Elevated serum bilirubin as a preoperative specific predictor for complicated appendicitis in children

Mohamed Rabae Abdella[a], Naglaa Sayed[b]

[a]Department of General Surgery, Faculty of Medicine, El Minia University, Minya, Egypt, [b]Department of Pediatrics, Banha Teaching General Hospital, The General Organization for Teaching Hospitals and Institutes, Banha, Egypt

Correspondence to Mohamed Rabae Abdella, MD, Department of General Surgery, Faculty of Medicine, El Minia University, 5255, Minya, Egypt
Tel: 00966114322222; Fax: 3412799
e-mail: mrabea177@gmail.com

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Objective
The aim of the study was to evaluate the diagnostic yield of preoperative high serum total bilirubin (TB) for cases of appendicitis in conjunction with clinical and other laboratory findings.

Patients and methods
The current study included 417 children presenting with right iliac fossa pain. All patients underwent clinical examination and gave blood sample on admission for estimation of serum TB and C-reactive protein (CRP) and total leukocytic count (TLC) and underwent surgical exploration and management according to operative findings.

Results
Surgical exploration defined 134 cases of complicated appendicitis (CA), 219 cases of simple appendicitis, and 64 cases of noninflamed appendix. Mean preoperative TLC and serum CRP showed high sensitivity (88.7 and 83.6%, respectively) for detection of acute appendicitis (AA), despite the lower specificity of CRP for diagnosis (57.8%), whereas the specificity rate of elevated TLC was 71.9%. For discrimination between simple appendicitis and CA, elevated serum CRP showed higher specificity compared with elevated TLC (70.3 vs. 65.8%) despite the higher sensitivity of elevated TLC compared with elevated serum CRP (91.8 vs. 80.6%). Serum TB showed the highest specificity rate for defining cases of AA and CA (79.7 and 86.3%, respectively) despite the low sensitivity for both. Receiver operating characteristic curve analysis defined the severity of rebound tenderness in the form of significant, sensitive, and elevated TLC as the most significant specific predictor for AA. Serum TB greater than 1 mg/dl was the most significant specific predictor for the diagnosis of CA.

Conclusion
Combined estimation of TLC and serum CRP and TB improves the diagnostic yield by combining the high sensitivity of TLC and CRP with the high specificity of TB, allowing early detection of cases that could develop CA and enabling better decision for patient discharge.

Keywords:
appendicitis, C-reactive protein, preoperative serum total bilirubin, total leukocytic count

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Introduction

Appendicitis represents one of the most common causes of abdominal pain among patients referred to the emergency department, and appendicectomy is one of the most frequent surgical interventions reported in hospitals, with worldwide prevalence. However, the diagnosis of appendicitis may be elusive and fraught with pitfalls because of the absence of a pathognomonic sign or symptom, the poor predictive value of associated laboratory testing, and its varied presentation at diagnosis [1–4].

The rate of negative appendicectomy still imposes a burden on health service resources, and, despite the extraordinary advances in modern radiography imaging and diagnostic laboratory investigations, the accurate diagnosis of acute appendicitis (AA) remains an enigmatic challenge. Although there are various diagnostic aids for appendicitis, no single test can reduce the rate of negative appendicectomy to zero [5–7].

The role of inflammatory markers for diagnosis of AA or for anticipation of the presence of complications is still a matter of debate. Sengupta *et al.* [8] suggested that patients experiencing lower abdominal pain, with normal white cell count and C-reactive protein (CRP) values, are unlikely to have AA and can be safely sent home. In contrast, Monneuse *et al.* [9] documented that the diagnosis of AA cannot be excluded when the patient presents with isolated rebound tenderness in the right lower quadrant even without fever and biological inflammatory signs. Vaughan-Shaw *et al.* [10] found that appendicitis in the presence of normal inflammatory markers is not uncommon and disagreed with the view of Sengupta *et al.* [8], who suggested that patients with normal white cell count and CRP are unlikely to have appendicitis, and recommended that clinicians be wary of normal inflammatory markers in patients with a high clinical suspicion of appendicitis.

The development of jaundice in sepsis is well recognized and has been associated with a variety

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of causative bacteria, with Gram-negative bacteria being most commonly implicated. Jaundice has been associated with appendicitis and studies have shown hyperbilirubinemia to be a useful predictor of appendiceal perforation [11,12]. However, these studies did not focus on the value of bilirubin as a marker for AA. Thus, the current prospective study aimed to evaluate the diagnostic yield of preoperative high serum total bilirubin (TB) for cases of appendicitis in conjunction with clinical and other laboratory findings.

