Is hyperbilirubinaemia in appendicitis a better predictor of perforation than C-reactive protein? – a prospective study

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Abstract

Purpose To compare the performance for the prediction of perforated appendicitis of total bilirubin versus C-reactive protein (CRP), white blood cell count, the time period of symptoms' evolution, and systemic inflammatory response syndrome (SIRS).

Methods Prospective observational study, applying receiver operating characteristics curve analysis to compare the sensitivity and specificity of the tested variables.

Results The period of symptom's evolution was prolonged (105.2 ± 79.3 hours vs. 38.6 ± 17.5 hours), and CRP levels were higher in perforated appendicitis (176 ± 82.6 mg/l vs. 80 ± 76 mg/l). Most patients with perforated appendicitis had a SIRS score higher than 3 points. CRP (>76.7 mg/l), the time period of symptoms' evolution (>34.5 hours), and SIRS (3 points or more), were the best cutoff values to predict perforated appendicitis.

Conclusions Perforated appendicitis may be suspected based on CRP, SIRS and the time period of symptoms' evolution. We do not recommend the use of total bilirubin to predict perforation in appendicitis.

Keywords Acute appendicitis · Hyperbilirubinaemia · Perforated appendicitis · Hepatic dysfunction in sepsis

Introduction

Perforated appendicitis is determined by patient's pre-hospital factors, such as the time period of symptoms' evolution which comprises the period of time from the onset of symptoms until the patient presents to medical evaluation or surgery [1–5]. The incidence of perforated appendicitis in adults has been reported from 13–37% or higher [1, 2, 4]. Research on the importance of in-hospital delay has determined that perforation does not occur in the hospital-phase of patients waiting surgery for appendicitis [3, 4, 6]. The risk of rupture was negligible within the first 24 hours, climbed to 6% after 36 hours from the onset of symptoms and remained steady at approximately 5% for each ensuing 12 hours period, establishing a 36 hours period from the onset of symptoms to surgery as a low risk period for appendiceal perforation [3, 6, 7], consequently in-hospital delay is not an independent factor of perforation although delays may contribute if patients are left to wait unduly [3, 4, 6]. Perforated appendicitis has been associated to early [6–9] and long-term complications [8], hence the importance of its accurate diagnosis and early treatment. Moreover, the removal of normal appendices has known ethic, economic, and legal implications [10]. Radiologic studies, such as computed tomography, magnetic resonance imaging or ultrasonography, are highly sensitive and specific to diagnose and confirm perforated appendicitis; however they are not always available in third world institutions or emergency units in developing countries where we must rely on the clinic and laboratory tests to suspect appendicitis and other abdominal emergencies. As a

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consequence clinical and laboratory research on typical [11, 12] and atypical clinical presentations of appendicitis [13], laboratory test and inflammatory markers [11, 14], and diagnostic scores [14, 15], has been undertaken. However, we as well as others believe that the diagnosis of appendicitis is clinical [12–16]. The most commonly laboratory tests used to support the diagnosis of appendicitis are white blood cell count (WBC) and C-reactive protein (CRP) [11, 17, 18], these markers have been studied together with other parameters in an effort to improve and predict the preoperative diagnosis of perforated appendicitis, nonetheless only an elevated CRP, a prolonged period of symptom's evolution, and fever have been identified as useful markers of perforation [17, 18]. Recently, it has been proposed that an elevated total bilirubin (TB) level could be used as a specific marker for the prediction of perforated appendicitis [19, 20]. The rationale for this proposal is based on the hepatic dysfunction occurring during bacterial sepsis secondary to Gram negative bacteria [21], such as *Escherichia coli*, which is the main bacteria present in patients with appendicitis [22, 23]. Consequently a low-grade hyperbilirubinaemia, often unnoticed in septic patients not presenting clinically evident jaundice, is present in patients with gram-negative infections [24]. Our purpose with this study was to compare the performance of TB versus other well known unspecific inflammatory markers (WBC and CRP), the time period of symptoms' evolution from the onset of symptoms to surgery, and the systemic inflammatory response syndrome (SIRS), to suspect perforated appendicitis.

