of non-perforated appendicitis, and score value ≥ 1 for 40.5% of cases, signifying the probability of perforation of the appendix.

The distribution of score values for postoperative diagnosis is shown below (table 6). One can observe the predominance of the diagnosis of perforated appendicitis for the score value of 2 (90.3%) and the predominance of the diagnosis of non-perforated appendicitis (phlegmonous or gangrenous) for the score value of 0 (93.6%). \

Table 6: Distribution of bilirubinemia score for different postoperative diagnosis

SCORE	Acute appendicitis					
	PhAA		GAA		PAA	
	%	CI (95 %)	%	CI (95 %)	%	CI (95 %)
0	25.50%	18.9%-33.0%	68.2%	60.3%-75.4%	6.4%	3.1%-11.4%
1	9.20%	3.8%-18.1%	47.4%	35.8%-59.2%	43.4%	32.1%-55.3%
2	3.20%	0.1%-16.7%	6.5%	0.8%-21.4%	90.3%	74.2%-8.0%

The mean score value for the postoperative diagnosis is 0.2 for PhAA, 0.3 for GAA and 1.6 for PAA, as shown in the chart (6):

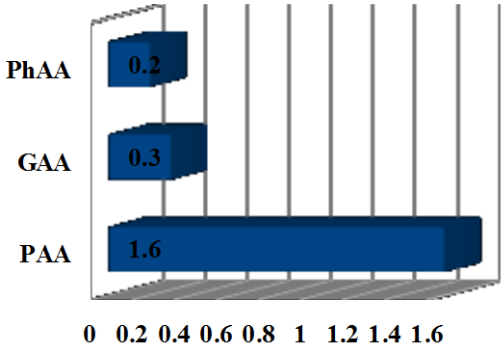

Chart 6: Mean score value for different postoperative diagnosis

Introducing the data to the 2x2 contingency table, we obtained the following data for the predictive value of the bilirubinemia score ≥ 1 for appendiceal perforation:

- prevalence 26.9%
- sensitivity of the test (Se) 85.9%
- specificity of the test (Sp) 76.2%
- PPV=57.0% and NPV=93.6%
- OR = 19.5
- RR = 8.9
- p<0.005,

  which validates the hypothesis.

DISCUSSION

Interpreting the statistical results we can sustain the fact that a bilirubin score higher than 1 has a good sensitivity and specificity for the correlation between the rise of total bilirubin level and/or the ratio between direct and total bilirubin level and the perforation of the appendix in an acute appendicitis.

The high negative predictive value of the tests helps to exclude the risk of perforation of the appendix for the patients with acute appendicitis that have not an rise of TB above 1.2 mg/dL or DB/TB ratio more than 0.3. The high value of OR shows the strong correlation between the bilirubin score/TB rise and appendicular perforation.

The risk ratio shows that the risk of perforation of the appendix is 4.5 times higher in patients with acute appendicitis and TB > 1.2 mg/dL than those with TB within normal ranges and as high as 9 times for those patients with acute appendicitis that have TB higher than 1.2 mg/dL and/or DB/TB ratio higher than 0.3 than those with normal values.

These data are concordant with the data from other studies and publications.

The test, being fast, cheap and safe, might be useful in selecting the group of patients with acute appendicitis that require a rapid instalment of therapeutical measures, as this group is prone to serious complications from this disease.

CONCLUSIONS

For the case of patients clinically diagnosed with acute appendicitis, the association of total hyperbilirubinemia rises the probability of appendiceal perforation.

The rise of bilirubin especially in its direct compound, expressed by the DB/TB ratio, is correlated with appendiceal perforation and has predictive value for a ratio higher than 0.3.

The bilirubin score consisting of the value of total bilirubinemia and the direct-total bilirubinemia ratio best defines the risk of appendiceal perforation, as it is 9 times higher for a score ≥ 1.

Patients at risk for appendiceal perforation might be defined by the diagnosis of acute appendicitis and a bilirubin score ≥ 1.

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