Patients and methods

The current prospective study was conducted at Departments of General Surgery and Pediatrics, Al-Jafel Hospital (KSA) from July 2007 to October 2013. After obtaining approval from the local ethical committee for the study protocol and after obtaining fully informed written parents' consent, all patients presenting to the emergency department with right iliac fossa (RIF) pain were included in the study. Demographic and disease-related data were obtained from all patients. All of them underwent clinical examination for evaluation of other associated symptoms: temperature at the time of admission for categorization of patients according to a temperature cutoff point of 38.5°C; occurrence of vomiting, dysuria, diarrhea or bowel disturbances; clinical signs including the presence and severity of rebound tenderness, which was graded as light, moderate, or severe rebound tenderness; and presence of pain radiation and/or muscle guarding. All patients gave blood samples on admission to the emergency department for estimation of serum CRP and TB, for total leukocytic count (TLC), and for determination of the percentage of polymorphonuclear leukocytes. All laboratory investigations were conducted at the hospital laboratory. Thereafter, all patients underwent surgical exploration and management according to operative findings. Excised specimens were examined histopathologically for defining the extent of inflammation if present.

Statistical analysis

The obtained data were presented as mean ± SD, ranges, numbers, and ratios. The sensitivity and specificity of the estimated parameters as predictors were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) compared with the null hypothesis that AUC = 0.05. Regression analysis (stepwise method) was used for stratification of the studied parameters as specific predictors. Statistical analysis was conducted using the SPSS (version 15, 2006; SPSS Inc., Chicago, Illinois, USA) for Windows statistical package. A *P* value less than 0.05 was considered statistically significant.

Results

The current study included 417 patients, 188 (45.1%) boys and 229 (54.9%) girls, presenting to the emergency department with pain in the RIF since a mean duration of 10.4 ± 3.1 h (range 2–18 h). The mean age of the enrolled patients was 10.7 ± 3 years (range 5–15 years); however, the majority of patients (246 patients; 59%) were older than 10 years. Vomiting was the most common presenting symptom other than pain and was reported in 139 (33.3%) patients, whereas 85 (20.4%) patients had dysuria and 55 (13.2%) patients had diarrhea. A total of 163 (39.1%) patients had temperature higher than 38.5°C. All patients had rebound tenderness of varying severity; 136 (32.6%) patients had light and 123 (29.5%) patients had medium rebound tenderness, whereas 158 (37.9%) patients had strong rebound tenderness with muscle guarding. Pain radiation was documented by 189 (45.3%) patients (Table 1).

Thirty patients had an appendicular mass that could not be mobilized and was drained for a second

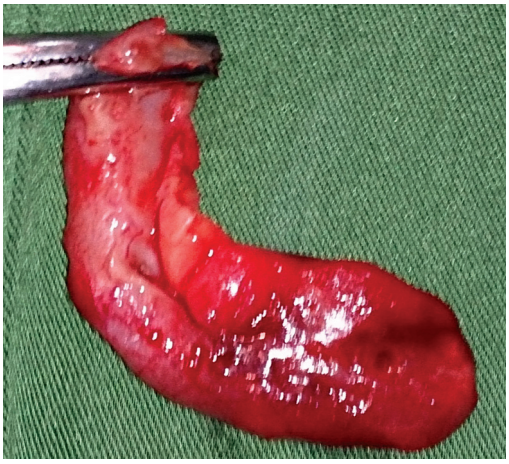
Table 1 Demographic and disease-related data

Data	Findings
Age (years)	
Strata	
<10	
N (%)	171 (41)
Mean	7.4 ± 1.2 (5–10)
>10	
N (%)	246 (59)
Mean	13 ± 1.2 (11–15)
Total	10.7 ± 3 (5–15)
Sex	
Males	188 (45.1)
Females	229 (54.9)
Duration of disease (h)	10.4 ± 3.1 (2–18)
Other presenting symptoms	
Vomiting	139 (33.3)
Diarrhea	55 (13.2)
Dysuria	85 (20.4)
Clinical signs	
Temperature (°C)	
<38.5	254 (60.9)
>38.5	163 (39.1)
Rebound tenderness	
Light	136 (32.6)
Medium	123 (29.5)
Strong	158 (37.9)
Pain radiation	189 (45.3)

Data are presented as mean ± SD and numbers; ranges and percentage are given in parenthesis.