Patients and methods

Design of the study, inclusion and exclusion criteria

A prospective observational study, comprising a non-randomised cohort which was followed-up from admission to the emergency unit of our institution to discharge from the hospital, was conducted. The sample was calculated based on the 200 adult patients operated for appendicitis every year at our institution. With a power of 80%, an error of 5%, and 95% confidence intervals, a sample of 132 patients was required. From October 2007 to September 2008 we included 143 consecutive adult patients older than 15-years-of-age in the database, and for the purposes of this study, nine patients (6.3%) were excluded from the analysis because the removed appendix was normal, consequently the cohort analysed comprised 134 patients operated on for appendicitis and confirmed by the histopathological report. Other exclusion criteria were appendectomy performed incidentally or for other indications, risk factors for hepatic disease such as alcoholism, a history of viral hepatitis, Gilbert's disease, Dubin-Johnson syndrome, benign recurrent intra-hepatic cholestasis, and other documented biliary, haemolytic or liver diseases associated with hyperbilirubinaemia, no other patient was ex-

cluded based on these criteria. At admission demographic and clinical data, and the time period of symptoms' evolution was recorded, and a blood sample was drawn, and the SIRS score was calculated. All patients were followed-up during the postoperative period and any complication was recorded. After discharge from the hospital the histopathological report was recorded. All pathological specimens were processed by the same pathologist, who was not aware of the study and who is experienced in gastroenterological pathology.

Definitions and normal values

Non-perforated appendicitis was defined as the acute inflammation of the mucosa, with polymorphonuclear infiltration of the appendiceal wall without evidence of necrosis or gangrene [2, 13, 15]. Perforated appendicitis was defined as the rupture of the appendiceal wall to the serosal surface evidenced at surgery by the surgeon or at histological analysis of the specimen by the pathologist [2, 13, 15]. According to our institutional laboratory, normal values were considered for WBC at $<10,300 \text{ mm}^3$, for CRP when levels were from 0–10 mg/l, and for TB when levels were from 0 to 1.2 mg/dl [13, 15, 25]. SIRS was defined as a body rectal temperature higher than 38°C or lower than 36°C , a heart rate higher than 90 min, a respiratory rate higher than 20 min, and a WBC higher than $12,000 \text{ mm}^3$ or lower than $4,000 \text{ mm}^3$ [26], one point was assigned for every positive parameter which yield a score ranging from 0–4 points. The time period of the symptoms' evolution was measured from the onset of symptoms to operation.

Statistics

Continuous variables were reported as mean $\pm$ SD, and analysed with the Mann-Whitney U-test. Categorical variables were reported as percentages and analysed with the Fisher's exact test, a p value <0.05 was significant. To compare the sensitivity and specificity of the following test variables: WBC, CRP, TB, time period of the symptom's evolution, and SIRS, and their performance in the prediction of perforated appendicitis, a receiver operating characteristics (ROC) curve analysis was performed. The state variable was the histopathology reporting perforated appendicitis. When the area under the curve is closer to 1.0, it denotes a higher sensitivity and specificity; while an area under the curve, closer to 0.5, denotes a poor sensitivity and specificity, 95% confidence intervals were calculated, and p value was significant at <0.05 . The best cutoff values with better sensitivity and specificity were determined for the test variables. The database was analysed with the statistical software SPSS 11.0 (Chicago, IL, USA).

Results

Demographics, time period of symptoms' evolution and length of hospital stay

There were no differences in gender between patients with non-perforated and perforated appendicitis. Patients with perforated appendicitis had a mean age higher than patients with non-perforated appendicitis (37.8 ± 16.8 vs. 30.2 ± 14.8 years, $p=0.076$). The time period of symptoms' evolution was prolonged for patients with perforated appendicitis (105.2 ± 79.3 vs. 38.6 ± 17.5 h, $p=0.002$), as well as the length of hospital stay (4.7 ± 2.5 vs. 1.7 ± 0.6 days, $p=0.041$), with a stay of more than 3 days for 59% ($p<0.0001$) patients with perforated appendicitis. Eighty-nine percent ($p=0.011$) patients with non-perforated appendicitis had a stay of 2 days or less (Table 1).

Laboratory tests

WBC values were similar in both groups. CRP levels were higher in perforated appendicitis (176 ± 82.6 vs. 80 ± 76 mg/l, $p = 0.001$), as well as TB values (1.04 ± 0.5 vs. 0.7 ± 0.3 mg/dl, $p = 0.047$) (Table 2).

SIRS

An elevated heart and respiratory rate, and fever, were present in most patients with perforated appendicitis, while leucocytosis was common in both groups. Many patients with non-perforated appendicitis had a SIRS score between 0 and 2 points (59%, $p = 0.025$), most patients with perforated appendicitis had a SIRS score between 3 and 4 points (65.3%, $p = 0.011$) (Table 3).

Table 1 Demographics, time period of symptoms' evolution, and length of hospital stay

	Cohort (n = 134 to 100%)	Non-perforated appendicitis (n = 85 to 63.4%)	Perforated appendicitis (n = 49 to 36.6%)	<i>p</i> *
Gender: male/female	63/71 (47%/53%)	39/46 (46%/54%)	24/25 (49%/51%)	0.367
Age (yr) (mean $\pm$ SD)	33 $\pm$ 16 (15–80)	30.2 $\pm$ 14.8 (15–76)	37.8 $\pm$ 16.8 (16–80)	0.076
Symptom's evolution (h) (mean $\pm$ SD)	67.6 $\pm$ 53.5 (11–533)	38.6 $\pm$ 17.5 (11–82)	105.2 $\pm$ 79.3 (17–533)	0.002
Hospital stay (days) (mean $\pm$ SD)	2.8 $\pm$ 2 (1–14)	1.7 $\pm$ 0.6 (1–3)	4.7 $\pm$ 2.5 (2–14)	0.041
0–2 days	85 (63%)	76 (89%)	20 (41%)	0.011
>3 days	49 (37%)	9 (11%)	29 (59%)	<0.0001

SD: Standard deviation

*Mann-Whitney U-test or Fischer's exact test according to the type of variable

Table 2 Laboratory tests

Test	Cohort	Non-perforated appendicitis	Perforated appendicitis	<i>p</i> *
WBC ($>10.300 \text{ mm}^3$)	15,874 $\pm$ 4,731 (2,850–26,500)	15,276 $\pm$ 4,428 (6,500–25,100)	16,910 $\pm$ 5,097 (2,850–26,500)	0.187
CRP (0–10 mg/l)	109 $\pm$ 98.6 (1.1–349)	80 $\pm$ 76 (1.1–349)	176 $\pm$ 82.6 (34.4–347.7)	0.001
Total bilirubin (0–1.2 mg/dl)	0.8 $\pm$ 0.4 (0.1–2.6)	0.7 $\pm$ 0.3 (0.1–1.16)	1.04 $\pm$ 0.5 (0.57–2.6)	0.047

*Mann-Whitney U-test

Table 3 Systemic inflammatory response syndrome (SIRS)

Variable	Cohort (n = 134 to 100%)	Non-perforated appendicitis (n = 85 to 63.4%)	Perforated appendicitis (n = 49 to 36.6%)	<i>p</i> *
Rectal temperature $>37.5^\circ\text{C}$	110 (82)	66 (77.6)	44 (90)	0.027
Heart rate >100 min	63 (47)	32 (37.6)	31 (63.3)	0.007
Respiratory rate >18 min	45 (33.6)	23 (27)	22 (45)	0.014
Leucocytosis $>12,000 \text{ mm}^3$	114 (85)	69 (81.2)	45 (92)	0.084
Points: 0–2	67 (50)	50 (59)	17 (34.7)	0.025
Points: 3–4	67 (50)	35 (41)	32 (65.3)	0.011

*Fischer's exact test

ROC curve analysis

The comparison of TB values with the other tested variables, WBC, CRP, the time period of the symptoms' evolution, and SIRS is shown in Fig. 1, this analysis demonstrates that TB performs similarly as WBC count, and the time period of symptoms' evolution for the prediction of perforated appendicitis, but inferiorly to SIRS score and mainly to CRP which are better predictors. This is evidenced in Table 4, where the area under the curve for CRP (0.767, $p < 0.0001$) and for SIRS (0.670, $p = 0.001$) are higher than the area under the curve of TB and other variables. In Fig. 2 the performance of CRP against the other variables was tested and confirms the better performance of CRP for the prediction of perforated appendicitis.