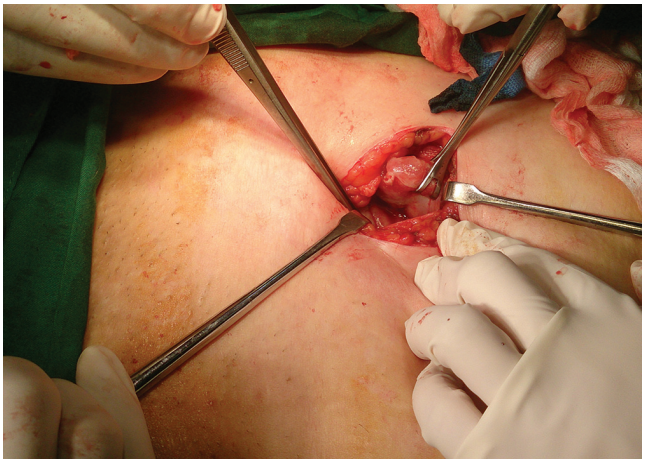
setting later on. Another 56 patients had a localized appendicular abscess that was drained; the appendix was found to have a thick edematous fragile wall but with a healthy base, thus allowing appendicectomy, and the stump was covered by an omental patch and the wound was drained. Forty cases had a localized appendicular abscess that was drained, but unfortunately exploration of its contents was not possible and appendicectomy was hazardous and thus postponed. Eight cases had generalized peritonitis, which was drained after peritoneal toilet, and appendicectomy was postponed. These 134 cases were collectively considered as complicated appendicitis (CA) (Figs. 1–3). The remaining 283 cases had a smooth intraoperative course with an uneventful outcome (Fig. 4). Histopathological examination of excised specimens (n = 339) revealed a noninflamed appendix in 64 (15.3%) patients (negative outcome).

Figure 1



Excised appendix with gangrenous spots in its tip.

Figure 3

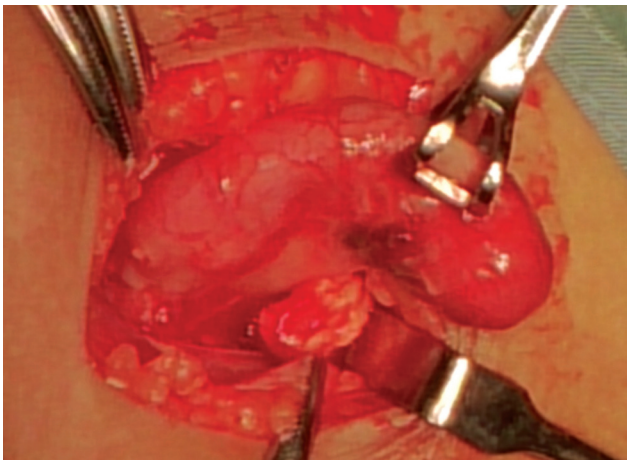


The appendix could not be delivered out of the wound and was bluntly dissected; the appendix had a healthy base and thus facilitated in-situ appendectomy.

Eighty-seven specimens showed inflammation with cellular infiltrate extending through the full thickness of the wall, and 132 specimens showed inflammation with cellular infiltrate not extending through the full thickness of the wall; these 219 cases were collectively considered as simple appendicitis (SA). Fifty-six specimens showed inflammation with cellular infiltrate extending through the full thickness of the wall, with endarteritis obliterans in the mesoappendiceal vessels with necrotic spots and minor perforations in some specimens. These specimens were considered as CA (Table 2).

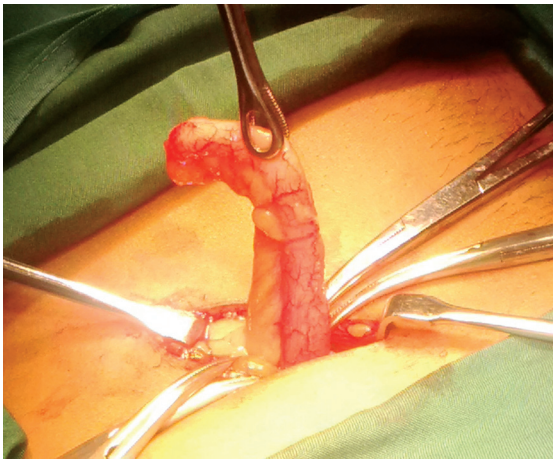
The mean preoperative TLC was 11.5 ± 2.6 (range 4.3–17.3 × 10^3 cells/ml); 87 (20.9%) patients had TLC less than 10 000 cells/ml, 282 (67.6%) had TLC in the range of 10 000–14 900 cells/ml, and 48 (11.5%) had

Figure 2



Appendix delivered out of the wound; the appendix was edematous with multiple spots of perforated gangrenous sites on the mesenteric side near the tip. The appendix appeared congested with a thickened inflamed mesoappendix.

Figure 4



The appendix was delivered out of the wound and appeared mildly inflamed with a normal-appearing mesoappendix.

TLC greater than 15 000 cells/ml (Fig. 5). The mean preoperative serum CRP level was 21.1±13 (range 4–63 g/l); 95 (22.7%) patients had a mean serum CRP less than 10 g/l, 298 (71.5%) patients had a serum CRP level in the range of 10–49 g/l, and 24 (5.8%) patients had a mean serum CRP level greater than or equal to 50 mg/l (Fig. 6). The mean preoperative serum TB was 1.32 ± 0.55 (range 0.54–2.31 mg/dl); 162 (38.8%) patients had a mean serum TB less than 1 mg/dl and 255 (61.2%) patients had a mean serum TB greater than 1 mg/dl (Table 3 and Fig. 7).

Evaluation of the test validity characteristics of the estimated laboratory parameters for exclusion of AA among patients presenting with RIF pain showed high sensitivity and

Table 2 Operative findings and histopathological diagnosis

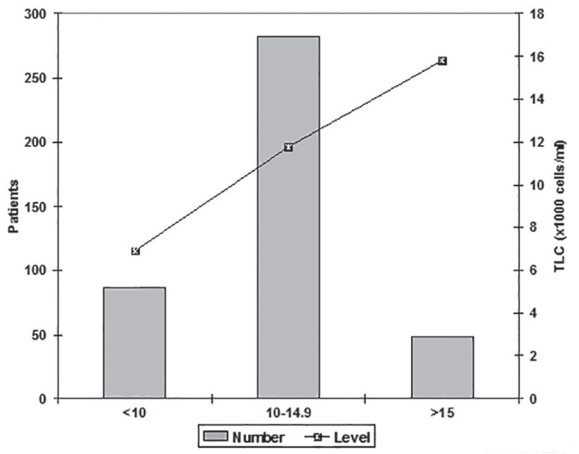
Data	*N* (%)
Negative appendicectomy (noninflamed appendix)	64 (15.3)
Simple appendicitis	
Full-thickness inflammatory infiltrate	87 (20.9)
Partial-thickness inflammatory infiltrate	132 (31.7)
Complicated appendicitis	
Mass	30 (7.2)
Localized abscess including resectable appendix	56 (13.4)
Localized abscess including unresectable appendix	40 (9.6)
Generalized peritonitis	8 (1.9)

Table 3 Laboratory data of the studied patients

Parameters	Frequency [*n* (%)]	Value
TLC (10^3 cells/ml)		
Strata		
<10	87 (20.9)	6.9 ± 0.9 (4.3–8.9)
10–14.9	282 (67.6)	11.8 ± 1.6 (10.3–14.9)
>15	48 (11.5)	15.8 ± 0.6 (15.2–17.3)
Total	417 (100)	11.5 ± 2.6 (4.3–17.3)
PNL%		
Strata		
70–84%	162 (38.8)	11 ± 3 (5.1–17.3)
85%	255 (61.2)	9.3 ± 2.5 (4.3–12.9)
Total	417 (100)	
Serum CRP (g/l)		
Strata		
<10	95 (22.7)	6.9 ± 1.1 (4–9)
10–49	298 (71.5)	22 ± 8.6 (12–49)
≥50	24 (5.8)	56.8 ± 3.1 (52–63)
Total	417 (100)	21.1 ± 13 (4–63)
Serum TB (mg/dl)		
Strata		
<1	162 (38.8)	0.72 ± 0.08 (0.54–0.98)
>1	255 (61.2)	1.7 ± 0.34 (1.08–2.31)
Total	417 (100)	1.32 ± 0.55 (0.54–2.31)