Cutoff values

Values representing the best sensitivity and specificity for all tested variables were calculated based on ROC curve analysis. CRP (>76.7 mg/l), the time period of the symptoms' evolution (>34.5 hours), and SIRS (3 points or more),

were the cutoff values with the best performance for prediction of perforated appendicitis. WBC ($>16,650$ mm³) and TB (>0.76 mg/dl) performed inferiorly (Table 5).

Complications and length of stay

Most patients with non-perforated appendicitis did not have any postoperative complications (98%, $p = 0.002$). The most common complication presented, mostly in patients with perforated appendicitis, was superficial surgical site infection (14.2%, $p = 0.004$), other complications such as pneumonia, postoperative ileus, residual intra-abdominal abscess and deep venous thrombosis, presented only in patients with perforated appendicitis (Table 6).

Discussion

Gender, age, and the time period of symptoms' evolution

Gender and age of presentation was similar to what has been reported elsewhere [1–7, 9, 11–16]. The time period

A. WBC vs. TB

B. CRP vs. TB

C. Symptom's evolution vs. TB

D. SIRS vs. TB

Fig. 1 Total bilirubin values versus WBC, CRP, the time period of symptoms' evolution, and SIRS

of symptoms' evolution was significantly more prolonged (105.2 ± 79.3 h, $p = 0.002$), which supports previous observations on the influence of time on the risk of perforation [1–7, 9, 13, 16]. Moreover, this variable together with SIRS and CRP, was one of the strongest predictors of perforation in this study, with a sensitivity of 0.65 at its better cutoff value (>34.5 h). This observation has been previously described, the study of Bickell et al. [3] established a period of 36 hours after the onset of symptoms as a low risk period for perforation with a risk of 2% or less, after 36 hours the risk progressively increased.

Laboratory tests: WBC and CRP

The diagnostic value of CRP and WBC has been established in patients with appendicitis [11, 25, 27–32]. It has been demonstrated that CRP could differentiate between children with non-perforated from children with perforated appendicitis [25]; this observation has also been reported in adults [28, 32]. WBC is more important supporting the clinical diagnosis of appendicitis (perforated or non-perforated) [27–29, 31], because it has a low sensitivity and specificity it has little value in the diagnosis of perforated

Table 4 Receiver operating characteristics (ROC) curve analysis

Test result variable	Area under the curve	Standard error	95% Confidence intervals	<i>p</i>
WBC	0.623	0.051	0.524/0.723	0.018
CRP	0.767	0.043	0.682/0.851	<0.0001
Total bilirubin	0.633	0.051	0.533/0.732	0.011
Time period of symptoms' evolution	0.649	0.050	0.551/0.747	0.004
SIRS	0.670	0.047	0.578/0.762	0.001

A. CRP vs. WBC

B. Symptom's evolution vs. CRP

C. SIRS vs. CRP

Fig. 2 CRP levels versus WBC, the time period of symptoms' evolution, and SIRS

Table 5 Cutoff values, sensitivity and specificity

Variable (normal value)	Cutoff value	Sensitivity	Specificity
WBC (<10,300 mm ³)	16,650 mm ³	0.61	0.36
CRP (0–10 mg/l)	76.7 mg/l	0.75	0.35
Total bilirubin (0–1.2 mg/dl)	0.76 mg/dl	0.57	0.51
Time period of symptom's evolution (h)	34.5 h	0.65	0.42
SIRS (0 points)	3 points	0.65	0.41

Table 6 Postoperative complications

Complication	Cohort (n = 134 to 100%)	Non-perforated appendicitis (n = 85 to 63.4%)	Perforated appendicitis (n = 49 to 36.6%)	<i>p</i> *
None	118 (88)	83 (98)	35 (71.4)	0.002
Superficial surgical site infection	9 (6.7)	2 (2.4)	7 (14.2)	0.004
Pneumonia	4 (3)	-	4 (8.1)	0.244
Postoperative ileus	2 (1.5)	-	2 (4)	0.765
Residual intra-abdominal abscess	1 (0.7)	-	1 (2)	0.843
Deep venous thrombosis	1 (0.7)	-	1 (2)	0.843