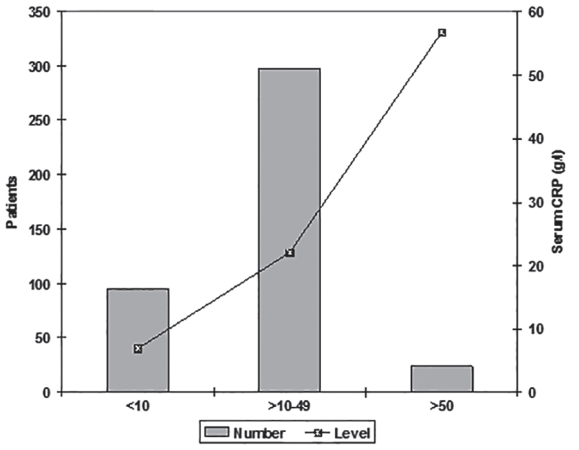
Data are presented as mean ± SD and numbers; ranges and percentages are given in parenthesis; CRP, C-reactive protein; PNL%, percentage of polymorphonuclear leukocytes; TB, total bilirubin; TLC, total leukocytic count.

Figure 5



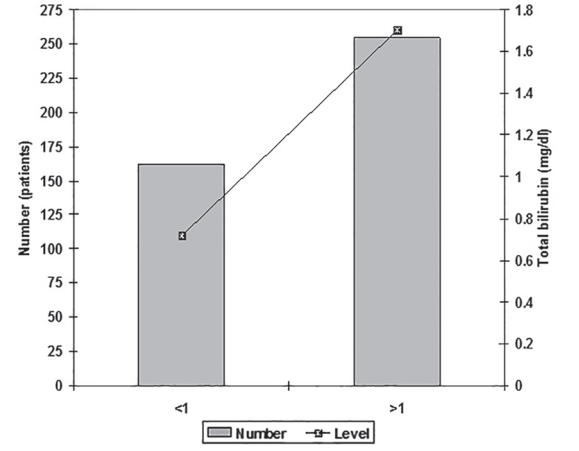
Patients' distribution according to total leukocytic count (TLC) category and mean count for each category.

Figure 6



Patients' distribution according to serum C-reactive protein (CRP) category and the mean level for each category.

Figure 7



Patients' distribution according to serum total bilirubin level and the mean level for each category.

positive predictive value for TLC and for estimation of serum CRP, whereas serum TB and TLC showed a high specificity (Fig. 8). For defining cases with probable CA, TLC showed the highest sensitivity and serum TB showed the highest specificity (Table 4 and Fig. 9).

The ROC curve analysis of the estimated laboratory parameters and clinical data defined severity of rebound tenderness as a significant (P = 0.019) sensitive predictor with AUC of 0.408 for the presence of AA, whereas occurrence of vomiting was a nonsignificant predictor for AA. Concerning laboratory data, elevated TLC was the most significant (P = 0.0003) specific predictor for AA, with AUC of 0.803, followed by high serum CRP, with AUC of 0.741, and serum TB greater than 1 mg/dl, with AUC of 0.707 (Fig. 10). For diagnosis of CA, all clinical data were nonsignificant sensitive predictors, whereas serum TB more than 1 mg/dl was found to be the most significant (P = 0.0001) specific predictor, with AUC of 0.805, followed by elevated TLC, with AUC of 0.788, and high serum CRP, with AUC of 0.755 (Table 5 and Fig. 11).

Regression analysis of the estimated laboratory parameters and clinical data defined TLC as a significant predictor for the presence of AA in three models, high serum CRP in two models, and serum TB more than 1 mg/dl in one model, whereas clinical data were nonsignificant predictors in the three models and were excluded. For diagnosis of CA, serum TB more than 1 mg/dl was the most significant predictor in four models, followed by elevated TLC in three models, elevated serum CRP in two models, and severity of rebound tenderness in one model, whereas the presence of fever and occurrence of vomiting were nonsignificant predictors in the three models and were excluded (Table 6).

Discussion

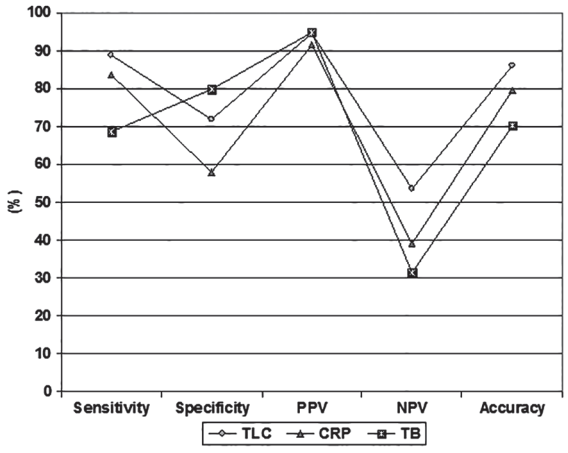
The current study detected significantly higher serum TB in patients with CA compared with those with uncomplicated SA, with significantly higher serum TB

Table 4 Test validity characters for estimated laboratory parameters

	Patients' distribution				Test validity characters (%)				
	T+	T−	F+	F−	Sensitivity	Specificity	PPV	NPV	Accuracy
Exclusion of AA (n = 417)									
TLC	313	46	18	40	88.7	71.9	94.6	53.5	86.1
CRP	295	37	27	58	83.6	57.8	91.6	38.9	79.6
TB	242	51	13	111	68.6	79.7	94.9	31.5	70.3
Defining CA (n = 353)									
TLC	123	144	75	11	91.8	65.8	62.1	92.9	75.6
CRP	108	154	65	26	80.6	70.3	62.4	85.6	74.2
TB	100	189	30	34	74.6	86.3	76.9	84.8	81.9

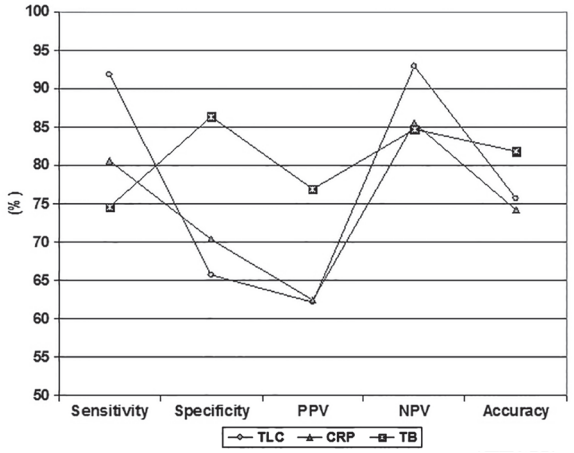
AA, acute appendicitis; CA, complicated appendicitis; CRP, C-reactive protein; F-, false negative; F+, false positive; NPV, negative predictive value; PPV, positive predictive value; T, true negative; T+, true positive; TB, total bilirubin; TLC, total leukocytic count.

Figure 8



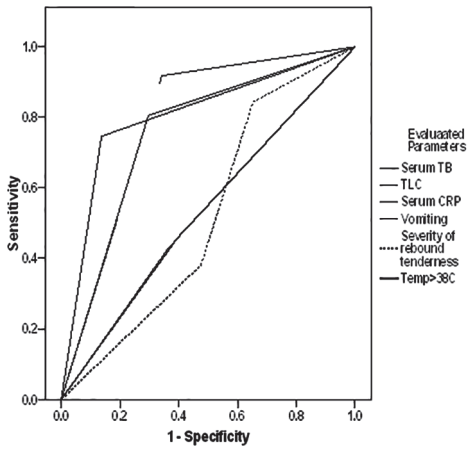
Test validity characteristics of estimated laboratory parameters for exclusion of acute appendicitis among patients with right iliac fossa pain. CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value; TB, total bilirubin; TLC, total leukocytic count.

Figure 9



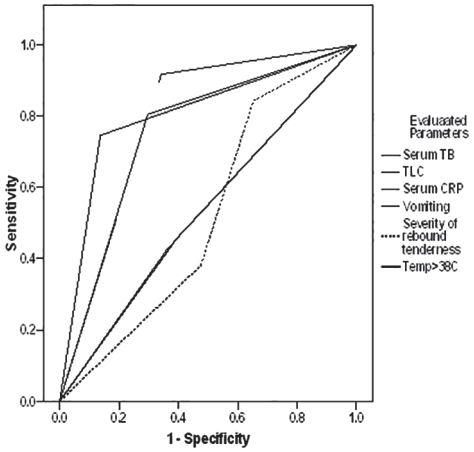
Test validity characteristics of estimated laboratory parameters for diagnosis of complicated appendicitis among patients with right iliac fossa pain. CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value; TB, total bilirubin; TLC, total leukocytic count.

Figure 10



Receiver operating characteristic curve analysis of clinical and laboratory data for exclusion of acute appendicitis in the studied patients. CRP, C-reactive protein; TB, total bilirubin; TLC, total leukocytic count.