*Fischer's exact test

appendicitis [28, 31]. In this study, CRP levels were significantly elevated in patients with perforated appendicitis (176 ± 82.6 mg/l, $p = 0.001$), with an area under the curve of 0.767 ($p < 0.0001$). And at a cutoff value higher than 76.7 mg/l, they had a sensitivity of 0.75, though a low specificity (0.35), CRP performed better than any other inflammatory marker, laboratory test, clinical variable, or SIRS to predict perforated appendicitis. CRP has been established as a useful and more sensitive marker of sepsis than WBC or fever [33, 34]. CRP was the first acute phase protein identified in 1930 by Tillet and Francis [34] and currently is well established as a sensitive although unspecific marker capable of differentiating infection from sepsis. Elevation in serum CRP levels is seen with most invasive infections, gram-positive and gram-negative bacterial systemic infections cause marked CRP rises, even in immunodeficient patients [34], CRP has also been identified as a marker of infection in patients with SIRS [35]. As a consequence, the increased levels shown by CRP in advanced perforated appendicitis are easily explained; patients with perforated appendicitis have a systemic infection caused by gram-negative bacteria, mainly *Escherichia coli* [22, 23], these patients often have a SIRS, consequently their CRP levels rise progressively along with the time of evolution of appendicitis, from the onset to diagnosis and treatment.

Total bilirubin and hyperbilirubinaemia

Hyperbilirubinaemia in acute appendicitis has been related mostly to severe septic complications such as septic thrombophlebitis of mesenteric and porta veins [36], in those cases TB level rises mildly just like in sepsis of any other cause. Recently some researchers have proposed that

hyperbilirubinaemia could be used to support the diagnosis of perforated appendicitis [19, 20]. They argue that the cause of elevated bilirubin is directly related to the pathogenesis of appendicitis and the invasion of gram-negative bacteria into *muscularis propria* of the appendix, leading to direct invasion or translocation into the portal venous system and into the hepatic parenchyma interfering with the excretion of bilirubin into the bile *canaliculi* by a mechanism caused by the bacterial endotoxin [19]. Though this argument has sense, and hepatic dysfunction during bacterial sepsis by gram-negatives has been sufficiently proved [21, 24, 37], the use of bilirubin levels to support the diagnosis of perforated appendicitis does not seem to make sense because, as we have demonstrated, other serologic tests (CRP), and clinical variables (SIRS, time period of symptoms evolution) performed better than TB in the ROC curve analysis, and have a better sensitivity to predict perforation in patients with appendicitis.

SIRS

The components of SIRS are simple inflammatory parameters easily measured in any patient presenting with suspected appendicitis. Some components of SIRS, tachycardia and fever, have been shown to have a predictive value for the prediction of perforated appendicitis [4, 17]. The study of Estrada et al. [19], measured SIRS and did not reach a significant value to predict perforation, however they found that 22% patients with perforated appendicitis had more than 2 SIRS points compared to 15% patients with non-perforated appendicitis. Our study found that 65.3% patients with perforated appendicitis had 3 or 4 SIRS points compared with 41% patients with non-perforated appendi-

citis, this difference being significant ($p = 0.011$), moreover the components of SIRS performed better than other variables, except CRP for the prediction of perforation. In the ROC curve analysis the cutoff point reached by SIRS was 3 points with specificity of 0.65, consequently we may argue that SIRS is a relatively good predictor of perforation.

Length of hospital stay and postoperative complications

Length of hospital stay is directly related to postoperative complications which present with a higher frequency in perforated appendicitis [7, 9, 17, 18]. The length of hospital stay has decreased, and currently patients with non-perforated appendicitis have a median hospital stay of 2 days [3], and patients with perforated appendicitis a median of 7.5 ± 3 days [1, 3]. In this study, length of hospital stay for patients with non-perforated appendicitis was 1.7 ± 0.6 days and for patients with perforated appendicitis 4.7 ± 2.5 days. Postoperative complications are the main cause of prolonged hospital stays, however late complications account for a small but important morbidity leading to even other surgical procedures [8]. Nevertheless, perforation in patients with appendicitis is the main cause of postoperative morbidity and prolonged hospital stays [1, 3, 9].

Conclusions

The diagnostic of perforated appendicitis may be suspected based on the clinical presentation, physical examination and supported by the time period of patient's symptoms' evolution, CRP, and SIRS. CRP and WBC though unspecific are useful for the diagnosis of appendicitis, perforated or non-perforated. We do not recommend the use of TB to predict perforation in appendicitis.

Conflict of interest The authors do not have any disclosable interest

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