Figure 11



Receiver operating characteristic curve analysis of clinical and laboratory data for the diagnosis of complicated appendicitis in the studied patients. CRP, C-reactive protein; TB, total bilirubin; TLC, total leukocytic count.

Table 5 Receiver operating characteristic curve analysis of clinical and laboratory data for exclusion of acute appendicitis and diagnosis of complicated appendicitis in the studied patients

Data	AUC	SE	Significance	95% CI	
				Lower	Upper
For exclusion of acute appendicitis					
Clinical data					
Occurrence of vomiting	0.448	0.040	0.183	0.370	0.526
Severity of rebound tenderness	0.408	0.039	0.019	0.331	0.484
Temperature >38.5°C	0.428	0.042	0.065	0.345	0.510
Laboratory data					
Serum TB	0.707	0.039	0.0009	0.631	0.783
TLC	0.803	0.035	0.0003	0.735	0.870
Serum CRP	0.741	0.033	0.0007	0.677	0.805
For diagnosis of complicated appendicitis					
Clinical data					
Occurrence of vomiting	0.532	0.032	0.308	0.470	0.595
Severity of rebound tenderness	0.519	0.031	0.545	0.459	0.580
Temperature >38.5°C	0.531	0.032	0.324	0.469	0.593
Laboratory data					
Serum TB	0.805	0.026	0.0001	0.754	0.855
TLC	0.788	0.024	0.0006	0.740	0.836
Serum CRP	0.755	0.027	0.0008	0.702	0.807

AUC, area under curve; CI, confidence interval; CRP, C-reactive protein; TB, total bilirubin; TLC, total leukocytic count; Significance: $P > 0.05$, nonsignificant; $P < 0.05$, significant.

Table 6 Regression analysis of clinical and laboratory data for exclusion of acute appendicitis and diagnosis of complicated appendicitis in the studied patients

Data	β	*t*	Significance
For exclusion of acute appendicitis			
Model 1			
TLC	0.464	12.196	0.0002
Serum CRP	0.272	7.239	0.0008
Serum TB	0.232	6.102	0.0009
Model 2			
TLC	0.505	12.935	0.0002
Serum CRP	0.298	7.935	0.0008
Model 3			
TLC	0.539	13.048	0.0001
For diagnosis of complicated appendicitis			
Model 1			
Serum TB	0.431	12.014	0.0002
TLC	0.357	9.945	0.0005
Serum CRP	0.283	7.947	0.0008
Severity of rebound tenderness	0.082	2.459	0.014
Model 2			
Serum TB	0.430	11.918	0.0003
TLC	0.359	9.937	0.0005
Serum CRP	0.278	7.765	0.0008
Model 3			
Serum TB	0.489	12.810	0.0002
TLC	0.418	10.936	0.0004
Model 4			
Serum TB	0.613	14.536	0.00009

β, standardized coefficient; CRP, C-reactive protein; *t*, unpaired *t*-test; TB, total bilirubin; TLC, total leukocytic count; Significance: $P > 0.05$, nonsignificant; $P < 0.05$, significant.

levels in those with SA compared with those with a noninflamed appendix. Moreover, the serum bilirubin level showed high predictability for CA among patients with AA, with high AUC on the ROC curve analysis. Regression analysis showed that elevated serum

TB was the most significant predictor in all studied statistical models, despite the low sensitivity. Moreover, low serum TB showed statistically high sensitivity as a screening test for exclusion of AA in susceptible cases of RIF pain, despite the low specificity.

These data indicate the ability of at-admission serum TB for stratification of cases of acute RIF pain and could discriminate between cases free of appendicitis and those with AA and between cases with complicated and those with SA. In line with these data, Emmanuel *et al.* [13] reported that mean TB levels were higher in patients with SA compared with those with a noninflamed appendix, with more patients with SA having hyperbilirubinemia on admission (30 vs. 12%), and that hyperbilirubinemia showed specificity of 88% and positive predictive value of 91% for AA and specificity of 70% for perforation or gangrene.

Giordano *et al.* [14] documented that hyperbilirubinemia had a sensitivity of 0.49, specificity of 0.82, positive and negative likelihood ratios of 2.51 and 0.58, and ROC curve analysis for AUC of 0.73 as a predictor of perforation in AA and concluded that patients with hyperbilirubinemia combined with symptoms and signs consistent with severe AA should be considered for early appendectomy. Burcharth *et al.* [15] reported that serum TB was significantly higher in patients with appendiceal perforation compared with patients with appendicitis without perforation and that elevated serum TB had a sensitivity ranging from 38 to 77% and a specificity ranging from 70 to 87% in predicting appendiceal perforation. They concluded that elevated serum TB has low sensitivity but higher specificity for determining the risk of perforation in appendicitis.

As regards TLC and CRP, both markers showed high sensitivity (88.7 and 83.6%, respectively) for detection of AA among cases of RIF pain despite the lower specificity of CRP for diagnosis (57.8%); the specificity rate for elevated TLC was 71.9%. For discrimination between SA and CA, elevated serum CRP showed higher specificity compared with elevated TLC (70.3 vs. 65.8%) despite the higher sensitivity of elevated TLC compared with elevated serum CRP (91.8 vs. 80.6%).

These findings are in agreement with those of Sand *et al.* [16], who found the specificity of hyperbilirubinemia for appendiceal perforation to be 86 versus 55 and 35% for TLC and CRP, respectively, whereas the sensitivity was 70% for hyperbilirubinemia compared with 81% for TLC and 96% for CRP. They concluded that patients with hyperbilirubinemia and clinical symptoms of appendicitis should be identified as having a higher probability of appendiceal perforation compared with those with normal bilirubin levels. Käser *et al.* [17] found hyperbilirubinemia to be a statistically significant marker of perforation in AA despite documenting that CRP is superior to TB for anticipation of perforation in AA.

Atahan *et al.* [18] found that assessment of preoperative TB is useful for the differential diagnosis of perforated versus suppurative AA, whereas WBC assessment is effective for diagnosing the presence versus absence of appendicitis. They concluded that symptom duration, WBC, and TB should be used as independent parameters in the early diagnosis of appendix perforation. Noh *et al.* [19] found WBC, CRP, and TB levels to be significantly higher in CA and the most sensitive markers for diagnosing CA were WBC followed by CRP, whereas bilirubin levels showed the highest specificity at 74.8%.

D'Souza *et al.* [20] reported that hyperbilirubinemia was significantly associated with appendicitis versus RIF pain of other etiologies and with perforated appendicitis versus SA and that bilirubin had a higher specificity (0.96%) compared with WBC (0.71%) and CRP (0.62%), but a lower sensitivity (0.27 vs. 0.68 and 0.82%, respectively), for the presence of appendicitis and a higher specificity (0.82%) than both WBC (0.34%) and CRP (0.21%), but a lower sensitivity, for perforated appendix. McGowan *et al.* [21] also found that the sensitivity and specificity of CRP were 78.57 and 63.01%, respectively, and that for bilirubin were 62.96 and 88.31%.

The reported increased serum levels of TB up to the level of hyperbilirubinemia indicated hepatic derangement, which could be attributed to the possibility of sepsis-induced hepatic dysfunction. Multiple studies tried to explore the underlying pathogenetic mechanisms for such an assumption; Deutschman *et al.* [22] using an animal model of cecal ligation and double puncture to induce severe sepsis simulating fecal peritonitis and intestinal gangrene found that cecal ligation and puncture induced cholestasis, steatosis, and hepatocellular injury in interleukin-6 (IL-6) –/– but not IL-6 +/+ mice and concluded that the absence of IL-6 is an important determinant of hepatic dysfunction and mortality in sepsis. Schonhoff *et al.* [23] reported that during sepsis-induced cholestasis there is a decrease in sodium-taurocholate cotransporting polypeptide-dependent uptake of bile acids and an increase in nitric oxide levels in hepatocytes. Bhogal *et al.* [24] documented that infections cause systemic and intrahepatic increase in proinflammatory cytokines, which result in impaired bile flow, and several other mediators of impairment in bile flow have been identified under conditions of

sepsis, such as increased nitric oxide production and decreased aquaporin channels. Recknagel *et al.* [25] also documented that polymicrobial sepsis produces profound hepatocellular dysfunction in the absence of traditional cytokine-mediated mechanisms of cellular injury and this questions the central role of cytokines and the ensuing oxidative stress as key molecular events in mediating liver dysfunction.

It could be concluded that no single laboratory parameter has the efficacy for discrimination between cases of AA; however, combined estimation of TLC and serum CRP and TB improves the diagnostic yield by combining the high sensitivity of TLC and CRP with the high specificity of TB, allowing early detection of cases that could develop CA and enabling better decision making for patient discharge or motivating further investigations in patients free of appendicitis.

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Conflicts of interest

None declared.

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